UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Illicit Substance Use and risk of HIV Transmission among Men who have Sex with Men

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy in Public Health (Epidemiology)

by

Lydia Nicole Drumright

Committee in Charge:

University of California, San Diego

Professor Steffanie A. Strathdee, Chair
Professor Maria Rosario G. Araneta
Professor Susan J. Little

San Diego State University

Professor Vanessa L. Malcarne
Professor Donald J. Slymen

University of California, Los Angeles

Professor Pamina M. Gorbach

2006

The dissertation of Lydia Nicole Drumright is approved, and it

Is acceptable in quality and form for publication on microfilm:

_____

_____

_____

_____

_____

_____
Chair

University of California, San Diego

San Diego State University

2006

DEDICATION

To all of the people in my life who profoundly influenced my education and encouraged me to go further, I dedicate this work. Passing on knowledge, inspiration, encouragement, and the excitement of learning to another person are some of the greatest gifts one can give.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I am thankful for my dissertation committee and all of the time and support they have provided. After experiencing the process, I appreciate what a huge commitment it is to participate on a committee. I cannot thank my committee chair, Steffanie Strathdee, enough for taking me in half-way through my dissertation process, believing in me, supporting me, encouraging me, and giving me the opportunity to develop my skills and conceptualize and carry out my research. Steffanie, I will always be indebted to you, and I am looking forward to continuing our work together, you are a wonderful mentor. I would also like to thank the members of my dissertation committee: Happy Araneta, for guidance and support in both research and political matters I am grateful, I hope that one day I will master your level of grace and diplomacy; Pamina Gorbach, whom I have conducted research with from the being of my doctoral training, I am thankful for all of the opportunities that you have given to me in research and networking and the fun times that we have shared; Susan Little, I am grateful for the opportunity you gave me to work with your cohort, for mentoring me on my dissertation grant, for all of the research and emotional support that you have provided, and for always standing behind me, I look forward to our future collaborations; Vanessa Malcarne, thank you for joining my committee in the middle of my dissertation process without even knowing me and providing fresh new insight to my research, you have helped tremendously; and Don Slymen, who has taught more of my classes than any professor I have ever had, I still refer to your notes, thank you for teaching me about statistics and giving me the confidence to take on more and more difficult analyses.

I would also like to thank those who co-authored my dissertation manuscripts, Tom Patterson and Eric Daar. I thank Tom for his expertise, humor, and help both in conceptualization and communication of concepts related to club drug use. I thank Eric for his wonderful comments, kind words, and commitment to assisting in data collection, even with the absence of space or time to do so.

I am grateful to my friends, classmates, and colleagues who provided me with humor, emotional support, and a distraction when I needed it most. Thank you all for sharing your lives with me and adding joy to my years of doctoral training. I would also like to thank all of the students that I taught throughout my doctoral training for reminding me of the joy of teaching others and the beauty of learning.

To all of the participants who gave their time and provided details of their most intimate lives I am grateful, without their willingness I could not have conducted my research. I would also like to thank them for sharing their stories with me and reminding me that world is filled with beautiful, resourceful people.

Last, but not least, I would like to recognize my family and all of the love and support they have provided to me throughout this process and my life. I am so thankful for my parents, Suzanne Retzinger and Thomas Scheff, for always believing in me, supporting me, and encouraging me, you are wonderful parents. I am grateful for my brother, Thomas Drumright, and sister, Jennifer Drumright, who have always been available to hear my complaints and cheer me up at any hour. For my grandfather, L. Peter Reztinger, I am grateful for his undying confidence in me and unconditional love.

Most of all, I would like to acknowledge my husband, Simon Frost. Thank you for finding me, for loving me just the way I am, for always believing in me, for supporting me, and for tolerating my ups and downs throughout the dissertation

process. You inspire me with your enthusiasm, brilliance, and perseverance and you bring me joy with your wit, charm, and gentleness; everyday I spend with you is a gift.

The contents of Chapter 2 have been accepted for publication as they appear in this dissertation in Substance Use and Misuse, 2006, Drumright, LN; Patterson, TM; Strathdee, SA. Club Drugs as Causal Risk Factors for HIV Acquisition among MSM: A Review. Substance Use and Misuse. 2006; *in press*.

The contents of Chapter 4 have been submitted for publication as they appear in this dissertation to Journal of Acquired Immune Deficiency Syndromes, 2006, Drumright, LN; Little, SJ; Strathdee, SA; Araneta, MRG; Slymen, DS; Malcarne, VL; Daar, ES; Gorbach, PM. Unprotected anal intercourse and substance use among men who have sex with men with recent HIV infection.

The contents of Chapter 5 have been submitted for publication as they appear in this dissertation to Sexually Transmitted Diseases, 2006, Drumright, LN; Strathdee, SA; Little, SJ; Araneta, MRG; Slymen, DS; Malcarne, VL; Daar, ES; Gorbach, PM. Unprotected anal intercourse and substance use before and after HIV diagnosis among recently HIV infected men who have sex with men.

CURRICULUM VITA

EDUCATION:

2006	Ph.D.	Epidemiology (Public Health) University of California, San Diego, School of Medicine and San Diego State University, School of Public Health.
1999	M.P.H.	Community Health and Health Education California State University, Northridge
1995	B.S.	Biochemistry/ Cell Biology University of California, San Diego

PROFESSIONAL EXPERIENCE:

Public Health

1/00 – 12/05	Doctoral Research Assistant School of Public Health University California, Los Angeles School of Medicine University California, San Diego Antiviral Research Center San Diego, CA
9/99 – 3/00	Volunteer Field Epidemiology and Public Health Graduate School of Public Health San Diego State University Field site: Baja, Mexico
7/98 – 8/99	Intern/ Student Professional Worker Acute Communicable Disease Control Unit Los Angeles County Department of Health Los Angeles, CA

Laboratory Research

11/99– 4/00	Research Associate Althea Technologies San Diego, CA

9/96- 8/97 Research Associate
Laboratory of John Kelsoe, MD
Department of Psychiatry,
School of Medicine
University of California, San Diego
San Diego, CA

7/95- 9/96 Research Assistant
Laboratory of Thomas Hope, PhD
Infectious Disease Laboratory
Salk Institute for Biological Studies
San Diego, CA

Teaching Experience

9/02-Present Instructor (Graduate Teaching Associate)
Sexually Transmitted Diseases
Graduate School of Public Health
San Diego State University
San Diego, CA

9/02 – 12/03 Instructor (Graduate Teaching Associate)
SPSS Laboratory
Graduate School of Public Health
San Diego State University
San Diego, CA

2/02 – 12/03 Instructor (Graduate Teaching Associate)
SAS Laboratory
Graduate School of Public Health
San Diego State University
San Diego, CA

9/01 – 9/02 Instructor (Graduate Teaching Assiociate)
Evaluation and Measurement in Health Education
Community Health Education
Graduate School of Public Health
San Diego State University
San Diego, CA

8/00 – 6/02 Teaching Assistant
Epidemiology
Graduate School of Public Health
San Diego State University
San Diego, CA

8/98 – 9/99 Teaching Assistant
Biostatistics Laboratory
Health Sciences Department
California State University, Northridge
Northridge, CA

GRANTS:

11/03-01/06 Universitywide AIDS Research program (UARP), University of California, Pre-doctoral Dissertation Award.
Mentor: Susan J. Little, Associate Professor of Medicine, University of California, San Diego, School of Medicine, Antiviral Research Center.

PUBLICATIONS:

Smith GJ, Donello, JE, Beeche AA, **Drumright, LN**, Hope TJ. "Structural analysis of the human hepatitis B virus cis-acting RNA export element". *Molecular Biology of the Cell.* 1996; 7: 2791-2791 Suppl. S.

Drumright LN, Gorbach PM, Holmes KK. "Do People Really Know Their Sex Partners?: Concurrency, Knowledge of Partner Behavior and Sexually Transmitted Diseases within Partnerships**"** *Sexually Transmitted Disease.* 2004; 31(7): 437-442.

Gorbach PM, **Drumright LN**, Holmes KK "Discord, Discordance & Concurrency: Comparing Individual and Partnership Analyses of New Partnerships of Young Adults at High Risk". *Sexually Transmitted Diseases*, 2005; 32(1): 7-12.

Gorbach PM, **Drumright LN**, Daar ES, Little SJ. Transmission behaviors of recently HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr*. In press.

Drumright LN, Patterson TL, Strathdee SA. Club Drugs as Causal Risk Factors for HIV Acquisition among MSM: A Review **.** *Substance Use and Misuse.* In press.

ORAL PRESENTATIONS:

Drumright LN, Gorbach PM, Holmes KK. "Discord, Discordance and Concurrency in Partnerships." Present by Drumright LN at CDC 2002 National STD Conference San Diego, CA March 4-7.

Drumright LN, Barrett-Connor E, Garland C, Kritz-Silverstien D, Morton D. "Is Calcium Intake Associated with Reduced Blood Pressure?" Present by Drumright LN at 2001 San Diego County Epidemiology Exchange Conference, San Diego, CA May 11.

Drumright LN, Gorbach PM, Holmes KK. "Partnership concurrency and sexually transmitted diseases." 2003. International Society for Sexually Transmitted Disease Research Congress, Ottawa, ON July 27-30. Abstract # 474.

Drumright LN, Gorbach PM, Daar ES, Little SJ. "Risk Reduction and Partnerships Patterns of MSM with recent HIV infection" 2004. 2nd International Workshop on Acute HIV-1 Infection, Washington, DC, May 3-5.

ADDITIONAL PRESENTATIONS / POSTERS:

Gorbach PM, **Drumright LN**, Holmes KK. "Concurrency and STD in New Sexual Partnerships." Poster #P29, CDC 2002 National STD Conference San Diego, CA March 4-7.

Julie Yasuda, Gorbach PM, **Drumright LN**, Holmes KK. "Health Protective Sexual Communication Scale in STD Clinics." Poster #P93, CDC 2002 National STD Conference San Diego, CA March 4-7.

Gorbach PM, **Drumright LN**, Leigh-Brown AJ, Frost SDW, Little S. "Partnership Types and Primary HIV Infection and Transmission." Poster #P20, 2002 Universitywide AIDS Research Program Conference Sacramento, CA February 22.

Gorbach PM, **Drumright LN**, Daar ES, Little SJ. "Partnership types among men with recent HIV infection". 2003. International Society for Sexually Transmitted Disease Research Congress, Ottawa, ON July 27-30. Abstract # 545.

Gorbach PM, **Drumright LN**, Garnett GP, Holmes KK. "The Natural History of New Sexual Partnerships: A Niche for Bacterial STDs" 2004. Abstract # CDC National Sexually Transmitted Disease Conference, Philadelphia, PA, March 7-11.

Drumright LN, Gorbach PM, Little SJ. "Sexually Transmitted Diseases and Sildenafil Use: Risks for HIV Transmission Among MSM" 2004. Poster #P20, 2004 Universitywide AIDS Research Program Conference Los Angeles, CA February 21.

Gorbach PM, **Drumright LN**, Daar ES, Little SJ. "Transmission behavior following HIV diagnosis". Poster # 981; 2005 Conference on Retroviruses and Opportunistic Infections, Boston, MA February 22-26.

Frost SDW, Cheng WS, **Drumright LN**, Leigh Brown AJ, Richman D, Little SJ, Gorbach PM. "Bath-houses, bars, and bridges: patterns of sexual partner recruitment in a cohort of MSM with recent HIV infection." 2005. Paper # 169, 2005 Conference on Retroviruses and Opportunistic Infections, Boston, MA February 22-26.

Drumright LN, Gorbach PM, Daar ES, Little SJ. Drug Use and Unprotected Anal Intercourse among Men who have Sex with Men who were Recently Infected with HIV. 2005. The 16th Biennial Meeting of the International Society for Sexually Transmitted Diseases Research (ISSTDR); July 10-13, 2005; Amsterdam, The Netherlands. Abstract MP-049.

HONORS / AWARDS:

05/01 San Diego County Epidemiology Exchange Conference 2001 Student Prize Award for best research project and presentation, May 2001

07/00 Scholarship award for University of Washington 2000 STD Training Course, July 2000

09/98 James R. Simpson Scholarship Recipient 1998-1999

09/98 Charlotte Ann Resnick Memorial Scholarship Recipient 1998-1999

ABSTRACT OF THE DISSERTATION

Illicit Substance Use and risk of HIV Transmission among Men who have Sex with Men

by

Lydia Nicole Drumright

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2006

San Diego State University, 2006

Professor Steffanie A. Strathdee, Chair

Human immunodeficiency virus type 1 (HIV) continues to disproportionately affect men who have sex with men (MSM). Recent concern has focused on the use of 'club' drugs among MSM as a risk factor for HIV acquisition and transmission. To determine the extent to which the current literature demonstrates a causal association between use of individual 'club' drugs and risk for HIV among MSM, Hill's criteria for causation was applied to existing studies. A theoretical framework that demonstrates potential pathways through which these drugs could be associated with HIV acquisition is proposed, and definitions of what constitutes a 'club' drug discussed.

Building upon this review, and addressing the Centers for Disease Control and Prevention's call for research addressing prevention among HIV positive individuals, substance use as a risk factor for unprotected anal intercourse (UAI) was investigated among MSM with recent HIV infection. All MSM were interviewed using a computer assisted survey instrument (CASI) on average 5 weeks after HIV diagnosis and 13

weeks after estimated date of infection. Associations between substance use and UAI in within-subjects analyses were modeled using conditional logistic regression (CLR). Associations between substance use and UAI in the entire sample were examined using generalized estimating equations (GEE). GEE models that included interactions between timing of sexual activity (before versus after diagnosis) and substance use were used to examine change in associations between UAI and substance use before and after HIV diagnosis.

Among participants, 16% reported no UAI with any of their last three partners; 60% (n=116) reported UAI with some, but not all, of their last three partners; and 24% reported UAI with all of their last three partners. In multivariate CLR (n=116) and GEE (n=194) models, UAI was associated with use of methamphetamine (OR: 4.9 and 2.7 respectively), marijuana (OR: 4.0 and 1.9 respectively) and erectile dysfunction medications when used with a main partner (OR: 26.0 and 17.1 respectively). In GEE models (n=207) that examined interactions between UAI and substance use before and after HIV diagnosis, UAI was associated with methamphetamine use alone (OR=4.80, 95% CI: 1.4, 16.1) and a combination of methamphetamine and other substances (OR=4.11, 95% CI: 1.9, 8.8) before diagnosis. After HIV diagnosis, UAI was associated with use of substances other than methamphetamine (OR=1.96, 95% CI: 1.3, 5.3) and a combination of methamphetamine and other substances (OR=5.08, 95% CI: 2.3, 11.2), but not methamphetamine alone.

These analyses indicate that a direct association may exist between use of methamphetamine and may be differentially associated with UAI based on knowledge of HIV status. These findings have implications for both prevention of high risk sexual behavior and substance use among recently HIV infected MSM.

I. INTRODUCTION

Since acquired immune deficiency syndrome (AIDS) was first recognized through outbreaks of Kaposi's sarcoma and Pneumocystis pneumonia in 1981 among homosexual men in the United States [1], over 25 million deaths have been attributed to human immunodeficiency virus type 1 (HIV-1) and AIDS [2]. Currently, it is estimated that 40 million people are living with HIV worldwide [2]. In many developing countries especially in sub-Saharan Africa, high HIV-1 mortality rates [3] have resulted in economic decline and decreased life expectancies, leaving millions of children orphaned [2;4].

Due to immune system damage through destruction of CD4 helper T-cells, HIV has also contributed to increased incidence and prevalence of other infectious diseases that were declining prior to the pandemic, including tuberculosis [5-8], and malaria [9;10]. HIV co-infection has also contributed to increased morbidity and mortality of other infectious diseases such as hepatitis C [11-13] and hepatitis B [14]. The effects of the HIV pandemic have been devastating worldwide. Despite advances in HIV care and treatment, most notably the advent of antiretroviral therapy (ART), HIV transmission continues unabated. In most regions of the world, HIV incidence rates either have remained stable or continue to increase [2].

In this introduction, the epidemiology of HIV in the third decade of the pandemic is reviewed, including summaries of the origins of HIV, HIV transmission, clinical epidemiology of HIV/AIDS, and estimates of HIV/AIDS prevalence worldwide and within the United States. The United States epidemic among men who have sex with men (MSM) is also reviewed, including changes in prevalence and incidence of HIV and sexually transmitted infections (STIs); changes in sexual behavior; and risk factors for

HIV transmission in this population. Illicit substance use as a risk factor for HIV transmission and acquisition among MSM is briefly introduced. Finally, the purpose, aims and rationale for the three studies in this dissertation are presented, which collectively examine substance use as a risk factor for HIV transmission and acquisition among MSM.

A. Origins of HIV-1

The current scientifically accepted belief is that HIV types 1 and 2 both originated from simian immunodeficiency virus (SIV). HIV-1 and HIV-2 are believed to have originated from SIV strains carried by primates in different regions of Africa. HIV-1 is most closely related to SIV from chimpanzees (SIVcpz), whereas HIV-2 is more closely related to SIV from sooty mangabeys [15]. HIV-1 and HIV-2 also have different clinical outcomes in humans, with HIV-2 causing a less severe disease than HIV-1 [16]. Since HIV-1 accounts for the largest proportion of HIV/AIDS cases worldwide and is more virulent than HIV-2 [17], this summary of the origins of HIV focuses specifically on HIV-1.

HIV-1 Transmission from Primates to Humans

Analyses of sequences of SIVcpz isolated from the chimpanzee subspecies *Pan troglydytes troglydytes* indicate that it is a genetic hybrid, closely related to SIV found in red capped mangabeys and greater spot-nosed monkeys [18]. This suggests that chimpanzees may have been infected with two strains of HIV from other primates, which recombined to form SIVcpz and an additional virus (HIV-1) that subsequently was capable of infecting humans. Humans that lived in rural villages that bordered the jungle are believed to have been exposed to this third virus through direct contact with

chimpanzee in what is now the Democratic Republic of the Congo (DRC) through exposure to contaminated meat or blood (e.g., eating bush-meat, being bitten by chimpanzees kept as pets). SIV antibodies have been found among those who hunt and prepare bush-meat, indicating that exposure to SIV continues in human populations [19;20].

Early Transmission of HIV-1 among Humans

Based on the systematic timing of viral evolution that is observed in HIV-1, it is estimated that the main group of HIV-1, group M, arose in the DRC around 1930 [21;22]. However, more than one theory of how group M originally spread to other regions of Africa has been presented. The most commonly accepted scientific argument is that transmission occurred largely due to sexual activity; however, some have argued for iatrogenic transmission [23]. Differences in the dynamics of hepatitis C and HIV-1 in Africa suggest that iatrogenic transmission is not responsible for the high observed rates of HIV transmission [24]. A recent study in rural Zimbabwe failed to find an association between medical injections and HIV serostatus [25].

Transmission of HIV-1 to the United States

When the syndrome that later became known as AIDS was first recognized in 1981, the CDC investigated its origins using epidemiological interviews before biological testing was available. From these interviews, presence of AIDS symptoms among gay men was significantly associated with attending bathhouses [26]. Additionally, through epidemiological interviews, it was concluded that a gay male airline steward from Canada was the index case of HIV in the United States [27]. However, current evidence of the epidemic spread of HIV in the United States now refutes that theory. The earliest

HIV infected tissue sample that has been identified in the United States came from a teenage male who died in 1969 [28], and the date that the most recent common ancestor of the current United States HIV strains entered the United States has been estimated to be 1968 (+/- 1.4 years) [29]. Current epidemiological evidence suggests that HIV spread from the Congo to Haiti, via Haitian men who participated in the United Nations Educational, Scientific, and Cultural Organization in the Congo between 1960 and 1975. It was then believed to have been brought back to the United States by gay tourists visiting the Haitian city Port-au-Prince [30].

Currently, the predominant subtype of HIV-1 in the Unites States is subtype (clade) B [31;32]. This is believed to be the original clade that entered the Unites States population. Clade B is also found in Western Europe, South America, Canada, Mexico, Australia, New Zealand, Japan, and Korea, [31;33]. HIV diversity is greatest in Africa, where all clades of group M are found [32]. Group O, for other, and group N, for new, are also found in Africa [32]. Some regions outside of Africa report co-circulation of two or more dominant clades of group M, such as B and F in South America and B, C and E in South East Asia [32]. Additionally, recombination of the major clades has been observed in Southeast Asia [34;35] and Africa [35] and recombinant subtypes can be found in South America, South East Asia, Africa, China, and Europe [36]. The most common recombinants reported are AG, found in 31 percent of infections in West Africa, and AE, found in 63 percent of infections in South East Asia [35]. It has been estimated that 56 percent of HIV infections worldwide are due to clade C, 23 percent are due to A, 8 percent are due to B, 5 percent are due to D, and the remaining 8 percent are due to other clades or recombinants [33].

B. Biology and Clinical Epidemiology of HIV-1

HIV-1 is a human retrovirus, belonging to the lentivirus class [37]. HIV-1, like other lentiviruses, is a single-stranded RNA virus [37], however in HIV-1, two identical copies of this RNA strand are packaged, along with the reverse transcriptase protein, in each virus capsid [38]. Coating the outside of the virus are approximately 12 to 15 envelope 'spikes' that can bind to the CD4 molecule, which is expressed at high levels on the surface of activated CD4+ T helper lymphocytes [39].

HIV gains entry to a host cell through binding to a chemokine coreceptor (in humans, CCR5 or CXCR4) and the CD4 molecule [40-42], and results in a cascade within the virion to activate the virus. At this time, reverse transcriptase is activated and the RNA copies are reverse transcribed into a linear DNA duplex, which is integrated into the host genome becoming a provirus [38]. Many of these infected cells rapidly make new viral particles by harnessing the host cell's DNA replication and protein synthesizing systems [38]. However, in other cells, the provirus remains inactive for varying lengths of time, from months to years [43;44].

Due to the high error rate of HIV-1 reverse transcriptase and the lack of a proofreading mechanism for DNA polymerase II, on average one mutation occurs each viral replication cycle [45-47], which results in great genetic diversity among HIV within a single individual, and an even greater degree of viral genetic divergence between individuals. Even genetic variants that do not have a replication advantage are maintained at low levels in the host [48]. Given selection pressure from the host immune response or antiviral medication, most variants will proliferate [38]. Additionally, HIV-infected cells are eliminated and new cells are infected approximately every two days [49;50], suggesting rapid replication with the opportunity for rapid viral evolution.

This has made HIV-1 vaccine development for prevention and drug development for treatment very difficult.

Acute Infection

During the earliest stages of HIV-1 infection, the virus tends to be localized within the site of exposure. However, HIV-1 rapidly begins to replicate and disseminate throughout the body, and grows exponentially with a doubling time of 10-20 hours [51;52], to reach peak viral titers which may exceed 10 million copies of viral RNA in the plasma. Before the immune system can mount a response, HIV infects lymph tissues and organs and other cells, establishing what is thought to be permanent infection of the host [53].

During this time, individuals may develop flu-like symptoms, consisting of fever, myalgia, rash, night sweats, arthralgia, malaise, headache, pharyngitis, lymphadenopathy, fatigue, oral or genital ulcers, thrush, weight loss, nausea, and vomiting [54-57]. The most commonly reported symptoms associated with acute HIV infection are fever, night sweats, rash, lymphadenopathy, and fatigue [55;56;58;59]. Approximately 40-90 percent of people with recent HIV-1 infection may experience acute viral symptoms [56], although some remain asymptomatic [60]. During acute infection people experience high plasma viral loads which have been associated with increased infectiousness and a greater likelihood of transmission to others [51;52;61;62].

Complications of Chronic HIV-1 Infection

Acute HIV-1 infection is followed by a period where viral loads drop, which may be due to a combination of the elicitation of cellular and humoral HIV specific immune

responses, and exhaustion of target cells [51;63;64]. After approximately 3-6 months of infection, the viral load settles down to a relatively stable level known as the 'viral setpoint', which represents a dynamic equilibrium between high rates of viral replication and clearance by the host's immune system [49;50;65]. The viral setpoint can vary by several orders of magnitude between individuals, and high viral loads have been associated with high infectivity and more rapid progression to AIDS [66-68]. After a long, but variable, period of infection during which the individual is generally asymptomatic, progression to AIDS may occur.

AIDS

Progression to AIDS is characterized by a sharp increase in viral load and a corresponding decrease in CD4 T-cell count [53], which can result in susceptibility to opportunistic infections (OIs) due to debilitated immune response. AIDS was originally defined by illnesses resulting from one or more OIs. Kaposi's sarcoma and pneumocystic pneumonia were the first OIs recognized as part of the syndrome that became known as AIDS [1;69]. By 1983 (before HIV-1 was identified), AIDS was defined as diminished ability of immune functioning in response to an as yet unidentified infection with no known reason for lower immune functioning [69]. In 1985, the case definition for AIDS was changed to a positive serological test for human T cell lymphotropic virus type III/ lymphadenopathy associated virus (HTLV-III/ LAV, now known as HIV-1) and one or more of 26 OIs or isosporiasis, bronchial or pulmonary candidiasis, or non-Hodgkins lymphoma [70]. In 1993, the CDC expanded their definition of AIDS to include healthy HIV positive people with a CD4 positive T cell count of less than 200 per µl of blood [71].

Before the advent of ART, the estimated median duration of time between HIV infection and progression the AIDS was seven to eleven years in developed countries [53;72], and the median survival time after infection was eight to twelve years [72;73]. This ‘asymptomatic’ stage ranged from one to 15 years, and appeared to be related to host immune response [74]. With the development of ART, time from HIV-1 infection to AIDS diagnosis has increased [75-77]. In Hong Kong, the median survival time after AIDS diagnosis increased from 29.8 months prior to 1997 to greater than 70 months after 1996 [78]. The majority of new AIDS cases in the United States are reported on the basis of a low T cell count in the presence of HIV infection, not based on OIs [71].

In environments where nutrition may be incomplete and few medical resources are available, median survival time from HIV diagnosis is much shorter [79-83]. This may be due to lower overall health or diagnosis later in the course of HIV-1 infection, lack of access to treatment and greater exposure to opportunistic infections. Conversely, some individuals, known as long-term survivors or long-term non-progressors, may never reach the AIDS stage. Long-term survival with HIV infection in the absence of ART has been attributed to both the host immune response [84] and HIV genetic mutations [85;86].

HIV Testing

In 1983, HIV (then called HTLV-III/LAV) was discovered as the infectious agent that caused AIDS [87]. In 1985, the first enzyme-linked immunosorbant assay (ELISA) test for detection of HIV antibody in blood samples was approved by the United States Food and Drug Administration (FDA) [88]. In 1987, the FDA approved the first Western Blot for commercial use in the detection of HIV infection in plasma and developed regulations requiring screening of all blood and plasma from donors in the United States

[88]. Currently, a number of HIV testing kits are approved by the FDA for commercial use, including multiple enzyme immunosorbant assays (EIAs), Western Blot, and a nucleic acid test for HIV-1 RNA [89]. For more detail on these tests see Methods, section C: Screening and D. Inclusion and Exclusion Criteria, Definition of Acute and Early Infection, and Estimated Date of Infection.

HIV/AIDS Treatment

At the time of writing, there were four classes of antiretroviral drugs licensed for treatment of HIV infection. The first class of HIV medications to be developed were nucleoside reverse transcriptase inhibitors (NRTIs), which inhibit viral replication by causing chain termination during reverse transcription [90]. In 1987, AZT (3'-azido-2'-deoxythymidine), also known as zidovudine or ZDV, a drug that had been originally developed to treat cancer in 1964 [91], was the first drug approved by the FDA to treat HIV/AIDS [91], following a clinical trial by Burroughs-Wellcome (now GlaxoSmithKline) that demonstrated improved CD4+ counts in AIDS patients [92]. Soon after widespread use of AZT, viral resistance was demonstrated in people who used the drug for 6 months or more [90;93]. Single therapy had limited effectiveness in HIV treatment. However, development of NRTIs continued and FDA approval was received for didanosine (ddI) in 1991, zalcitabine (ddC) in 1992, stavudine (d4T) in 1994, lamivudine (3TC) in 1995, and abacavir in 1998 [91].

Between 1989 and 1994 the second class of anti-HIV drugs, protease inhibitors, were developed in response to the National Institutes of Allergy and Infectious Diseases (NIAID) supported basic research on protease enzymes in HIV [94]. Protease inhibitors, act at a later stage of the viral lifecycle following transcription of the provirus, by inhibiting the cleavage of the viral polypeptide by the viral protease [95]. HIV-1 virions

are still produced in the presence of protease inhibitors, but are non-infectious. In 1995, saquinavir was approved by the FDA, and in 1996, ritonavir and indinavir were approved for single therapy and combination therapy, with one or more of the NRTIs [94]. When used in combination with NRTIs, this dual combination therapy became the first successful treatment for HIV [96;97]. However, in early *in vitro* [98-100] studies and subsequent studies *in vivo* [101;102] HIV-1 resistance to protease inhibitors was documented.

Shortly after FDA approval of the first protease inhibitors, the first of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine, was approved by the FDA in 1996 [91]. NNRTIs, like NRTIs also inhibit reverse transcription, however NNRTIs directly interfere with the active site of reverse transcriptase [103;104]. As with the previous anti-retroviral agents, resistance to NNRTIs was observed [105]. However, treatment with multiple classes of anti-retroviral medications was demonstrated to be highly effective after the advent of NNRTIs [106-109], and soon became the recommended standard of care [110].

Recently a fourth class of anti-HIV drugs was developed, fusion inhibitors. The first fusion inhibitor, enfuvirtide, was approved by the FDA in 2003 [111]. These are small molecules which interfere with the binding of envelope spikes to CD4+ [112;113]. It has been suggested that some fusion inhibitors may be effective against HIV group O, in addition to group M [114], which is promising as most ART is specific only to HIV group M. As with all other anti-HIV drugs, resistance to enfuvirtide has been reported [115]. Active development of new fusion inhibitors is underway [116].

Despite continuous development of ART regimens, HIV-1 drug resistance persists due to rapid evolution of the virus. It has been estimated that among those receiving HIV care in the United States, 73 percent of patients with HIV viremia have

resistance to at least one or more antiretroviral drug [117]. Single and multidrug resistant strains of HIV not only develop within the individual, they are also transmitted to others and it appears that the percentage of newly infected individuals with drug resistant HIV is increasing [118]. Research into the effect that successful ART regimens to treat HIV/AIDS have had on HIV risk behaviors will be discussed in section H: Risk factors for HIV-1 infection among MSM.

C. HIV-1 Transmission

At the outset of the HIV-1 epidemics in the United States and Western Europe, transmission of HIV-1 was originally attributed to sexual activity between men, contaminated blood products, and injection drug use [119]. Later reports indicated that HIV-1 was transmitted through heterosexual contact [120] and maternal transmission (i.e., vertical transmission and breastfeeding) [121;122]. Although HIV-1 can be isolated from other body fluids, such as saliva [123;124], transmission has not been documented from such fluids and is unlikely due to low levels of virus in these fluids. Different routes of HIV transmission, proportions attributed to these routes, and regions that report these routes of transmission are described below.

Parenteral Transmission

Early in the United States HIV epidemic, HIV acquisition was reported among recipients of blood transfusions due to contaminated blood products [125]. However, hemophiliacs comprised only a small portion of the AIDS cases reported early on in the epidemic [69]. People continued to become infected with HIV through blood transfusions until 1985 when the first HIV test (ELISA) became available [88]. Iatrogenic infection of HIV-1 through transfusion became less common worldwide than when the

pandemic was first recognized; however, transfusion-related HIV infection still occurs, albeit rarely. In the United States, one person received a transfusion of HIV infected blood in Texas in 2000 [126] and two others received transfusions of HIV infected blood from one person in Florida in 2002 [127]. In both cases, the donors were in the acute phase of HIV-1 [126;127], and therefore tested HIV-antibody negative. Currently, the risk of receiving HIV infected blood from a transfusion in the United States is estimated to be 1 in 1.4 million to 1 in 1.8 million units of transfused blood [128;129]. Although transfusion associated infection in developed countries, such as Canada, Australia, the United States, and Western Europe is uncommon, some developing countries continue to report HIV-1 infections associated with blood transfusions, due to lack of adequate screening measures and the practice of paying blood donors. In 2004, the World Health Organization estimated that 5-10 percent of annual HIV infections worldwide are a result of transfusion with infected blood or blood products [130].

HIV can also be transmitted through reuse of needles or contaminated injection equipment. Transmission of HIV from needle punctures in clinical settings has been rare [53]. In the beginning of the United States epidemic, about 20 percent of all AIDS cases were attributed to injection drug use [69]. Incidence of HIV among injection drug users (IDUs) between 1984 and 1999 varied by location and time, and studies from the eastern United States historically reported higher incidence rates than the western United States [131]. In recent years, the United States has seen a decline in the number of new HIV/AIDS cases among IDUs [132]. However high prevalence of HIV/AIDS among IDUs in Southeast and Central Asia [133-135], South America [136] and Eastern Europe [137] is reported and injection drug use is contributing significantly to the HIV epidemic in these regions [134;138-141].

HIV prevalence among IDUs varies widely from no infection to 80 percent depending on the region of the world in which IDUs live [142;143], however the majority of HIV infected IDUs live in low-income countries [143]. For example, in Georgia [144] and the Russian Federation [137], 70 percent of all HIV cases have been attributed to injection drug use. The HIV epidemics in South East Asia, Central Asia, and Eastern Europe have been primarily attributed to injection drug use and commercial sex work resulting from poverty, and to social and political upheaval [2;145;146]. In these countries, the intersection between injection drug use and use of or work in the commercial sex industry is believed to have caused exponential growth of their HIV epidemics [2;145;146].

Sexual Transmission

Sexual contact remains the most important mode of HIV transmission worldwide. Sexually, HIV is transmitted most efficiently through anal and vaginal intercourse [147-149]; oral-genital contact may also be associated with HIV transmission [150;151], but it is less efficient than other penetrative forms of sexual contact [147;152;153]. Transmission of HIV attributed to sexual contact between men or heterosexual contact varies by region throughout the world.

In many developed countries (e.g., Canada [154-156], Australia [157-159], Western Europe [160-163], United States [131;132]), MSM have carried the greatest HIV burden for most of the epidemic. Additionally, high HIV prevalence has been reported among MSM in many Latin American countries [164-166]. Reports also indicate that HIV prevalence may be increasing among MSM in Thailand [167]. Historically, many other regions of the world that are experiencing HIV epidemics, such as Sub-Saharan Africa, have reported little or no sexual contact among men. It is

unclear if this is due to a lack of HIV transmission among MSM or if there are cultural barriers preventing acknowledgement of sexual activity between men. In 2004, it was estimated that 5-10 percent of all HIV cases worldwide were a result of sexual contact between men [168].

Although MSM have been disproportionately affected by the HIV epidemic in many regions of the world, heterosexual contact is the most common source of HIV transmission worldwide [2]. Among people living with HIV today, the majority of cases have been attributed to heterosexual transmission. Africa is home to two thirds of all people living with HIV in the world, where 97 percent of transmission is attributed to heterosexual contact [168]. The rapid spread of HIV in Sub-Saharan African countries has been attributed to poverty, war, the subordinate position of women, and lack of medical care [2;169]. Worldwide, the proportion of HIV infected people who are women is increasing, mostly due to heterosexual contact [168]. Additionally, coinfection with ulcerative STIs has been shown to enhance sexual transmission of HIV among both heterosexual and MSM populations [66;170-173].

Maternal Transmission

It has been estimated that 13-35 percent of mothers who do not receive ART transmit HIV-1 to their infants *in utero* or through delivery [174-176]. In addition to transmission *in utero* and during delivery, one third of all vertical transmission has been attributed to breast feeding [177]. Two thirds of all HIV-1 infections among children are attributed to maternal transmission [178]. In developed countries maternal transmission of HIV is now uncommon, due to HIV testing in pregnancy or delivery and subsequent use of ART regimens such as nevirapine [179-181]. Currently, 95 percent of all cases of maternal transmission occur in developing countries [182]. Use of nevirapine has

begun to reduce maternal transmission in many impoverished countries, including those in Sub-Saharan Africa [183].

D. HIV/AIDS in the United States

In the United States, it has been estimated that nearly one million people have died from HIV/AIDS since the recognition of the epidemic in 1981 [184]. More than one million (range 1,039,000 to 1,185,00) people were estimated to be living with HIV or AIDS by the end of 2004 [132]. Among HIV cases diagnosed in the United States between 2001 and 2004 in the 33 states that had name-based reporting, 71 percent were men [132]. The majority of men (61%) reported sexual contact with other men as their primary risk factor, followed by heterosexual contact (17%), injection drug use (16%), and sexual contact with other men combined with injection drug use (5%). Women primarily reported heterosexual sexual contact (76%) and injection drug use (21%) as risk factors for acquisition. Half of all HIV cases diagnosed between 2001 and 2004 were among Black or African American men and women [132]. Nearly half (49%) of the HIV diagnoses among Black or African American men between 2001 and 2004 were among MSM [132]. Since the beginning of the HIV epidemic, Black or African American and Hispanic people have been proportionally over-represented in HIV/AIDS cases [185].

The number of HIV/AIDS diagnoses decreased annually for all risk categories including IDU, except MSM, which increased significantly by 8% between 2003 to 2004 [132]. Since the beginning of the HIV epidemic in the United States, MSM have carried a disproportionate burden of infection and continue to do so [132;186]. Between 2001 and 2004, 44 percent of all HIV/AIDS diagnoses were among MSM [132]. Therefore,

there is a need to develop studies that enable us to better understand determinants of HIV transmission and risk behavior among MSM in the United States.

HIV/AIDS in California

It is estimated that there are over 39,000 people in the State of California living with HIV, and over half (58%) live in Southern California [187]. The counties that report the greatest number of cases are Los Angeles, San Francisco, and San Diego [187]. Reported cases of HIV/AIDS in California follow similar trends to the rest of the United States. Approximately 91% of all people living with HIV/AIDS in California are men, and 74% reported sexual contact with men as their primary risk factor for HIV acquisition [188].

Recent reports have raised concern regarding increased HIV and STI transmission and increased sexual risk-taking among MSM in urban centers in California. In 2001, reports from San Francisco indicated that HIV incidence may be increasing among MSM [189;190]. In a recent, statewide population-based study of HIV prevalence among MSM, 19.1 percent were HIV-positive, and higher HIV prevalence was observed among MSM who reported ever injecting recreational substances [191]. In addition to reports of increasing incidence and high prevalence of HIV among MSM, reports of syphilis outbreaks among MSM in San Francisco and Los Angeles [192] and increases in rectal gonorrhea in San Francisco [193] have raised concern about increased HIV transmission among MSM in California, which is described in more detail in section G below.

HIV/AIDS in San Diego

San Diego is the second largest county in California, with about 2.6 million residents [194]. This county has the third largest number of HIV/AIDS cases in California, behind Los Angeles and San Francisco [187]. Between July of 2002 and December of 2004, 90 percent of all HIV/AIDS cases reported were among men, of whom 79% were MSM [195], a slightly higher proportion than California overall. Of the 4,647 cases of HIV reported to the San Diego County Health and Human Services Agency between 2002 and 2004, a higher proportion were Caucasian (62%) and a lower proportion were Black or African American (13%), than those reported overall in the United States (36% and 50% respectively) and California (49% and 20% respectively) cases [195]. A higher proportion of Hispanic HIV cases were diagnosed between 2002 and 2004 in San Diego (22%) than the overall United States (14%), but this was similar to those diagnosed in the entire state of California (25%) during this time period [195]. As reported for the United States overall, there was a significant increase in HIV/AIDS diagnoses among MSM in San Diego county from 3.3% in 2000 to 5.0% in 2003 [195].

E. Estimating HIV/AIDS Prevalence and Incidence

Estimates of HIV prevalence are biased by many factors that may differ between countries or even within state and local regions in the United States. Worldwide estimates are based on algorithms and models derived from HIV testing data from pregnant women attending antenatal clinics, household HIV testing surveys, and vital statistics in countries with a generalized epidemic, and on high-risk groups (e.g., IDUs, MSM, sex workers) in countries with low-level or concentrated epidemics [196;197]. Additionally, data from HIV voluntary counseling and testing sites are used when

available [197]. Although these methods provide the best estimates currently available [198], they can still be biased by repeat testing, selected antenatal clinic attendance, failing to report HIV/AIDS as the underlying cause of disease on death certificates, and lack of access to HIV voluntary counseling and testing.

Wealthier countries tend to have better estimates of HIV prevalence than do developing countries due to more advanced surveillance systems; however, in the United States, estimates may also be biased by a number of factors. Lack of HIV testing among at-risk individuals could result in underestimates of HIV prevalence. It has been estimated that 25 percent of HIV infected individuals [199], and possibly 48 percent of HIV infected MSM [200], in the United States are unaware of their HIV serostatus.

Anonymous HIV testing is still used in many States due to HIV related discrimination [201;202]. Use of such data may contribute to underestimates or over-estimates of prevalence depending on how many times an infected individual receives a positive test result. Inconsistent reporting procedures among states and U.S. territories may also contribute to inaccurate estimates. For example, in California, as with many states, HIV/AIDS surveillance information was based on AIDS cases only until 2002 [195], which is a poor predictor of HIV infection due to the long duration of time between infection and AIDS. Currently, the United States Centers for Disease Control and Prevention (CDC) only consider data from states with name-based reporting to be reliable [132;203], which includes 33 of the 50 states and two of the three US territories.

Accurate estimates of HIV incidence are even more difficult to calculate than HIV prevalence. Those who are infected with HIV may be diagnosed years after incident infection [204] and may differ from those diagnosed early in terms of their sociodemographic and risk profile [205]. Therefore, reports of HIV incidence often come

from relatively small prospective studies in selected risk groups, as opposed to national data, and may reflect local but not national trends.

F. Increases in HIV and STI Incidence and Risky Sexual Behavior among MSM

In recent years there have been a number of reports of increasing incidence in HIV among MSM worldwide [132;155;206-216]. Similarly, incidence of STIs has also been increasing among MSM [217-230]. Additionally, a number of recent studies point to an increase in risky sexual behaviors as the potential cause for these increases in STI and HIV incidence among MSM [231-238]. Some have suggested that these increases could lead to a resurgence in the HIV epidemic for MSM [239].

Reports of HIV and STI have shown a strong trend toward increasing incidence since the late 1990s. At the height of the HIV epidemic in the early 1980's, incidence rates of HIV among MSM were as high as 19.8 per 100 person years [240]. After this initial surge, a drop in HIV incidence was reported, which has been attributed to significant behavior change among MSM [241-243], as well as death due to AIDS [244-246]. From 1991 until 1997, estimated HIV incidence in the United States remained fairly stable [247]. However, longitudinal studies [248;249], retrospective studies [250], and cross-sectional surveillance studies [132;210;251-255] spanning the time period 1998 until present have shown an upward turn in HIV incidence among MSM in the United States [132;256-259] and in many other countries worldwide [210;215;260-262] (Table 1). Additionally, those studies that have not shown an increase in incidence, have shown stable HIV incidence rates above 2 percent [263]. These trends have also been seen among MSM in San Diego County [195].

Similarly, increasing incidence of STIs and multiple STI outbreaks have been reported among MSM (Table 2). Reports from the CDC have indicated that while there

was a drop in new diagnoses of primary and secondary syphilis cases in United States from 1997 to 1998 [264], there was a 12.4 percent increase in primary and secondary cases from 2001 to 2002 [265]. At this time the incidence of primary and secondary syphilis among men was higher (3.8/100,000) than the rate in women (1.1/100,000). In the western United States, incidence of primary and secondary syphilis increased by 64.3 percent from 2001 to 2002 and the rates among men in San Francisco (78.8/100,000) and Los Angeles (7.7/100,000) were higher than the rest of the country [266]. Additionally, the percent of MSM with primary or secondary syphilis who were HIV positive increased from 20 percent in 1999 to 48 percent in 2001 [267]. Surveillance in Guilford County, North Carolina [268]; King County, Washington [269]; New York City [270]; Houston, Texas [224]; Amsterdam [271]; and Ireland [228] has demonstrated similar trends of increasing incidence in syphilis among MSM. These data suggest that MSM are engaging in higher risk sexual behaviors which may be driving STI transmission. Data from San Diego County [272] demonstrate that the incidence of primary and secondary syphilis among men is 12 times higher and the incidence rate of gonorrhea is almost twice as high as the rate in women.

A review of studies of HIV and syphilis coinfection has shown that 64-90 percent of MSM with primary or secondary syphilis are sero-positive for HIV [273]. Gonorrhea reports in STI clinics across the United States indicated that while gonorrhea incidence may have declined in the general population, incidence continued to increase among MSM [274]. In a Denver STD clinic, from 1990 to 1995, 8.3 percent of MSM were diagnosed with gonorrhea, whereas in a subsequent time period from 1996 to 2001, 11.7 percent had gonorrhea [222]. Additionally, there has been a substantial increase in fluoroquinolone resistant gonorrhea isolated from MSM in STI clinics in the United States [275].

It has been suggested that the increase in incidence of both HIV and STIs among MSM are due to a relapse in risky sexual behavior [273;276], in particular increases in the number of casual sexual partners and amount of unprotected anal intercourse (UAI). Increases in the proportion of MSM in the Amsterdam cohort reporting UAI were reported as early as 1993 [277] and have since been reported among HIV positive and HIV negative MSM, as well as those who are unaware of their HIV sero-status [232] (Table 3). Increases in the proportion of MSM reporting participating in UAI have been reported in both longitudinal and cross-sectional data comparisons in San Francisco [236;278], London [232], Australia [235], and Los Angeles [237]. Reported increases in these risky sexual behaviors, as well as HIV and STI, indicate the need for a greater understanding of precursors to this risk behavior in order to help prevent further HIV and STI infections among MSM.

G. Risk Factors for HIV-1 among MSM

Existing data on HIV and STI risk behaviors suggest that a number of risk factors may be contributing to the resurgence in risky behavior among MSM. Recent research has focused on new concepts such as partner types and partner mixing patterns, HIV/AIDS prevention “burnout” and beliefs about ART (referred to as “HIV treatment optimism”), psychosocial and self-identification issues, and new venues for MSM to meet sexual partners as risk factors for HIV acquisition. Additionally, risk factors that were identified early on, such as UAI, multiple sexual partners, and drug use, continue to be reported.

Research on partnership mixing patterns has revealed the influence of social-sexual aspects on HIV transmission, including higher risks for those in partnerships that are discordant for age, ethnicity, education, sexual experience and geography [279-

281]. Additionally, research on types of sexual partners that might be associated with higher HIV risk has revealed that sexual contact with main partners may carry the greatest risk for HIV transmission and UAI [282-284].

Shortly after effective ART regimes were first prescribed, researchers reported that MSM may be experiencing feelings of decreased risk of mortality associated with HIV due to the advent of effective therapy [285-291]. However, a recent meta-analysis has indicated that elevated sexual risk behavior has not been observed in regard changes in beliefs due to ART [289]. Additionally, it has been suggested that MSM may be tired of 'worn-out' prevention messages about safer sexual practices and therefore may practice risky behaviors, such as "bare backing" (i.e., UAI) [292;293].

Psychological problems, such as depression, and identification with the gay community have also been attributed to increased risk of HIV among MSM. In particular, increases in risky sexual behavior including UAI have been associated with depression [294-296], self-identifying as gay [297], and having a lack of connection with one's ethnic community among Latino MSM [298]. High risk sexual behaviors and HIV prevalence have been reported to increase with number of psychological problems among MSM as well [299].

New venues that provide avenues for risky sexual behaviors, such as the internet, sex clubs, circuit parties and renewed interest in bathhouses have been associated with increased UAI [300], sexual risk taking [301], STI [302], and HIV prevalence [303]. Additionally, types of sexual activity [304], sexual behaviors among HIV infected individuals [305] and repeat HIV testing [306] have been explored recently for associations with HIV transmission.

Very early on in the HIV epidemic in the United States, sexual activity among men was linked to having symptoms consistent with AIDS [307]. Throughout the

epidemic, UAI has been consistently associated with an AIDS diagnosis [308], HIV seropositivity [309;310], or seroconversion [311]. Recent longitudinal studies continue to report UAI as a major risk factor for HIV seroconversion [312]. Additionally, new studies that try to quantify per act transmission probabilities have been conducted among MSM [313]. Reporting an increased number of sexual partners was also identified as a risk factor for AIDS and HIV early on in the epidemic [309;314]. Higher numbers of sexual partners continue to be associated with increased likelihood of seroconversion [312].

In 1981, a case-control study was conducted among MSM with and without Kaposi's sarcoma (KS), which demonstrated that those with KS were more likely to use nitrite inhalants [315], indicating that early studies suggested associations between AIDS and substance use. However, these studies mistakenly assumed nitrite use as the cause for KS [316], not AIDS and HIV infection [317]. Later longitudinal studies of HIV risk among MSM demonstrated that recreational substance use in general (i.e., substance type was not specified) was associated with UAI [318;319]. Currently, reports of higher proportions of substance use among MSM than within the general population [320] and reports of high frequency of methamphetamine use [321-324] and erectile dysfunction medication (EDM) [325-327] misuse among MSM have raised concern about substance use as a risk factor for UAI and HIV transmission.

H. Substance Use and Risk for HIV among MSM

At the beginning of the United States HIV epidemic, concern about substance use and HIV transmission focused primarily on IDUs and parenteral HIV transmission. MSM-IDUs were considered to be at exceptionally high risk for HIV acquisition since they could potentially experience both parenteral and sexual exposures. HIV incidence among IDUs during the early 1980s was exceptionally high [328], however in recent

years declines in HIV prevalence have been observed among IDUs in the United States [132;329].

Recently, non-injection illicit substance use, particularly methamphetamine use, has gained attention as a risk factor for HIV acquisition among MSM. Of particular concern is the use of substances referred to as ‘club drugs’ among MSM in urban centers of the United States, which have been associated with higher rates of UAI [330-339], STI [340-342] and prevalence [343-347] and incidence [348-353] of HIV. Risk behaviors such as UAI [339;354], having a high frequency of one-time sexual partners [355], a greater likelihood of STI [356], and more sero-discordant partners among HIV positive MSM [357] have been reported among users of multiple types of substances (’polydrug’ users) as compared to single substance users. Additionally, risk of HIV transmission through use of a combination of abuse of medically controlled substances, such as erectile dysfunction medication (e.g., Viagra®, Levitra®, Cialis®), has become a concern among MSM [326;327;333;358-362]; specifically, use of EDMs in combination with illicit substances and abuse of EDMs to lengthen the duration of time for sexual activity in the absences of sexual dysfunction.

Additionally, California is a state that has high levels of drug circulation and availability. Clandestine methamphetamine laboratories are common in many regions of California [363;364] and trafficking of illicit substances between Mexico and California makes San Diego a common transshipment zone [364]. Additionally, surveillance data from the United States, California, and San Diego County suggest that MSM are at high risk of HIV transmission and acquisition. It is therefore important to continue to study dynamics of HIV transmission among this population and to use the findings to implement innovative and appropriate prevention programs. Understanding how use of illicit recreational substances, often referred to as ‘party’ or ‘club’ drugs, affect HIV risk

among MSM requires further study. Due to the high circulation of illicit substances and HIV risk among local MSM, San Diego is an appropriate urban center for such studies.

I. Purpose of the Dissertation

The overall purpose of the collective studies for this dissertation is to expand the understanding of the relationship between HIV risk and illicit substance use, including prescription medications that are misused such as erectile dysfunction medications (EDMs). This was accomplished by conducting three publishable studies including: a review of the current literature examining criteria for causal associations between substance use and risk for HIV and STI; a study that utilizes different statistical techniques to examine the likelihood of increased unprotected anal intercourse (UAI) among recently HIV infected MSM when using illicit substances than when not using (Chapter 4); and a study that examines if there is a shift in substance use or type of substance use associated with UAI before and after HIV diagnosis among MSM (Chapter 5).

J. Research Objectives

To develop a better understanding of how substance use may contribute to HIV transmission, different primary research objectives were addressed in three independent manuscripts. These objectives were designed to test the hypothesis of association between illicit substance use and risk of HIV or STI, while studying underlying interactions of partnership dynamics and the effect of HIV diagnosis.

Objective for Manuscript 1: The first objective of the first study was to conduct an exhaustive review of the literature pertaining to associations between the use of ‘club

drugs' and HIV/STI acquisition or unprotected anal intercourse (UAI) among MSM. The second objective was to create an inclusive definition for the term 'club drugs'. The third objective was to create a conceptual framework that explains how the illicit substances could be causally associated with HIV, STI or UAI. The fourth objective was to assess the potential for meeting Sir Bradford Hill's criteria for causation [365]. The final objective was to recommend future research needs in order to conclude or refute a causal association between each substance and UAI.

Objective for Manuscript 2: The overall objective of the second manuscript was to conduct three different statistical analyses to capture three potential measures of association between substance use and unprotected anal intercourse (UAI), in order to provide evidence for or against a causal association. The objectives of each of the three analyses were: 1) to examine cross-sectional trends in UAI and substance use; 2) to estimate associations between use of specific recreational substances and EDM on UAI while using individuals as their own control in within-subjects analyses; and 3) to determine if recreational substance use was associated with UAI when considering all participants, including those with no variation in UAI between partners in a situational analysis.

Objective for Manuscript 3: The objective for the third manuscript was to determine if associations between substance use and unprotected anal intercourse (UAI) among recently HIV infected men who have sex with men (MSM) differ before and after HIV diagnosis.

K. Hypotheses

A number of hypotheses were tested in each of the two manuscripts that were based on independent data analysis in order to elucidate the true association between substance use and HIV. No hypotheses were generated for the first manuscript, as it was based on a review of the literature.

Manuscript 2: Five hypotheses were tested in this study of substance use and UAI.

Hypothesis 1**:** Recently infected, HIV-positive MSM will report a higher likelihood of EDM or illicit substance use during unprotected anal intercourse (UAI) than when having anal intercourse with a condom.

Hypothesis 2: Substances which are likely to be causally associated with UAI will be associated with UAI in both within-subjects analyses and situational analyses.

Hypothesis 3: Substances that are associated with UAI, but are unlikely to have a direct causal association (e.g., are associated with UAI because people with risk taking personalities are more likely to use drugs and to have UAI), will be associated with UAI only in situational analyses, but not in within-subjects analyses.

Hypothesis 4: Associations between substance use and UAI will not be as strong with main partners as with other partner types.

Hypothesis 5: MSM who report UAI with more of their last three partners will be more likely to report substance use than those who report no UAI.

Manuscript 3: Three hypotheses were tested in this study of change in substance use and UAI after HIV diagnosis.

Hypothesis 1: Different substances will be associated with UAI based on whether or not they were used with sexual partners before or after HIV diagnosis.

Hypothesis 2: Use of illicit drugs that contribute to the risk of HIV acquisition, such as methamphetamine, will be associated with UAI before, but not after HIV diagnosis.

Hypothesis 3: Drugs that are often used to cope with depression and trauma, such as marijuana, will be associated with UAI after, but not before HIV diagnosis.

L. Rationale for the Proposed Manuscripts

Each of the manuscripts presented in this dissertation was designed to contribute to the understanding of the true associations between 'club drug' use and risk of HIV and STI transmission among MSM. The specific contributions to the literature of each manuscript are described below.

Manuscript 1: A growing number of studies have examined club drugs as risk factors for HIV transmission and acquisition among MSM. In order to expand on these previous studies it is important to understand what conclusions can be drawn from them and what has yet to be examined. Manuscript 1 will help to focus the needs for establishing or refuting a causal association between HIV acquisition and individual substances that are considered club drugs.

Manuscript 2**:** One hypothesis of how illicit substances could increase one's risk for HIV acquisition is that individuals have riskier sexual activity than usual when using illicit substances. However, others hypothesize that the associations between substance use and UAI are confounded by personality traits, such as risk taking. Within-subjects analyses, which use the individuals as their own controls, are able to control for unknown or unmeasured individual factors, such as personality; therefore removing the

possibility of confounding by personality. Within-subjects analyses have never been used to examine associations between erectile dysfunction medication (EDM) use and UAI and only one other study has used such an analysis to examine associations between a combination of methamphetamine, marijuana and amyl nitrates and UAI. This study addresses associations between UAI and individual substances. Additionally, this study utilizes data from recently HIV-infected MSM and therefore is likely to capture information about sexual activity which resulted in the participants' HIV acquisition or transmission to another due to high viral loads during early infection.

Manuscript 3: Evidence suggesting that illicit drug use, especially methamphetamine, contributes to UAI and HIV acquisition among MSM is growing. In order for HIV transmission to occur during UAI the sexual partners must be sero-discordant. MSM with recent HIV infection have higher viral loads which are not controlled by the immune system and therefore may be more infectious. Prevention efforts focusing on early diagnosis have been suggested. For such prevention efforts to be effective, newly infected individuals must modify their sexual behavior. It is therefore important to determine whether the use of illicit drugs that contribute to UAI before diagnosis, continue to contribute to UAI after diagnosis or if there is a change in behavioral pattern. Such information could help to direct programs focusing on prevention for HIV positive individuals. No known study has yet examined change in association between UAI and illicit drug use before and after HIV diagnosis.

M. Dissertation Chapters

The three studies previously described are tied into this dissertation with additional chapters. Chapter 2 includes the first study, an exhaustive review of the

literature concerning associations between the use of ‘club drugs’ and HIV/STI acquisition or unprotected anal intercourse (UAI) among MSM. This study serves as the background literature in understanding the needs of future research pertaining to non-injection substance use and risk for HIV/STI acquisition among MSM. Manuscript 1, Chapter 2, has been published in its entirety in the journal, *Substance Use and Misuse*. Chapter 3 reviews the methods used for collection and analysis of all data in manuscripts 2 and 3. Although the methods are presented in the second and third manuscripts, the methods section of the dissertation describes recruitment of subjects, data collection, and data analyses in additional detail. Chapter 4 includes the second manuscript, which examines substance use as a risk factor for UAI among MSM with recent HIV infection. Study 2 has been submitted for publication as it appears in Chapter 4 and is currently under review. Chapter 5 includes the third and final manuscript of this dissertation study. This study of changes in associations between UAI and substance use before and after HIV diagnosis has been submitted for publication and is currently under review. The fifth and final chapter, which concludes this dissertation discusses the overall knowledge obtained from the three studies together, presents study strengths and limitations, and provides recommendations for future research needs.

Table 1-1: Recent Studies Showing an Increase in HIV Incidence or Prevalence (MSM= men who have sex with men; IDU= injection drug user)

First Author	Year	Location	Population	Sample Size	Study Design	Change in Incidence
Hogg [155]	2001	Vancouver	MSM	668	Longitudinal	1995: 0.6/100 person years 2000: 3.7/ 100 person years
del Romero [366]	2001	Madrid	MSM	267	Longitudinal	1988: 4.71/ 100 person years 1995: 1.06/ 100 person years 2000: 2.16/ 100 person years
Kellogg [367]	2001	San Francisco	MSM	2893	Retrospective Cohort	1996: 2.9/100 person years 1998: 4.7/100 person years (MSM IDU)
Bluthenthal [368]	2001	San Francisco	MSM IDU	992	Comparison of cross-sectional data	1989: 35-45% 1996: 25% 2000: 42%
Calzavara [369]	2002	Ontario	HIV testers	All sero-converters Ontario 1996-1999	Comparison of cross-sectional sero-conversion data	1992: 1.23/ 100 person years 1996: 0.79/100 person years 2000: 1.16/ 100 person years
Dukers [210]	2002	Amsterdam	MSM	3090	Cross-sectional comparisons	1995: 0.9/ 100 person years 2001: 4.4/ 100 person years
Weinstock [370]	2002	Atlanta, Baltimore, Chicago, Denver Houston , New Orleans, Los Angeles Miami, Newark	Anonymous HIV testers in STD clinics	129, 774	Comparison of cross-sectional data from and STD clinic	Percent incidence stable among MSM from 1991 to 1997 at 7.1%
CDC [371]	2003	United States	All HIV diagnoses in the 29 states in which reporting occurred	Sero-converters US 1999-2002	Comparison of reported newly diagnosed cases	Among MSM incidence increased 3% from 1999 to 2002
Kihara [215]	2003	Japan	All reported HIV cases	NA	Comparison of surveillance data by years	100 cases 1990; >500 cases 1999; 10 fold increase in prevalence 1987 to 2000
CDC [372]	2004	North Carolina	US Surveillance data	All African Americans with HIV	Comparison of surveillance data by years	1998: 65 2002: 92 per 100,000 African Americans
CDC [132]	2005	United States	All HIV diagnoses in the 33 states that had name-based reporting	Sero-converters US 2000-2003	Comparison of reported newly diagnosed cases	Increase in HIV prevalence among MSM by 8% between 2003 and 2004

Table 1-2: Recent Studies Identifying a Change in STI Incidence or Outbreaks among MSM

First Author	Year	Location	Population	Sample Size	STI	Change in Incidence
CDC [373]	1998	Guilford, NC	Guilford County residents	Unclear	Syphilis incidence	1994: 62 cases; 1996: 153 cases; 1997: 153 cases. Rate in Guilford county 40.5/100,000 higher than NC 10.9/100,000 in 1997.
Williams [229]	1999	King County, WA	All syphilis case records from 1987 to 1998	555	Syphilis incidence	Decrease in syphilis 1989-1996, increase from 1996 to 1998; 68% MSM, of those 66% HIV+
CDC [374]	1999	King County, WA	MSM STD clinic attendees with bacterial STI	427	Syphilis incidence	1995: 6 cases; 1996: 1 case; Jan-June 1999: 46 cases 1997 to 1999 3 fold increase in STI; 1996: 0/100,000 syphilis 1999: 90/100,000
CDC [375]	1999	San Francisco	Community based sample of MSM	4173	Rectal gonorrhea	1994 1997 Rates/ 100,000 21 38
Stolte [376]	2001	Amsterdam	MSM attending STD clinic	6103	Rectal gonorrhea Syphilis	1998 1999 rectal GC 4.0% 6.8% syphilis 0.4% 1.4%
Fox [377]	2001	Unite States STD Clinics	Gonorrhea isolates and case information	34942	Gonorrhea incidence	1992 1999 % MSM 4.5% 13.2%
CDC [378]	2002	New York, NY	All reported syphilis cases	282	Primary & secondary syphilis	117 cases in 2000; 282 in 2001. Rate was 3.5/100000 in 2001, higher in males (6.9). Male: female ratio was 13.8:1, up from 3.6:1 in 1999. Of 86 MSM with syphilis, 20% were HIV+ in 1999, 49% in 2000 and 48% in 2001.
Rietmeijer [222]	2003	Denver, CO	MSM STD clinic attendees	Unspecified	Gonorrhea incidence	1990-1995: 8.1% 1996-2001: 12.9%
CDC [379]	2003	United States	United States Census Population	Surveillance Data	Syphilis incidence	12.4% increase between 2001/2002 (rate = 2.2 to 2.4/100000). 20.8% increase in cites > 200000 (rate=4.8 to 5.8).64.3% increase in West US. Rates higher in men (3.8) than women (1.1). Rate higher in SF (78.8) than LA (7.7) men. More cases in LA (359) than SF (315).
D'Souza [224]	2003	Houston, TX	Syphilis cases	285	Syphilis incidence (outbreak)	2000-2002: Slight increase in syphilis overall, great increase in MSM; 2000 2001 2002 % cases MSM: 10% 26% 47%
CDC [380]	2004	Massachusetts, New York, GISP	GC Isolates from United States from Men	1284	Gonorrhea incidence	GC incidence increasing in men . Prevalence of resistant isolates higher in MSM than hetero men MSM Other Men GISP: 4.9% 0.4% MA: 11.1% 1.8% NYC: 12.5% 1.6%
Hopkins [228]	2004	Ireland	Country surveillance data	19,601	Syphilis incidence	Increased 140 fold 1998-2001 among MSM
CDC [381]	2004	San Francisco, Los Angeles	MSM with syphilis from STD & HIV testing centers 1998-2002	SF: 426 LA: 501	Syphilis incidence	1998 2000 2002 SF: 8 NA 512 per 100,000 LA: NA 67 299 per 100,000
CDC [382]	2004	San Francisco	Reported syphilis cases among MSM 1998-2002	434	Syphilis incidence	1998 2002 Percent cases MSM: 22% 88%

* MSM- men who have sex with men; GISP- gonorrhea isolates surveillance program; GC- gonorrhea; HIV+- HIV positive; HIV- HIV negative; STD- sexually transmitted disease

Table 1-3: Recent Studies Identifying a Change in Sexual Risk Taking Behavior among MSM

First Author	Year	Location	Population	Sample Size	Study Design	Risk Behavior	Change in Risk Behavior
De Wit [277]	1993	Amsterdam	MSM in STD clinic	310	Longitudinal	UAI	Increased from 29.% from January to June 1991, to 40.7% July to December 1991.
Ekstrand [231]	1999	San Francisco	Adult, Unmarried MSM	510	Longitudinal	UAI	Prevalence UAI: 1993: 37% 1997: 50%
Elford [232]	2002	London	MSM in London Gyms	2938	Comparison of cross-sectional surveys	UAI with sero-discordant casual partner	1998 2001 HIV+ 15.3% 38.8% HIV- 6.8 % 12.1% Unknown 2.1% 7.7%
Katz [383]	2002	San Francisco	Various MSM	Varies	Multiple cross-sectional surveys	Condom use UAI Multiple sex partners	1994 1999 Always condom use 70% 54% UAI 24% 45% Multiple sex partners 24% 45%
Rosser [234]	2002	Minneapolis-St. Paul	MSM	422	Randomized control trail intervention	Condom use	29% decrease in condom use in control group after 12 month follow up.
Van de Ven [235]	2002	Australia	MSM	1832	Comparison of cross-sectional studies	UAI	1992 1996 2002 UAI: 21.5% 24.7% 46.4%
Chen [236]	2003	San Francisco	MSM	10,579	Comparison of cross-sectional surveys	UAI	1999: 11.0% 2001: 16.0%
Wohl [237]	2004	Los Angeles	MSM with AIDS	568	Cross-sectional population based survey of persons diagnosed with AIDS	UAI Number sexual partners past month	1998 2001 2002 2003 UAI last sex: NA NA 11% 26% >10 sex part: 8% 11% 20% 25%
Stolte [384]	2004	Amsterdam	HIV negative MSM	217	Longitudinal	Selective positioning	Those reporting that they saw less risk of death due to HIV infection, reported increasing RUAI

* MSM- men who have sex with men; HIV+- HIV positive; HIV- HIV negative; STD- sexually transmitted disease

N. References

(1) Centers for Disease Control and Prevention. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men- New York City and California. *Morbidity and Mortality Weekly Report*. 1981; 30:305-308.

(2) UNAIDS. AIDS Epidemic Update: 2005. 2005. Geneva, World Health Organization. (Report)

(3) Blacker J. The impact of AIDS on adult mortality: evidence from national and regional statistics. *AIDS*. 2004; 18 Suppl 2:S19-S26.

(4) UNAIDS. An exceptional response to AIDS. 2005. Geneva, Joint United Nations Program on HIV/AIDS. (Report)

(5) World Health Organization. Global Tuberculosis Control. WHO Report 2005. 2005. Geneva, World Health Organization. (Report)

(6) World Health Organization. Tuberculosis- the global burden. http://www.who.int/tb/publications/tb_global_facts_sep05_en.pdf. 2005. (Electronic Citation) Accessed 9 January 2006

(7) Cahn P, Perez H, Ben G *et al*. Tuberculosis and HIV: a partnership against the most vulnerable. *J Int Assoc Physicians AIDS Care (Chic Ill)*. 2003; 2:106-123.

(8) Corbett EL, Watt CJ, Walker N *et al*. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med*. 2003; 163:1009-1021.

(9) World Health Organization. Malaria and HIV interactions and their implications for public health policy. 2004. Geneva, World Health Organization Press. (Report)

(10) Whitworth J. Effect of HIV-1 and increasing immunosupression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet*. 2000; 356:1051-1056.

(11) Soriano V, Martin-Carbonero L, Maida I *et al*. New paradigms in the management of HIV and hepatitis C virus coinfection. *Curr Opin Infect Dis*. 2005; 18:550-560.

(12) Arends JE, Boucher CA, Hoepelman AI. Hepatitis C virus and human immunodeficiency virus coinfection: where do we stand? *Neth J Med*. 2005; 63:156-163.

(13) Camino N, Sheldon J, Soriano V. Update on hepatitis C treatment in HIV-coinfected patients. *Minerva Gastroenterol Dietol*. 2004; 50:67-77.

(14) Shire NJ, Sherman KE. Management of HBV/HIV-coinfected Patients. *Semin Liver Dis*. 2005; 25 Suppl 1:48-57.

(15) Sharp PM, Bailes E, Chaudhuri RR *et al*. The origins of acquired immune deficiency syndrome viruses: where and when? *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*. 2001; 356:867-876.

(16) Bock PJ, Markovitz DM. Infection with HIV-2. *AIDS*. 2001; 15:S35-S45.

(17) Marlink R, Kanki P, Thior I *et al*. Reduced Rate of Disease Development After HIV-2 Infection As Compared to HIV-1. *Science*. 1994; 265:1587-1590.

(18) Bailes E, Gao F, Bibollet-Ruche F *et al*. Hybrid origin of SIV in chimpanzees. *Science*. 2003; 300:1713.

(19) Kalish ML, Wolfe ND, Ndongmo CB *et al*. Central African hunters exposed to simian immunodeficiency virus. *Emerging Infectious Diseases*. 2005; 11:1928-1930.

(20) Wolfe ND, Daszak P, Kilpatrick AM *et al*. Bushmeat hunting deforestation, and prediction of zoonoses emergence. *Emerging Infectious Diseases*. 2005; 11:1822-1827.

(21) Korber B, Muldoon M, Theiler J *et al*. Timing the ancestor of the HIV-1 pandemic strains. *Science*. 2000; 288:1789-1796.

(22) Rambaut A, Robertson DL, Pybus OG *et al*. Human immunodeficiency virus - Phylogeny and the origin of HIV-1. *Nature*. 2001; 410:1047-1048.

(23) Gisselquist D, Potterat JJ. Heterosexual transmission of HIV in Africa: an empiric estimate. *International Journal of Std & AIDS*. 2003; 14:162-173.

(24) Walker PR, Worobey M, Rambaut A *et al*. Sexual transmission of HIV in Africa - Other routes of infection are not the dominant contributor to the African epidemic. *Nature*. 2003; 422:679.

(25) Lopman BA, Garnett GP, Mason PR *et al*. Individual level injection history: A lack of association with HIV incidence in rural Zimbabwe. *Plos Medicine*. 2005; 2:142-146.

(26) Klovdahl AS. Social Networks and the Spread of Infectious-Diseases - the AIDS Example. *Social Science & Medicine*. 1985; 21:1203-1216.

(27) Auerbach DM, Jaffe HW, Curran JW *et al*. Cluster of Cases of the Acquired Immune-Deficiency Syndrome - Patients Linked by Sexual Contact. *American Journal of Medicine*. 1984; 76:487-492.

(28) Garry RF, Witte MH, Gottlieb A *et al*. Documentation of An AIDS Virus-Infection in the United-States in 1968. *Jama-Journal of the American Medical Association*. 1988; 260:2085-2087.

(29) Robbins KE, Lemey P, Pybus OG *et al*. US human immunodeficiency virus type 1 epidemic: Date of origin, population history, and characterization of early strains. *Journal of Virology*. 2003; 77:6359-6366.

(30) Vangroenweghe D. The earliest cases of human immunodeficiency virus type 1 group M in Congo-Kinshasa, Rwanda and Burundi and the origin of acquired immune deficiency syndrome. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*. 2001; 356:923-925.

(31) Kandathil AJ, Ramalingam S, Kannangai R *et al*. Molecular epidemiology of HIV. *Indian Journal of Medical Research*. 2005; 121:333-344.

(32) Wainberg MA. HIV-1 subtype distribution and the problem of drug resistance. *AIDS*. 2004; 18:S63-S68.

(33) Takebe Y, Kusagawa S, Motomura K. Molecular epidemiology of HIV: Tracking AIDS pandemic. *Pediatrics International*. 2004; 46:236-244.

(34) Takebe Y, Motomura K, Tatsumi M *et al*. High prevalence of diverse forms of HIV-1 intersubtype recombinants in Central Myanmar: geographical hot spot of extensive recombination. *AIDS*. 2003; 17:2077-2087.

(35) Najera R, Delgado E, Perez-Alvarez L *et al*. Genetic recombination and its role in the development of the HIV-1 pandemic. *AIDS*. 2002; 16:S3-S16.

(36) Thomson MM, Perez-Alvarez L, Najera R. Molecular epidemiology of HIV-1 genetic forms and its significance for vaccine development and therapy. *Lancet Infectious Diseases*. 2002; 2:461-471.

(37) Blattner WA, O'Brien TR, Mueller NE. Retroviruses- Human Immunodeficiency Virus. In: Evans AS, Kaslow RA, editors. Viral Infections of Humans: Epidemiology and Control. New York: Plenum Medical Book Company, 1997: 713-783.

(38) Swanstrom R, Wehbie R. The Biology of HIV, SIV, and other lentiviruses. In: Holmes KK, Sparling PF, Mardh P, Lemon SM, Stamm WE, Piot P *et al*., editors. Sexuall Transmitted Diseases. New York: McGraw-Hill, 1999: 215-229.

(39) Dalgleish AG, Beverley PCL, Clapham PR *et al*. The Cd4 (T4) Antigen Is An Essential Component of the Receptor for the AIDS Retrovirus. *Nature*. 1984; 312:763-767.

(40) Broder CC, Collman RG. Chemokine receptors and HIV. *Journal of Leukocyte Biology*. 1997; 62:20-29.

(41) Doranz BJ, Berson JF, Rucker J *et al*. Chemokine receptors as fusion cofactors for human immunodeficiency virus type 1 (HIV-1). *Immunologic Research*. 1997; 16:15-28.

(42) Wu LJ, Gerard NP, Wyatt R *et al*. CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5. *Nature*. 1996; 384:179-183.

(43) Li XD, Moore B, Cloyd MW. Gradual shutdown of virus production resulting in latency is the norm during the chronic phase of human immunodeficiency virus replication and differential rates and mechanisms of shutdown are determined by viral sequences. *Virology*. 1996; 225:196-212.

(44) Hermankova M, Siliciano JD, Zhou Y *et al*. Analysis of human immunodeficiency virus type 1 gene expression in latently infected resting CD4(+) T lymphocytes in vivo. *Journal of Virology*. 2003; 77:7383-7392.

(45) Mansky LM, Temin HM. Lower In-Vivo Mutation-Rate of Human-Immunodeficiency-Virus Type-1 Than That Predicted from the Fidelity of Purified Reverse-Transcriptase. *Journal of Virology*. 1995; 69:5087-5094.

(46) Pathak VK, Temin HM. Broad-Spectrum of Invivo Forward Mutations, Hypermutations, and Mutational Hotspots in A Retroviral Shuttle Vector After A Single Replication Cycle - Substitutions, Frameshifts, and Hypermutations. *Proceedings of the National Academy of Sciences of the United States of America*. 1990; 87:6019-6023.

(47) Pathak VK, Temin HM. Broad-Spectrum of Invivo Forward Mutations, Hypermutations, and Mutational Hotspots in A Retroviral Shuttle Vector After A Single Replication Cycle - Deletions and Deletions with Insertions. *Proceedings of the National Academy of Sciences of the United States of America*. 1990; 87:6024-6028.

(48) Coffin JM. HIV Population-Dynamics In-Vivo - Implications for Genetic-Variation, Pathogenesis, and Therapy. *Science*. 1995; 267:483-489.

(49) Wei XP, Ghosh SK, Taylor ME *et al*. Viral Dynamics in Human-Immunodeficiency-Virus Type-1 Infection. *Nature*. 1995; 373:117-122.

(50) Ho DD, Neumann AU, Perelson AS *et al*. Rapid Turnover of Plasma Virions and CD4 Lymphocytes in HIV-1 Infection. *Nature*. 1995; 373:123-126.

(51) Little SJ, Mclean AR, Spina CA *et al*. Viral dynamics of acute HIV-1 infection. *Journal of Experimental Medicine*. 1999; 190:841-850.

(52) Fiebig EW, Wright DJ, Rawal BD *et al*. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003; 17:1871-1879.

(53) Ambroziak J, Levy JA. Epidemiology, natural history, and pathogenesis of HIV infection. In: Holmes KK, Sparling PF, Mardh PA, Lemon SM, Stamm WE, Piot P *et al*., editors. Sexually Transmitted Diseases. 1999: 251-258.

(54) Taiwo BO, Hicks CB. Primary human immunodeficiency virus. *Southern Medical Journal*. 2002; 95:1312-1317.

(55) Daar ES, Little S, Pitt J *et al*. Diagnosis of primary HIV-1 infection. *Annals of Internal Medicine*. 2001; 134:25-29.

(56) Kahn JO, Walker BD. Acute human immunodeficiency virus infection. *New England Journal of Medicine*. 1998; 339:33-39.

(57) Vanhems P, Dassa C, Lambert J *et al*. Comprehensive classification of symptoms and signs reported among 218 patients with acute HIV-1 infection. *Journal of Acquired Immune Deficiency Syndromes*. 1999; 21:99-106.

(58) Sharghi N, Bosch RJ, Mayer K *et al*. The development and utility of a clinical algorithm to predict early HIV-1 infection. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2005; 40:472-478.

(59) Hecht FM, Busch MP, Rawal B *et al*. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. 2002; 16:1119-1129.

(60) Sarr AD, Eisen G, Gueye-Ndiaye A *et al*. Viral dynamics of primary HIV-1 infection in Senegal, West Africa. *Journal of Infectious Diseases*. 2005; 191:1460-1467.

(61) Pilcher CD, Tien HC, Eron JJ *et al*. Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *Journal of Infectious Diseases*. 2004; 189:1785-1792.

(62) Quinn TC, Wawer MJ, Sewankambo N *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *New England Journal of Medicine*. 2000; 342:921-929.

(63) Cao JH, McNevin J, Malhotra U *et al*. Evolution of CD8(+) T cell immunity and viral escape following acute HIV-1 infection. *Journal of Immunology*. 2003; 171:3837-3846.

(64) Phillips AN. Reduction of HIV concentration during acute infection: Independence from a specific immune response. *Science*. 1996; 271:497-499.

(65) Perelson AS, Neumann AU, Markowitz M *et al*. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time. *Science*. 1996; 271:1582-1586.

(66) Gray RH, Wawer MJ, Brookmeyer R *et al*. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet*. 2001; 357:1149-1153.

(67) Mellors JW, Munoz A, Giorgi JV *et al*. Plasma viral load and CD4(+) lymphocytes as prognostic markers of HIV-1 infection. *Annals of Internal Medicine*. 1997; 126:946-954.

(68) Vlahov D, Graham N, Hoover D *et al*. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users - Plasma viral load and CD4(+) cell count. *Jama-Journal of the American Medical Association*. 1998; 279:35-40.

(69) Centers for Disease Control and Prevention. Current trends update on acquired immune deficiency syndrome (AIDS)- United States. *Morbidity and Mortality Weekly Report*. 1982; 31:507-508.

(70) Centers for Disease Control and Prevention. Current Trends Revision of the Case Definition of Acquired Immunodeficiency Syndrome for National Reporting--United States. *Morbidity and Mortality Weekly Report*. 1985; 34:373-375.

(71) Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report*. 1992; 41.

(72) Babiker A, Darby S, De Angelis D *et al*. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet*. 2000; 355:1131-1137.

(73) Coutinho RA. Some aspects of the natural history of HIV infection. *Tropical Medicine & International Health*. 2000; 5:A22-A25.

(74) Levy JA. HIV Pathogenesis and Long-Term Survival. *AIDS*. 1993; 7:1401-1410.

(75) Pezzotti P, Napoli PA, Acciai S *et al*. Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. *AIDS*. 1999; 13:249-255.

(76) Sterne JAC, Hernan MA, Ledergerber B *et al*. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet*. 2005; 366:378-384.

(77) Porter K, Babiker AG, Darbyshire JH *et al*. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet*. 2003; 362:1267-1274.

(78) Wong KH, Chan KCW, Lee SS. Delayed progression to death and to AIDS in a Hong Kong cohort of patients with advanced HIV type 1 disease during the era of highly active antiretroviral therapy. *Clinical Infectious Diseases*. 2004; 39:853-860.

(79) Kitayaporn D, Tansuphaswadikul S, Lohsomboon P *et al*. Survival of AIDS patients in the emerging epidemic in Bangkok, Thailand. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1996; 11:77-82.

(80) Morgan D, Mahe C, Mayanja B *et al*. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS*. 2002; 16:597-603.

(81) Jaffer S. The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review (vol 82, pg 462, 2004). *Bulletin of the World Health Organization*. 2004; 82:571.

(82) Rangsin R, Chiu J, Khamboonruang C *et al*. The natural history of HIV-1 infection in young Thai men after seroconversion. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2004; 36:622-629.

(83) Hira SK, Shroff HJ, Lanjewar DN *et al*. The natural history of human immunodeficiency virus infection among adults in Mumbai. *National Medical Journal of India*. 2003; 16:126-131.

(84) Ochsenbein AF, Riddell SR, Brown M *et al*. CD27 expression promotes long-term survival of functional effector-memory CD8(+) cytotoxic T lymphocytes in HIV-infected patients. *Journal of Experimental Medicine*. 2004; 200:1407-1417.

(85) Rhodes DI, Ashton L, Solomon A *et al*. Characterization of three nef-defective human immunodeficiency virus type 1 strains associated with long-term nonprogression. *Journal of Virology*. 2000; 74:10581-10588.

(86) Geffin R, Wolf D, Muller R *et al*. Functional and structural defects in HIV type 1 nef genes derived from pediatric long-term survivors. *AIDS Research and Human Retroviruses*. 2000; 16:1855-1868.

(87) Gallo RC, Sarin PS, Gelmann EP *et al*. Isolation of Human T-Cell Leukemia-Virus in Acquired Immune-Deficiency Syndrome (AIDS). *Science*. 1983; 220:865-867.

(88) United States Food and Drug Aministration. HIV/AIDS Historical Time Line. http://www.fda.gov/oashi/aids/miles81.html. 2006. (Electronic Citation) Accessed 22 January 2006.

(89) United States Food and Drug Aministration. HIV testing. http://www.fda.gov/oashi/aids/test.html . 2006. (Electronic Citation) Accessed 23 January 2006.

(90) Richman DD, Guatelli JC, Grimes J *et al*. Detection of Mutations Associated with Zidovudine Resistance in Human-Immunodeficiency-Virus by Use of the Polymerase Chain-Reaction. *Journal of Infectious Diseases*. 1991; 164:1075-1081.

(91) Consumer Project on Technology. Notes on government role in the development of HIV/AIDS drugs. http://www.cptech.org/ip/health/sa/loveaffidavit/t12.html. 2006. (Electronic Citation) Accessed 30 January 2006.

(92) Yarchoan R, Klecker RW, Weinhold KJ *et al*. Administration of 3'-Azido-3'-Deoxythymidine, An Inhibitor of Htlv-Iii/Lav Replication, to Patients with AIDS Or AIDS-Related Complex. *Clinical Research*. 1986; 34:A511.

(93) Larder BA, Kemp SD. Multiple Mutations in HIV-1 Reverse-Transcriptase Confer High-Level Resistance to Zidovudine (Azt). *Science*. 1989; 246:1155-1158.

(94) National Institutes of Allergy and Infectious Diseases. NIAID Fact Sheet: Two New Protease Inhibitors Approved by FDA . NIDA website. 1996. (Electronic Citation) Accessed 30 January 2006.

(95) Wlodawer A, Vondrasek J. Inhibitors of HIV-1 protease: a major success of structure-assisted drug design. *Annual Review of Biophysics and Biomolecular Structure* 1998; 27: 249-284.

(96) Deeks SG, Smith M, Holodniy M *et al*. HIV-1 protease inhibitors - A review for clinicians. *Jama-Journal of the American Medical Association*. 1997; 277:145-153.

(97) Deminie CA, Bechtold CM, Stock D *et al*. Evaluation of reverse transcriptase and protease inhibitors in two-drug combinations against human immunodeficiency virus replication. *Antimicrobial Agents and Chemotherapy*. 1996; 40:1346-1351.

(98) Elfarrash MA, Kuroda MJ, Kitazaki T *et al*. Generation and Characterization of A Human-Immunodeficiency-Virus Type-1 (HIV-1) Mutant Resistant to An HIV-1 Protease Inhibitor. *Journal of Virology*. 1994; 68:233-239.

(99) Markowitz M, Mo HM, Kempf DJ *et al*. Selection and Analysis of Human-Immunodeficiency-Virus Type-I Variants with Increased Resistance to Abt-538, A Novel Protease Inhibitor. *Journal of Virology*. 1995; 69:701-706.

(100) Ho DD, Toyoshima T, Mo HM *et al*. Characterization of Human-Immunodeficiency-Virus Type-1 Variants with Increased Resistance to A C-2-Symmetrical Protease Inhibitor. *Journal of Virology*. 1994; 68:2016-2020.

(101) Boudes P, Geiger JM. HIV protease inhibitors: A review. *Therapie*. 1996; 51:319-325.

(102) Chrusciel RA, Romines KR. Recent developments in HIV protease inhibitor research. *Expert Opinion on Therapeutic Patents*. 1997; 7:111-121.

(103) Imamichi T. Action of Anti-HIV drugs and resistance: Reverse transcriptase inhibitors and protease inhibitors. *Current Pharmaceutical Design*. 2004; 10:4039-4053.

(104) Stolk LML, Luers JFJ. Increasing number of anti-HIV drugs but no definite cure - Review of anti-HIV drugs. *Pharmacy World & Science*. 2004; 26:133-136.

(105) Schmit JC, Cogniaux J, Hermans P *et al*. Multiple drug resistance to nucleoside analogues and nonnucleoside reverse transcriptase inhibitors in an efficiently replicating human immunodeficiency virus type 1 patient strain. *Journal of Infectious Diseases*. 1996; 174:962-968.

(106) Demeter LM, Meehan PM, Morse G *et al*. HIV-1 drug susceptibilities and reverse transcriptase mutations in patients receiving combination therapy with didanosine and delaviridine. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1997; 14:136-144.

(107) Balzarini J, Pelemans H, Karlsson A *et al*. Concomitant combination therapy for HIV infection preferable over sequential therapy with 3TC and non-nucleoside reverse transcriptase inhibitors. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93:13152-13157.

(108) Gazzard B. What we know so far. *AIDS*. 1996; 10:S3-S7.

(109) Hammer SM. Advances in antiretroviral therapy and viral load monitoring. *AIDS*. 1996; 10:S1-S11.

(110) DeClercq E. Development of resistance of human immunodeficiency virus (HIV) to anti-HIV agents: how to prevent the problem? *International Journal of Antimicrobial Agents*. 1997; 9:21-36.

(111) United States Food and Drug Aministration. FDA Approves First Drug in New Class of HIV Treatments for HIV Infected Adults and Children With Advanced Disease. FDA Website . 2003. (Electronic Citation) Accessed 30 January 2006.

(112) Schneider SE, Bray BL, Mader CJ *et al*. Development of HIV fusion inhibitors. *Journal of Peptide Science*. 2005; 11:744-753.

(113) Poveda E, Briz V, Soriano V. Enfuvirtide, the first fusion inhibitor to treat HIV infection. *AIDS Reviews*. 2005; 7:139-147.

(114) Chinnadurai R, Munch A, Dittmar MT *et al*. Inhibition of HIV-1 group M and O isolates by fusion inhibitors. *AIDS*. 2005; 19:1919-1922.

(115) Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *Journal of Antimicrobial Chemotherapy*. 2004; 54:333-340.

(116) Tremblay C. Effects of HIV-1 entry inhibitors in combination. *Current Pharmaceutical Design*. 2004; 10:1861-1865.

(117) Richman DD, Morton SC, Wrin T *et al*. The prevalence of antiretroviral drug resistance in the United States. *AIDS*. 2004; 18:1393-1401.

(118) Little SJ, Holte S, Routy JP *et al*. Antiretroviral-drug resistance among patients recently infected with HIV. *New England Journal of Medicine*. 2002; 347:385-394.

(119) Jaffe HW, Bregman DJ, Selik RM. Acquired Immune-Deficiency Syndrome in the United-States - the 1St 1,000 Cases. *Journal of Infectious Diseases*. 1983; 148:339-345.

(120) Centers for Disease Control and Prevention. Epidemiologic Notes and Reports Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) -- New York. *Morbidity and Mortality Weekly Report*. 1983; 31:697-698.

(121) Ammann AJ, Levy J. Laboratory Investigation of Pediatric Acquired-Immunodeficiency-Syndrome. *Clinical Immunology and Immunopathology*. 1986; 40:122-127.

(122) Centers for Disease Control and Prevention. Unexplained Immunodeficiency and Opportunistic Infections in Infants -- New York, New Jersey, California. *Morbidity and Mortality Weekly Report*. 1982; 31:665-667.

(123) Groopman JE, Salahuddin SZ, Sarngadharan MG *et al*. Htlv-Iii in Saliva of People with AIDS-Related Complex and Healthy Homosexual Men at Risk for AIDS. *Science*. 1984; 226:447-449.

(124) Levy JA, Greenspan D. HIV in Saliva. *Lancet*. 1988; 2:1248.

(125) Centers for Disease Control and Prevention. Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A. *Morbidity and Mortality Weekly Report*. 1982; 31:365-367.

(126) CBS News. HIV Contracted From Donated Blood. CBS News Website. 2002. (Electronic Citation) Accessed 26 January 2006.

(127) Associated Press. HIV-Tainted Blood Infects Two In Fla. CBS News Website . 2002. (Electronic Citation) Accessed 26 January 2006.

(128) Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *Journal of the American Medical Association*. 2003; 289:959-962.

(129) Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. *Lancet*. 2003; 361:161-169.

(130) World Health Organization. Strategy for Safe Blood Transfusion. http://w3.whosea.org/EN/Section10/Section17/Section53/Section478_1671.htm . 2005. (Electronic Citation) Accessed 26 January 2006.

(131) Quan VM, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2002; 31:188-201.

(132) Centers for Disease Control and Prevention. Trends in HIV/AIDS diagnosis- 33 states, 2001-2004. *Morbidity and Mortality Weekly Report*. 2005; 54:1149-1153.

(133) Razak MH, Jittiwutikarn J, Suriyanon V *et al*. HIV prevalence and risks among injection and noninjection drug users in northern Thailand: Need for

comprehensive HIV prevention programs. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:259-266.

(134) Nelson KE, Eiumtrakul S, Celentano DD *et al*. HIV infection in young men in northern Thailand, 1991-1998: Increasing role of injection drug use. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 29:62-68.

(135) Celentano DD, Jittiwutikorn J, Hodge MJ *et al*. Epidemiology of HIV-1 infection in opiate users in northern Thailand. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1998; 17:73-78.

(136) Rodriguez CM, Marques LF, Touze G. HIV and injection drug use in Latin America. *AIDS*. 2002; 16:S34-S41.

(137) World Health Organization. Injecting drug use drives the HIV/AIDS epidemic in eastern Europe and central Asia. Over 80% of those infected are under 30. http://www.euro.who.int/eprise/main/who/mediacentre/PR/2004/20041130_1 . 2004. (Electronic Citation) Accessed 26 January 2006.

(138) Chu TX, Levy JA. Injection drug use and HIV/AIDS transmission in China. *Cell Research*. 2005; 15:865-869.

(139) Krupitsky E, Zvartau E, Karandashova G *et al*. The onset of HIV infection in the Leningrad region of Russia: a focus on drug and alcohol dependence. *HIV Medicine*. 2004; 5:30-33.

(140) Hamers FF, Infuso T, Alix J *et al*. Current situation and regional perspective on HIV/AIDS surveillance in Europe. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S39-S48.

(141) Tran SD, Williams AB, Truong HT *et al*. Risk factors for HIV seropositivity in a sample of drug users in drug treatment in Ho Chi Minh City, Vietnam. *Journal of Acquired Immune Deficiency Syndromes*. 1998; 17:283-287.

(142) Hagan H, Des Jarlais DC. HIV and HCV infection among injecting drug users. Mount Sinai Journal of Medicine 67[5-6], 423-428. 2000.

(143) Aceijas C, Stimson GV, Hickman M *et al*. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS*. 2004; 18:2295-2303.

(144) Tkeshelashvili-Kessler A, del Rio C, Nelson K *et al*. The emerging HIV/AIDS epidemic in Georgia. *International Journal of STD & AIDS*. 2005; 16:61-67.

(145) Gorbach PM, Ryan C, Saphonn V *et al*. The impact of social, economic and political forces on emerging HIV epidemics. *AIDS*. 2002; 16 Suppl 4:S35-S43.

(146) Ghys PD, Saidel T, Vu HT *et al*. Growing in silence: selected regions and countries with expanding HIV/AIDS epidemics. *AIDS*. 2003; 17 Suppl 4:S45-S50.

(147) Vittinghoff E, Douglas J, Judson F *et al*. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *American Journal of Epidemiology*. 1999; 150:306-311.

(148) Wawer MJ, Gray RH, Sewankambo NK *et al*. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *Journal of Infectious Diseases*. 2005; 191:1403-1409.

(149) Varghese B, Maher JE, Peterman TA *et al*. Reducing the risk of sexual HIV transmission - Quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sexually Transmitted Diseases*. 2002; 29:38-43.

(150) Keet IPM, Vanlent NA, Sandfort TGM *et al*. Orogenital Sex and the Transmission of HIV Among Homosexual Men. *AIDS*. 1992; 6:223-226.

(151) Lifson AR, Omalley PM, Hessol NA *et al*. HIV Seroconversion in 2 Homosexual Men After Receptive Oral Intercourse with Ejaculation - Implications for Counseling Concerning Safe Sexual Practices. *American Journal of Public Health*. 1990; 80:1509-1511.

(152) Page-Shafer K, Shiboski CH, Osmond DH *et al*. Risk of HIV infection attributable to oral sex among men who have sex with men and in the population of men who have sex with men. *AIDS*. 2002; 16:2350-2352.

(153) Scully C, Porter S. HIV topic update: oro-genital transmission of HIV. *Oral Diseases*. 2000; 6:92-98.

(154) Geduld J, Gatali M, Remis RS *et al*. Estimates of HIV prevalence and incidence in Canada, 2002. *Can Commun Dis Rep*. 2003; 29:197-207.

(155) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(156) Archibald CP, Sutherland J, Geduld J *et al*. Combining data sources to monitor the HIV epidemic in Canada. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S24-S32.

(157) Dore GJ, Hoy JF, Mallal SA *et al*. Trends in incidence of AIDS illnesses in Australia from 1983 to 1994: the Australian AIDS cohort. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997; 16:39-43.

(158) Kaldor J, McDonald A. HIV/AIDS surveillance systems in Australia. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S18-S23.

(159) Kaldor J, McDonald AM, Blumer CE *et al*. The acquired immunodeficiency syndrome in Australia: incidence 1982-1991. *Med J Aust*. 1993; 158:10-17.

(160) Hamouda O. HIV/AIDS surveillance in Germany. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S49-S54.

(161) Brown AE, Sadler KE, Tomkins SE *et al*. Recent trends in HIV and other STIs in the United Kingdom: data to the end of 2002. *Sex Transm Infect*. 2004; 80:159-166.

(162) Murphy G, Charlett A, Jordan LF *et al*. HIV incidence appears constant in men who have sex with men despite widespread use of effective antiretroviral therapy. *AIDS*. 2004; 18:265-272.

(163) Smith E. HIV/AIDS surveillance in Denmark: the challenges ahead. *J Acquir Immune Defic Syndr*. 2003; 32 Suppl 1:S33-S38.

(164) Bautista CT, Sanchez JL, Montano SM *et al*. Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men. *Sex Transm Infect*. 2004; 80:498-504.

(165) Caceres CF. HIV among gay and other men who have sex with men in Latin America and the Caribbean: a hidden epidemic? *AIDS*. 2002; 16 Suppl 3:S23-S33.

(166) Calleja JM, Walker N, Cuchi P *et al*. Status of the HIV/AIDS epidemic and methods to monitor it in the Latin America and Caribbean region. *AIDS*. 2002; 16 Suppl 3:S3-12.

(167) Beyrer C, Sripaipan T, Tovanabutra S *et al*. High HIV, hepatitis C and sexual risks among drug using men who have sex with men in northern Thailand. *AIDS*. 2005; 19:1535-1540.

(168) UNAIDS. 2004 Report on the Gobal AIDS Epidemic. World Health Organization, editor. 4th Global Report. 2004. Geneva. (Report)

(169) Buve A, Bishikwabo-Nsarhaza K, Mutangadura G. The spread and effect of HIV-1 infection in sub-Saharan Africa. *Lancet*. 2002; 359:2011-2017.

(170) Reynolds SJ, Quinn TC. Developments in STD/HIV interactions: The intertwining epidemics of HIV and HSV-2. *Infectious Disease Clinics of North America*. 2005; 19:415-+.

(171) Corey L, Wald A, Celum CL *et al*. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: A review of two overlapping epidemics. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:435-445.

(172) Rompalo AM, Lawlor J, Seaman P *et al*. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. *Sexually Transmitted Diseases*. 2001; 28:448-454.

(173) Rotchford K, Strum AW, Wilkinson D. Effect of coinfection with STDs and of STD treatment on HIV shedding in genital-tract secretions - Systematic review and data synthesis. *Sexually Transmitted Diseases*. 2000; 27:243-248.

(174) Scarlatti G, Lombardi V, Plebani A *et al*. Polymerase Chain-Reaction, Virus Isolation and Antigen-Assay in HIV-1-Antibody-Positive Mothers and Their Children. *AIDS*. 1991; 5:1173-1178.

(175) Newell ML, Dunn D, Peckham CS *et al*. Risk-Factors for Mother-To-Child Transmission of HIV-1. *Lancet*. 1992; 339:1007-1012.

(176) Rossi P. Maternal Factors Involved in Mother-To-Child Transmission of HIV-1. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1992; 5:1019-1029.

(177) Scarlatti G. Mother-to-child transmission of HIV-1: advances and controversies of the twentieth centuries. *AIDS Rev*. 2004; 6:67-78.

(178) Moodley J, Moodley D. Management of human immunodeficiency virus infection in pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2005; 19:169-183.

(179) Vermund SH. Prevention of mother-to-child transmission of HIV in Africa. *Top HIV Med*. 2004; 12:130-134.

(180) Semprini AE, Fiore S. HIV and pregnancy: is the outlook for mother and baby transformed? *Curr Opin Obstet Gynecol*. 2004; 16:471-475.

(181) Newell ML, Thorne C. Antiretroviral therapy and mother-to-child transmission of HIV-1. *Expert Rev Anti Infect Ther*. 2004; 2:717-732.

(182) Merchant RH, Lala MM. Prevention of mother-to-child transmission of HIV--an overview. *Indian J Med Res*. 2005; 121:489-501.

(183) Vermund SH. Prevention of mother-to-child transmission of HIV in Africa. *Top HIV Med*. 2004; 12:130-134.

(184) Centers for Disease Control and Prevention. Division of HIV/AIDS Prevention: Basic Statistics. http://www.cdc.gov/hiv/stats.htm . 2005. (Electronic Citation) Accessed 27 December 2005.

(185) Centers for Disease Control and Prevention. Distribution of AIDS Cases, by Racial/Ethnic Group and Exposure Category, United States, June 1, 1981-July 4, 1988. *Morbidity and Mortality Weekly Report*. 1988; 37:1-3.

(186) Vu MQ, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002; 31:188-201.

(187) Office AIDS. HIV cases in California, cumulative as of November 30, 2005. 2005. California Department of Health Services, HIV/AIDS Epidemiology Branch. (Report)

(188) Office AIDS. California HIV surveillance report, cumulative cases as of November 30, 2005. 2005. Sacramento, California Department of Health and Human Services. (Report)

(189) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *J Acquir Immune Defic Syndr*. 2001; 28:59-64.

(190) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *J Acquir Immune Defic Syndr*. 2001; 28:264-269.

(191) Xia Q, Osmond DH, Tholandi M *et al*. HIV Prevalence and Sexual Risk Behaviors Among Men Who Have Sex With Men: Results From a Statewide Population-Based Survey in California. *J Acquir Immune Defic Syndr*. 2006; 41:238-245.

(192) Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men--San Francisco and Los Angeles, California, 1998-2002. *MMWR Morb Mortal Wkly Rep*. 2004; 53:575-578.

(193) Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men--San Francisco, California, 1994-1997. *MMWR Morb Mortal Wkly Rep*. 1999; 48:45-48.

(194) California AIDS Clearinghouse. San Diego County Statistics. http://www.hivinfo.org/directory05/sandiego05.html . 2005. (Electronic Citation)

(195) County of San Diego Health and Human Services Agency. HIV/AIDS Epidemiology Report. 2005. San Diego, County of San Diego. (Report)

(196) UNAIDS. Methods and assumptions for HIV estimates. UNAIDS website . 2005. (Electronic Citation) Accessed 9 January 2006

(197) UNAIDS. Understanding the latest estimates of the global AIDS epidemic-November 2005. UNAIDS Website . 2005. (Electronic Citation) Accessed 26 January 2006.

(198) Pisani E, Lazzari S, Walker N *et al*. HIV surveillance: a global perspective. *J Acquir Immune Defic Syndr*. 2003; 32 Suppl 1:S3-11.

(199) Fleming P, Byers RH, Sweeney PA, Daniels D, Karon JM, Janssen RS. HIV prevalence in the Unites States, 2000 [Abstract}. 9th Conference on Retroviruses and Opportunistic Infections, Seattle, Washington, February 24-28. 2002. (Abstract)

(200) Centers for Disease Control and Prevention. HIV prevalence, unrecognized infection, and HIV testing among men who hav sex with men- five U.S. cities June 2004- April 2005. *Morbidity and Mortaility Weekely Report*. 2005; 54:597-601.

(201) Grusky O, Roberts KJ, Swanson AN *et al*. Anonymous versus confidential HIV testing: client and provider decision making under uncertainty. *AIDS Patient Care STDS*. 2005; 19:157-166.

(202) Spielberg F, Branson BM, Goldbaum GM *et al*. Overcoming barriers to HIV testing: preferences for new strategies among clients of a needle exchange, a sexually transmitted disease clinic, and sex venues for men who have sex with men. *J Acquir Immune Defic Syndr*. 2003; 32:318-327.

(203) Centers for Disease Control and Prevention. HIV/AIDS surveillance report: cases of HIV infection and AIDS in the United States, 2004. Volume 16. 2005. Atlanta, US Department od Health and Human Services. (Report)

(204) Wortley PM, Chu ST, Diaz t. HIV testing patterns: where, why, and when were persons with AIDS tested for HIV? *AIDS*. 1995; 9:487-492.

(205) Centers for Disease Control and Prevention. Late versus early testing of HIV-16 sites, United States 2000-2003. *Morbidity and Mortaility Weekely Report*. 2003; 52:581-586.

(206) del Romero J, Castilla J, Garcia S *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988--2000. *AIDS*. 2001; 15:1319-1321.

(207) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *J Acquir Immune Defic Syndr*. 2001; 28:59-64.

(208) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *J Acquir Immune Defic Syndr*. 2001; 28:264-269.

(209) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(210) Dukers NH, Spaargaren J, Geskus RB *et al*. HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. *AIDS*. 2002; 16:F19-F24.

(211) Vu MQ, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002; 31:188-201.

(212) Weinstock H, Dale M, Gwinn M *et al*. HIV seroincidence among patients at clinics for sexually transmitted diseases in nine cities in the United States. *J Acquir Immune Defic Syndr*. 2002; 29:478-483.

(213) Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1145-1148.

(214) Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men--North Carolina, 2003. *MMWR Morb Mortal Wkly Rep*. 2004; 53:731-734.

(215) Kihara M, Ono-Kihara M, Feldman MD *et al*. HIV/AIDS surveillance in Japan, 1984-2000. *J Acquir Immune Defic Syndr*. 2003; 32 Suppl 1:S55-S62.

(216) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(217) Centers for Disease Control and Prevention. Outbreak of primary and secondary syphilis--Guilford County, North Carolina, 1996-1997. *MMWR Morb Mortal Wkly Rep*. 1998; 47:1070-1073.

(218) Centers for Disease Control and Prevention. Resurgent bacterial sexually transmitted disease among men who have sex with men--King County, Washington, 1997-1999. *MMWR Morb Mortal Wkly Rep*. 1999; 48:773-777.

(219) Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men--San Francisco, California, 1994-1997. *MMWR Morb Mortal Wkly Rep*. 1999; 48:45-48.

(220) Fox KK, del Rio C, Holmes KK *et al*. Gonorrhea in the HIV era: a reversal in trends among men who have sex with men. *Am J Public Health*. 2001; 91:959-964.

(221) Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men--New York City, 2001. *MMWR Morb Mortal Wkly Rep*. 2002; 51:853-856.

(222) Rietmeijer CA, Patnaik JL, Judson FN *et al*. Increases in gonorrhea and sexual risk behaviors among men who have sex with men: A 12-year trend analysis at the Denver Metro Health Clinic. *Sexually Transmitted Diseases*. 2003; 30:562-567.

(223) Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1117-1120.

(224) D'Souza G, Lee JH, Paffel JM. Outbreak of syphilis among men who have sex with men in Houston, Texas. Sexually Transmitted Diseases 30[12], 872-873. 2003. (Abstract)

(225) Centers for Disease Control and Prevention. Internet use and early syphilis infection among men who have sex with men--San Francisco, California, 1999-2003. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1229-1232.

(226) Centers for Disease Control and Prevention. Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men--United States, 2003, and revised recommendations for gonorrhea treatment, 2004. *MMWR Morb Mortal Wkly Rep*. 2004; 53:335-338.

(227) Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men--San Francisco and Los Angeles, California, 1998-2002. *MMWR Morb Mortal Wkly Rep*. 2004; 53:575-578.

(228) Hopkins S, Lyons F, Coleman C *et al*. Resurgence in infectious syphilis in Ireland - An epidemiological study. *Sexually Transmitted Diseases*. 2004; 31:317-321.

(229) Williams LA, Klausner JD, Whittington WLH *et al*. Elimination and reintroduction of primary and secondary syphilis. *American Journal of Public Health*. 1999; 89:1093-1097.

(230) Stolte IG, Dukers NH, de Wit JB *et al*. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. *Sex Transm Infect*. 2001; 77:184-186.

(231) Ekstrand ML, Stall RD, Paul JP *et al*. Gay men report high rates of unprotected anal sex with partners of unknown or discordant HIV status. *AIDS*. 1999; 13:1525-1533.

(232) Elford J, Bolding G, Sherr L. High-risk sexual behaviour increases among London gay men between 1998 and 2001: what is the role of HIV optimism? *AIDS*. 2002; 16:1537-1544.

(233) Katz MH, Schwarcz SK, Kellogg TA *et al*. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health*. 2002; 92:388-394.

(234) Rosser BRS, Bockting WO, Rugg DL *et al*. A Randomized controlled intervention trial of a sexual health approach to long-term HIV risk reduction for men who have sex with men: Effects of the intervention on unsafe sexual behavior. *AIDS Education and Prevention*. 2002; 14:59-71.

(235) Van de Ven P, Rawstorne P, Crawford J *et al*. Increasing proportions of Australian gay and homosexually active men engage in unprotected anal intercourse with regular and casual partners. *AIDS Care*. 2002; 14:335-341.

(236) Chen SY, Gibson S, Weide D *et al*. Unprotected anal intercourse between potentially HIV-serodiscordant men who have sex with men, San Francisco. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:166-170.

(237) Wohl AR, Johnson DF, Lu S *et al*. Recent increase in high-risk sexual behaviors among sexually active men who have sex with men living with AIDS in Los Angeles County. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:209-211.

(238) Stolte IG, Dukers NH, Geskus RB *et al*. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS*. 2004; 18:303-309.

(239) Wolitski RJ, Valdiserri RO, Denning PH *et al*. Are we headed for a resurgence of the HIV epidemic among men who have sex with men? *Am J Public Health*. 2001; 91:883-888.

(240) Vu MQ, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002; 31:188-201.

(241) Becker MH, Joseph JG. AIDS and behavioral change to reduce risk: a review. *American Journal of Public Health*. 1988; 78:394-410.

(242) Moatti JP, Dab W, Abenham L *et al*. Modifications of sexual-behavior related to AIDS - a survey in the Paris region. *Health Policy*. 1989; 11:15-30.

(243) Winkelstein W, Wiley JA, Padian NS *et al*. The San Francisco men's health study: continued decline in HIV seroconversion rates among homosexual/bisexual men. *American Journal of Public Health*. 1988; 78:1472-1474.

(244) Winkelstein W, Samuel M, Padian NS *et al*. The San Francisco mens health study 3: reduction in human-immunodeficiency-virus transmission among homosexual and bisexual men, 1982-86. *American Journal of Public Health*. 1987; 77:685-689.

(245) Blower SM, van Griensven GJP. Effect of differential mortality on risk-behavior change in cohort studies. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1993; 6:1364-1367.

(246) Chesson HW, Dee TS, Aral SO. AIDS mortality may have contributed to the decline in syphilis rates in the United States in the 1990s. *Sexually Transmitted Diseases*. 2003; 30:419-424.

(247) Vu MQ, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002; 31:188-201.

(248) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(249) del Romero J, Castilla J, Garcia S *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988--2000. *AIDS*. 2001; 15:1319-1321.

(250) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *J Acquir Immune Defic Syndr*. 2001; 28:59-64.

(251) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *J Acquir Immune Defic Syndr*. 2001; 28:264-269.

(252) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(253) Weinstock H, Dale M, Gwinn M *et al*. HIV seroincidence among patients at clinics for sexually transmitted diseases in nine cities in the United States. *J Acquir Immune Defic Syndr*. 2002; 29:478-483.

(254) Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1145-1148.

(255) Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men--North Carolina, 2003. *MMWR Morb Mortal Wkly Rep*. 2004; 53:731-734.

(256) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *J Acquir Immune Defic Syndr*. 2001; 28:59-64.

(257) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *J Acquir Immune Defic Syndr*. 2001; 28:264-269.

(258) Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men--North Carolina, 2003. *MMWR Morb Mortal Wkly Rep*. 2004; 53:731-734.

(259) Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1145-1148.

(260) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(261) del Romero J, Castilla J, Garcia S *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988--2000. *AIDS*. 2001; 15:1319-1321.

(262) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(263) Koblin B, Chesney M, Coates T. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. *Lancet*. 2004; 364:41-50.

(264) Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 1999. *MMWR Morb Mortal Wkly Rep*. 2001; 50:113-117.

(265) Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1117-1120.

(266) Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men--San Francisco and Los Angeles, California, 1998-2002. *MMWR Morb Mortal Wkly Rep*. 2004; 53:575-578.

(267) Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1117-1120.

(268) Centers for Disease Control and Prevention. Outbreak of primary and secondary syphilis- Gilford County, North Carolina, 1996-1997. *Morbidity and Mortality Weekly Report*. 1998; 47:1070-1073.

(269) Centers for Disease Control and Prevention. Resurgent bacterial sexually transmitted disease among men who have sex with men--King County, Washington, 1997-1999. *MMWR Morb Mortal Wkly Rep*. 1999; 48:773-777.

(270) Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men--New York City, 2001. *MMWR Morb Mortal Wkly Rep*. 2002; 51:853-856.

(271) Stolte IG, Dukers NH, de Wit JB *et al*. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. *Sex Transm Infect*. 2001; 77:184-186.

(272) County of San Diego Health and Human Services Agency. Sexually Transmitted Diseases Fact Sheet 1993-2004. http://www2.sdcounty.ca.gov/hhsa/documents/STDFactSheet2004.pdf. 2005. (Electronic Citation) Accessed 3 January 2006.

(273) Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sexually Transmitted Diseases*. 2000; 27:53-59.

(274) Fox KK, del Rio C, Holmes KK *et al*. Gonorrhea in the HIV era: a reversal in trends among men who have sex with men. *Am J Public Health*. 2001; 91:959-964.

(275) Centers for Disease Control and Prevention. Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men--United States, 2003, and revised recommendations for gonorrhea treatment, 2004. *MMWR Morb Mortal Wkly Rep*. 2004; 53:335-338.

(276) Stall RD, Hays RB, Waldo CR *et al*. The Gay '90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. *AIDS*. 2000; 14:S101-S114.

(277) Dewit JBF, Vandenhoek JAR, Sandfort TGM *et al*. Increase in Unprotected Anogenital Intercourse Among Homosexual Men. *American Journal of Public Health*. 1993; 83:1451-1453.

(278) Katz MH, Schwarcz SK, Kellogg TA *et al*. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health*. 2002; 92:388-394.

(279) Aral S. Elimination and reinterduction of sexually transmitted diseases: lessons to be learn? *American Journal of Public Health*. 1999; 89:995-997.

(280) Aral S, Hughes JP, Stoner B. Sexual mixing patterns in the spread of gonococcal and chlamydial infections. *American Journal of Public Health*. 1999; 89:825-833.

(281) Webster RD, Darrow WW, Paul JP. HIV infection and associated risks among young men who have sex with men in a Florida resort community. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:223-231.

(282) Choi KH, Han CS, Hudes ES *et al*. Unprotected sex and associated risk factors among young Asian and Pacific Islander men who have sex with men. *AIDS Educ Prev*. 2002; 14:472-481.

(283) Bingham TA, Harawa NT, Johnson DF *et al*. The effect of partner characteristics on HIV infection among African American men who have sex with men in the Young Men's Survey, Los Angeles, 1999-2000. *AIDS Educ Prev*. 2003; 15:39-52.

(284) Davidovich U, de Wit J, Albrecht N *et al*. Increase in the share of steady partners as a source of HIV infection: a 17-year study of seroconversion among gay men. *AIDS*. 2001; 15:1303-1308.

(285) Weber AE, Craib KJ, Chan K *et al*. Determinants of HIV serconversion in an era of increasing HIV infection among young gay and bisexual men. *AIDS*. 2003; 17:774-777.

(286) Katz MH, Schwarcz SK, Kellogg TA *et al*. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *American Journal of Public Health*. 2002; 92:388-394.

(287) Kelly JA, Hoffmann RC, Rompa D *et al*. Protease inhibitor combination therapies and perceptions of gay men regarding AIDS severity and the need to maintain safer sex. *AIDS*. 1998; 12:F91-F95.

(288) Vanable PA, Ostrow DG, McKirnan DJ *et al*. Impact of combination therapies on HIV risk perceptions and sexual risk among HIV-positive and HIV-negative gay and bisexual men. *Health Psychology*. 2000; 19:134-145.

(289) Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA*. 2004; 292:224-236.

(290) Adams AL, Becker TM, Lapidus JA *et al*. HIV infection risk, behaviors, and attitudes about testing - Are perceptions changing? *Sexually Transmitted Diseases*. 2003; 30:764-768.

(291) Dilley JW, Woods WJ, Sabatino J *et al*. Changing sexual behavior among gay male repeat testers for HIV: a randomized, controlled trial of a single-session intervention. *J Acquir Immune Defic Syndr*. 2002; 30:177-186.

(292) Suarez T, Miller J. Negotiating risks in context: A perspective on unprotected anal intercourse and barebacking among men who have sex with men - Where do we go from here? *Archives of Sexual Behavior*. 2001; 30:287-300.

(293) Odets W. AIDS education and harm reduction for gay men: physcological approaches for the 21st century. *AIDS Public Policy Journal*. 1994; 9:1-15.

(294) Perdue T, Hagan H, Thiede H *et al*. Depression and HIV risk behavior among Seattle-area injection drug users and young men who have sex with men. *AIDS Educ Prev*. 2003; 15:81-92.

(295) Parsons JT, Halkitis PN, Wolitski RJ *et al*. Correlates of sexual risk behaviors among HIV-positive men who have sex with men. *AIDS Educ Prev*. 2003; 15:383-400.

(296) Myers HF, Javanbakht M, Martinez M *et al*. Psychosocial predictors of risky sexual behaviors in African American men: implications for prevention. *AIDS Educ Prev*. 2003; 15:66-79.

(297) Centers for Disease Control and Prevention. HIV/STD risks in young men who have sex with men who do not disclose their sexual orientation--six U.S. cities, 1994-2000. *MMWR Morb Mortal Wkly Rep*. 2003; 52:81-86.

(298) O'Donnell L, Agronick G, San Doval A *et al*. Ethnic and gay community attachments and sexual risk behaviors among urban Latino young men who have sex with men. *AIDS Educ Prev*. 2002; 14:457-471.

(299) Stall R, Mills TC, Williamson J *et al*. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. *Am J Public Health*. 2003; 93:939-942.

(300) Crosby R, DiClemente RJ, Mettey A. Correlates of recent unprotected anal sex among men having sex with men attending a large sex resort in the South. *Sex Transm Dis*. 2003; 30:909-913.

(301) Mettey A, Crosby R, DiClemente RJ *et al*. Associations between internet sex seeking and STI associated risk behaviours among men who have sex with men. *Sex Transm Infect*. 2003; 79:466-468.

(302) Centers for Disease Control and Prevention. Internet use and early syphilis infection among men who have sex with men - San Fransisco, California, 1999-2003. *Morbidity and Mortality Weekly Report*. 2003; 52:1229-1233.

(303) Choi KH, McFarland W, Neilands TB *et al*. An opportunity for prevention: prevalence, incidence, and sexual risk for HIV among young Asian and Pacific

Islander men who have sex with men, San Francisco. *Sex Transm Dis*. 2004; 31:475-480.

(304) Page-Shafer K, Shiboski CH, Osmond DH *et al*. Risk of HIV infection attributable to oral sex among men who have sex with men and in the population of men who have sex with men. *AIDS*. 2002; 16:2350-2352.

(305) Centers for Disease Control and Prevention. Internet use and early syphilis infection among men who have sex with men--San Francisco, California, 1999-2003. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1229-1232.

(306) Fernyak SE, Page-Shafer K, Kellogg TA *et al*. Risk behaviors and HIV incidence among repeat testers at publicly funded HIV testing sites in San Francisco. *J Acquir Immune Defic Syndr*. 2002; 31:63-70.

(307) Centers for Disease Control and Prevention. A Cluster of Kaposi's Sarcoma and Pneumocystis carinii Pneumonia among Homosexual Male Residents of Los Angeles and range Counties, California. *Morbidity and Mortality Weekly Report*. 1982; 31:305-307.

(308) Detels R, Fahey JL, Schwartz K *et al*. Relation between sexual practices and T-cell subsets in homosexually active men. *Lancet*. 1983; 1:609-611.

(309) Jaffe HW, Hardy AM, Morgan WM *et al*. The acquired immunodeficiency syndrome in gay men. *Ann Intern Med*. 1985; 103:662-664.

(310) Weller IVD, Carne CA, Sattentau Q *et al*. Human-Immunodeficiency-Virus (HIV) Infection in the Regular Sexual Partners of Homosexual Men with AIDS and Persistent Generalized Lymphadenopathy. *Journal of Medical Virology*. 1987; 22:91-98.

(311) Kingsley LA, Detels R, Kaslow R *et al*. Risk factors for seroconversion to human immunodeficiency virus among male homosexuals. Results from the Multicenter AIDS Cohort Study. *Lancet*. 1987; 1:345-349.

(312) Buchbinder SP, Vittinghoff E, Heagerty PJ *et al*. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2005; 39:82-89.

(313) Degruttola V, Seage GR, Mayer KH *et al*. Infectiousness of HIV Between Male-Homosexual Partners. *Journal of Clinical Epidemiology*. 1989; 42:849-856.

(314) Valle SL. Sexually transmitted diseases and the use of condoms in a cohort of homosexual men followed since 1983 in Finland. *Scand J Infect Dis*. 1988; 20:153-161.

(315) Marmor M, Laubenstein L, William DC *et al*. Risk factors for Kaposi's sarcoma in homosexual men. *Lancet*. 1981; 319:1083-1087.

(316) Goedert JJ, Wallen WC, Mann DL *et al*. Amyl nitrite may alter T lymphocytes in homosexual men. *Lancet*. 1981; 319:412-416.

(317) Morabia A. Poppers, Kaposi's sarcoma, and HIV infection: empirical example of a strong confounding effect? *Prev Med*. 1995; 24:90-95.

(318) Doll LS, Byers RH, Bolan G *et al*. Homosexual Men Who Engage in High-Risk Sexual-Behavior - A Multicenter Comparison. *Sexually Transmitted Diseases*. 1991; 18:170-175.

(319) Stall R, McKusick L, Wiley J *et al*. Alcohol and drug use during sexual activity and compliance with safe sex guidelines for AIDS: the AIDS Behavioral Research Project. *Health Educ Q*. 1986; 13:359-371.

(320) Woody GE, VanEtten-Lee ML, McKirnan D *et al*. Substance use among men who have sex with men: comparison with a national household survey. *J Acquir Immune Defic Syndr*. 2001; 27:86-90.

(321) Anonymous. Special report: club drugs & HIV. Drug treatment best hope for meth-using MSMs. Researchers want to get word out about problem. *AIDS Alert*. 2002; 17:137-8, 143.

(322) Anonymous. Methamphetamine use is heightening risks among gay youth. 'Club drugs' dull safe-sex sensibilities. *AIDS Alert*. 2002; 17:121, 123-121, 125.

(323) Berger DS. Crystal methamphetamine and HIV--a catastrophe. *Posit Aware*. 2004; 15:43-45.

(324) Boddiger D. Metamphetamine use linked to rising HIV transmission. *Lancet*. 2005; 365:1217-1218.

(325) Anonymous. HIV-STD synergy worries public health officials. Drugs, Viagra play role in problem. *AIDS Alert*. 2004; 19:81-83.

(326) Breslau K. The 'sextasy' craze. Clubland's dangerous party mix: Viagra and ecstasy. *Newsweek*. 2002; 139:30.

(327) Crosby R, Diclemente RJ. Use of recreational Viagra among men having sex with men. *Sex Transm Infect*. 2004; 80:466-468.

(328) Vu MQ, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002; 31:188-201.

(329) Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1145-1148.

(330) Colfax GN, Mansergh G, Guzman R *et al*. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr*. 2001; 28:373-379.

(331) Colfax G, Vittinghoff E, Husnik MJ *et al*. Substance use and sexual risk: A participant- and episode-level analysis among a cohort of men who have sex with men. *American Journal of Epidemiology*. 2004; 159:1002-1012.

(332) Rusch M, Lampinen TM, Schilder A *et al*. Unprotected anal intercourse associated with recreational drug use among young men who have sex with men depends on partner type and intercourse role. *Sex Transm Dis*. 2004; 31:492-498.

(333) Chu PL, McFarland W, Gibson S *et al*. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr*. 2003; 33:191-193.

(334) Hirshfield S, Remien RH, Humberstone M *et al*. Substance use and high-risk sex among men who have sex with men: a national online study in the USA. *AIDS Care*. 2004; 16:1036-1047.

(335) Mulry G, Kalichman SC, Kelly JA. Substance Use and Unsafe Sex Among Gay Men - Global Versus Situational Use of Substances. *Journal of Sex Education & Therapy*. 1994; 20:175-184.

(336) Strathdee SA, Hogg RS, Martindale SL *et al*. Determinants of sexual risk-taking among young HIV-negative gay and bisexual men. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998; 19:61-66.

(337) Woody GE, Donnell D, Seage GR *et al*. Non-injection substance use correlates with risky sex among men having sex with men: data from HIVNET. *Drug Alcohol Depend*. 1999; 53:197-205.

(338) Clutterbuck DJ, Gorman D, McMillan A *et al*. Substance use and unsafe sex amongst homosexual men in Edinburgh. *AIDS Care*. 2001; 13:527-535.

(339) Ostrow DG, Beltran ED, Joseph JG *et al*. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. *J Subst Abuse*. 1993; 5:311-325.

(340) Hirshfield S, Remien RH, Walavalkar I *et al*. Crystal methamphetamine use predicts incident STD infection among men who have sex with men recruited online: A nested case-control study. *Journal of Medical Internet Research*. 2004; 6:42-49.

(341) Kim AA, Kent C, Klausner J. Risk facors for rectal gonococcal infection amidst resurgence in HIV transmission. *Sex Transm Dis*. 2003; 30:813-817.

(342) Tabet SR, Krone MR, Paradise MA *et al*. Incidence of HIV and sexually transmitted diseases (STD) in a cohort of HIV-negative men who have sex with men (MSM). *AIDS*. 1998; 12:2041-2048.

(343) Chmiel J, Detels R, Kaslow RA *et al*. Factors associated with prevalent HIV infection in the multicenter AIDS cohort. *American Journal of Epidemiology*. 1997; 126:568-577.

(344) Molitor F, Truax SR, Ruiz JD *et al*. Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. *Western Journal of Medicine*. 1998; 168:93-97.

(345) Harawa NT, Greenland S, Bingham TA *et al*. Associations of race/ethnicity with HIV prevalence and HIV-related behaviors among young men who have sex with men in 7 urban centers in the United States. *JAIDS-Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:526-536.

(346) Moss AR, Osmond D, Bacchetti P *et al*. Risk factors for AIDS and HIV seropositivity in homosexual men. *Am J Epidemiol*. 1987; 125:1035-1047.

(347) Seage GR, III, Mayer KH, Horsburgh CR, Jr. *et al*. The relation between nitrite inhalants, unprotected receptive anal intercourse, and the risk of human immunodeficiency virus infection. *Am J Epidemiol*. 1992; 135:1-11.

(348) Burcham JL, Tindall B, Marmor M *et al*. Incidence and risk factors for human immunodeficiency virus seroconversion in a cohort of Sydney homosexual men. *The Medical Journal of Australia*. 1989; 150:634-639.

(349) Page-Shafer K, Veugelers PJ, Moss AR *et al*. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994. *Am J Epidemiol*. 1997; 146:531-542.

(350) Chesney MA, Barrett DC, Stall R. Histories of substance use and risk behavior: Precursors to HIV seroconversion in homosexual men. *American Journal of Public Health*. 1998; 88:113-116.

(351) Ostrow DG, DiFranceisco WJ, Chmiel JS *et al*. A case-control study of human immunodeficiency virus type 1 seroconversion and risk-related behaviors in the Chicago MACS/CCS Cohort, 1984-1992. Multicenter AIDS Cohort Study. Coping and Change Study. *Am J Epidemiol*. 1995; 142:875-883.

(352) Ekstrand ML, Stall RD, Paul JP *et al*. Gay men report high rates of unprotected anal sex with partners of unknown or discordant HIV status. *AIDS*. 1999; 13:1525-1533.

(353) Buchbinder S, Vittinghoff E, Heagerty P *et al*. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 39:82-89.

(354) Colfax G, Coates TJ, Husnik MJ *et al*. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health*. 2005; 82:i62-i70.

(355) Stall RD, Paul JP, Greenwood GL *et al*. Alcohol use, drug use and alcohol-realted problems among men who have sex with men: the Urban Men's Health Study. *Addiction*. 2001; 96:1589-1601.

(356) Greenwood GL, White EW, Page-Shafer K *et al*. Correlates of heavy substance use among young gay and bisexual men: The San Francisco Young Men's Health Study. *Drug and Alcohol Dependence*. 2001; 61:105-112.

(357) Patterson TL, Semple SJ, Zians JK *et al*. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:I120-I126.

(358) Aldridge J, Measham F. Sildenafil (Viagra) is used as a recreational drug in England. *British Medical Journal*. 1999; 318:669.

(359) Anonymous. HIV-STD synergy worries public health officials. Drugs, Viagra play role in problem. *AIDS Alert*. 2004; 19:81-83.

(360) Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS*. 2002; 16:1425-1428.

(361) Sherr L, Bolding G, Maguire M. Viagra use and sexual risk behavior among gay men in London. *AIDS*. 2000; 14:2051-2052.

(362) Swearingen SG, Klausner JD. Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection. *American Journal of Medicine*. 2005; 118:571-577.

(363) National Institutes on Drug Abuse. NIDA info facts: nationwide trends. 2004. Bethesda, US Department of Health and Human Services. (Report)

(364) United States Drug Enforcement Administration. DEA State Facts Sheet: California. http://www.dea.gov/pubs/states/california.html. 2005. (Electronic Citation) Accessed 9 January 2006.

(365) HILL AB. The environment and disease: associations or causation? *Proceedings of the Royal Society of Medicine*. 1965; 58:295-300.

(366) del Romero J, Castilla J, Garcia S *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988--2000. *AIDS*. 2001; 15:1319-1321.

(367) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *J Acquir Immune Defic Syndr*. 2001; 28:59-64.

(368) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *J Acquir Immune Defic Syndr*. 2001; 28:264-269.

(369) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(370) Weinstock H, Dale M, Gwinn M *et al*. HIV seroincidence among patients at clinics for sexually transmitted diseases in nine cities in the United States. *J Acquir Immune Defic Syndr*. 2002; 29:478-483.

(371) Centers for Disease Control and Prevention. Increases in HIV diagnoses--29 States, 1999-2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1145-1148.

(372) Centers for Disease Control and Prevention. HIV transmission among black college student and non-student men who have sex with men--North Carolina, 2003. *MMWR Morb Mortal Wkly Rep*. 2004; 53:731-734.

(373) Centers for Disease Control and Prevention. Outbreak of primary and secondary syphilis--Guilford County, North Carolina, 1996-1997. *MMWR Morb Mortal Wkly Rep*. 1998; 47:1070-1073.

(374) Centers for Disease Control and Prevention. Resurgent bacterial sexually transmitted disease among men who have sex with men--King County, Washington, 1997-1999. *MMWR Morb Mortal Wkly Rep*. 1999; 48:773-777.

(375) Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men--San Francisco, California, 1994-1997. *MMWR Morb Mortal Wkly Rep*. 1999; 48:45-48.

(376) Stolte IG, Dukers NH, de Wit JB *et al*. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. *Sex Transm Infect*. 2001; 77:184-186.

(377) Fox KK, del Rio C, Holmes KK *et al*. Gonorrhea in the HIV era: a reversal in trends among men who have sex with men. *Am J Public Health*. 2001; 91:959-964.

(378) Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men--New York City, 2001. *MMWR Morb Mortal Wkly Rep*. 2002; 51:853-856.

(379) Centers for Disease Control and Prevention. Primary and secondary syphilis--United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1117-1120.

(380) Centers for Disease Control and Prevention. Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men--United States, 2003, and revised recommendations for gonorrhea treatment, 2004. *MMWR Morb Mortal Wkly Rep*. 2004; 53:335-338.

(381) Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men--San Francisco and Los Angeles, California, 1998-2002. *MMWR Morb Mortal Wkly Rep*. 2004; 53:575-578.

(382) Centers for Disease Control and Prevention. Internet use and early syphilis infection among men who have sex with men--San Francisco, California, 1999-2003. *MMWR Morb Mortal Wkly Rep*. 2003; 52:1229-1232.

(383) Katz MH, Schwarcz SK, Kellogg TA *et al*. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health*. 2002; 92:388-394.

(384) Stolte IG, Dukers NH, Geskus RB *et al*. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS*. 2004; 18:303-309.

II. MANSCRIPT 1

Club Drugs as Causal Risk Factors for HIV Acquisition among MSM: A Review

A. Abstract

We reviewed medical and psychology databases for articles demonstrating associations between HIV/STI risk and club drugs published between January 1980 and August 2005. Seventy-four articles were reviewed, of which 30 provided adjusted risk-ratios for associations between HIV/STI risk and club drug use among men who have sex with men. Definitions and lists of club drugs were broad and inconsistent. We constructed a theoretical framework of biologically plausible pathways for causation. Using Hill's criteria to examine club drugs as causal risk factors for HIV, we found the most evidence for methamphetamine and volatile nitrites; however more studies are needed.

B. Introduction

In many developed countries, human immunodeficiency virus type 1 (HIV) continues to disproportionately affect men who have sex with men (MSM) [1-6]. During the late 1980's and early to mid 1990's, there were reports of declining or stabilizing HIV incidence among MSM in the United States [7-10], Europe [11;12], Canada [3] and Australia [4]. This decline was attributed to a shift to less risky behavior [8;13;14] and death due to AIDS [15-17]. However, in recent years, there have been reports of increasing incidence of HIV [5;18-25] and sexually transmitted infections (STI) [26-39], and increased reports of risky sexual behavior among MSM [40-47]. Increased risk-taking behavior appears to be due in part to reduced concern surrounding HIV/AIDS coinciding with the advent of highly active anti-retroviral therapy (HAART) in 1996 [39;48;49]; however, increases in risky behavior were observed among MSM in Amsterdam as early as 1993 [50].

Recent concern has focused on the use of 'club' drugs among MSM such as methamphetamine, ketamine, and gamma-hydroxybutyrate (GHB), and on the role of these drugs as risk factors for HIV transmission [51-57]. The use of club drugs has been reported among MSM in the United States [54], Canada [58], Western Europe [59] and Australia [51]. The association between club drug use and HIV is complex, and involves many different facets of social, physical and psychological health. Club drugs can be administered through many routes including ingestion, inhalation and injection, and some are even used as a rectal suppository. Different definitions have been used to describe club drugs, and patterns of use may change over time as specific drugs move in and out of style. Psychosocial factors associated with both drug use and HIV risk behaviors further complicate the ability of researchers to disentangle causal relationships between drug use and HIV acquisition. In this review, we address the

potential role of club drugs as independent risk factors for HIV infection, applying Hill's criteria for causation [60]. We propose a theoretical framework which demonstrates potential pathways through which these drugs could be associated with HIV acquisition and discuss definitions that have previously been ascribed to club drugs. Finally, we discuss factors that confound the nature of the true associations, and summarize future research needs.

C. Methods

From December 2004 to August 2005, we completed an extensive literature search on club drugs and risk for HIV and STI acquisition among MSM. A range of electronic databases and search engines that contain psychology, medical, and biological references were used, including: Medline (Pubmed); The Web of Science; Science Direct; PsychINFO; and ArticleFirst. Keywords and terms for drugs included: club drugs; substance use; substance abuse; methamphetamine; methylendioxymethamphetamine, MDMA or ecstasy; ketamine; gamma-hydroxybutyrate or GHB; Rohypnol® or flunitrazepam; lysergic acid diethylamide or LSD; volatile nitrites, amyl nitrites, nitrites, or 'poppers'; and Viagra® or sildenafil. These terms were used in combination with the following keywords: HIV; sexually transmitted diseases or infections; STD; STI; men who have sex with men or MSM; gay men; homosexual men; bisexual men. Additionally, all reference lists from the articles obtained were reviewed for studies not already identified.

All articles examining drug use and STI/HIV risk among MSM identified through these methods were reviewed for content. Only peer-reviewed articles published in English were included. Only those articles providing multivariate analyses that included risk ratios between one of the defined club drugs and HIV, STI or HIV/STI risk factors,

such as unprotected anal intercourse (UAI), were considered in our assessment of causal associations. Additionally, studies examining risk among only drug using or HIV-positive populations were excluded from the assessment of causal associations. Hill's criteria [60] were applied to each drug to determine if sufficient evidence was available to classify each drug as a causal risk factor for HIV infection. Where applicable we tried to quantify quality of evidence for Hill's criteria. Very poor evidence to meet criterion was assigned if there were two or fewer studies providing evidence or fewer than 50% of studies provided evidence of the criterion. Some evidence to meet criterion was assigned if 50 to 70% of studies provided evidence of the criterion or there was some biological support for the criterion. Good evidence to meet criterion was assigned if 70 to 90% of studies provided evidence of the criterion or there was good biological support for the criterion. For strength of association, studies providing risk ratios of two or greater were considered sufficient to include in percent meeting criteria. However, not all criteria could be quantified and are therefore based on expert opinion.

D. Results

A total of 74 articles addressing HIV/STI risk and club drugs among MSM were identified and reviewed for content. When potential associations between club drug use and HIV/STI risk were considered, 44 papers were excluded. Eighteen papers did not provide sufficient risk ratio information; four examined club drug use among HIV positive MSM only; two examined HIV risk among drug users only; two were qualitative studies; four applied definitions that were not exclusive to particular drugs (e.g., 'uppers') and 14 were review articles. Overall, 30 articles met the above criteria and were considered in evaluation of causal associations between club drugs and HIV/STI risk.

Definitions of club drugs

Despite an increasing body of literature there are still no clear and consistent definitions or drug lists among studies; others have noted this inconsistency [61;62], and have referred to the term 'club drug' as "amorphous" [63]. Early studies [64] described club drugs as 'dance' or 'party' drugs (Table 1). Later studies expanded this definition to include situations in which these drugs were used, such as "drugs used at 'raves' or all night dance parties" [65;66]. Simons *et al.* described club drugs among college students, as "a loosely defined category of drugs from different classes… grouped due to their use at dance clubs and raves" [67]. Definitions were sometimes based on populations that reported use of a particular drug, such as "young people" [68;69] or "MSM" [70;71].

Although overlap was noted, 21 different sources, including government agencies, review articles and original research articles provided different definitions and lists of which drugs were considered club drugs or the most common club drugs (Table 1). Most often, club drugs included methylendioxymethamphetamine (MDMA), ketamine and GHB, while other sources included methamphetamine and cocaine. Some lists included legal substances, such as caffeine, while others included naturally occurring illicit drugs such as marijuana. None of these sources pointed to an authoritative source or a benchmark study previously establishing which drugs were club drugs.

Due to these inconsistencies in definitions, we used the current National Institute on Drug Abuse (NIDA) club drug list as a guide to which drugs are considered club drugs, even though this list differed from other government sources [61;69]. NIDA provides a list of the following drugs in documents [72] and websites [68;73] pertaining to club drugs: methamphetamine, MDMA, GHB, ketamine, flunitrazepam (Rohypnol®), and lysergic acid diethylamide (LSD). This drug list was most often framed in terms of

teen club drug use but lacked two potentially important ‘party’ or ‘sex’ drugs reportedly used among some groups of MSM, namely volatile nitrites and sildenafil citrate (Viagra®). Therefore, we expanded the NIDA list by including these two additional drugs.

We used the following criteria in our efforts to establish a definition that included our list of club drugs: drug class, physiological effects, mode of administration, method of production, legal standing, situation of use, populations which used the drug, social effects, myths or perceptions of effects by users, and periodicity of use (Table 2). Few of the drugs provided in any of the lists had the same physiological effects on the body (Table 3) [62]. Additionally, modes of administration vary within and between these drugs (e.g., methamphetamine is injected, snorted and swallowed [74] and volatile nitrites are inhaled); not all are produced synthetically (e.g., LSD is a product of ergot [75]); and some are illegal substances (e.g., methamphetamine) while others are legally controlled substances (e.g., sildenafil citrate). Characteristics that many of these drugs shared in common included: association with party, dance or club scenes; they have a reputation for being relatively ‘safe’ among users and are not listed among ‘hard’ drugs; they are often used in combination with one another; they have a perceived effect of enhancing social and/or sexual competence among users; and use has been more commonly reported in the literature among teens and MSM, although this appears to be changing [76].

Common traits did not provide sufficient inclusion/exclusion criteria to create a consistent definition of club drugs. In particular, period and regional differences may affect whether a given drug is considered a club drug. Drugs of choice may change over time due to availability [77;78], price, formulation and other market factors, and may differ from region to region (e.g., methamphetamine and amphetamine are more

commonly reported in the western part of the United States and cocaine and heroin are more common in the eastern region [79;80]). If one chooses to use the situational definition, the list of drugs which may be considered club drugs will change both over time and by region. If drugs are classified by population beliefs in safety, the list may be reduced by changing beliefs and awareness. People who use different types of 'club' drugs have very different characteristics and may not belong to the same populations [81;82]. We therefore suggest that 'club' drugs may not be a definitive group or class of drugs and research should focus on particular drugs rather than a classification of drugs such as 'club' drugs.

Theoretical Model for Club Drug Use as a Risk Factor HIV/STDs

A range of plausible pathways in which drugs could serve as risk factors for HIV/STI infection have been proposed through both quantitative and qualitative studies. Theoretically, one can consider risks in two categories: the direct effects of the drug, and the behaviors resulting from these effects. Figure 1 describes the potential pathways in which drug use may contribute to risk of HIV and/or STI acquisition. We have limited the number of potential pathways to those where there is some evidence of biologic plausibility based on our review of the literature. On the left we depict the possible direct effects of the drug on the user, whereas the middle section describes the possible behaviors that may result from the corresponding effects. Note that a specific drug (e.g., methamphetamine) could have many possible direct effects (e.g. reduction in physical pain, altered mental state, increased sexual desires) which could result in one or more risk behaviors.

As described in Table 3, direct effects of club drugs may include; altered mental states or loss of muscle control (e.g. ketamine [83;84], GHB [66]); enhanced sexual

function (e.g. methamphetamine [85;86], sildenafil citrate [87-89]) or increased sexual/social desires and/or confidence (e.g. methamphetamine [70;90], MDMA [91]); vasodilation (e.g. volatile nitrites [92], sildenafil citrate [93;94]); or decreased sensation of pain (e.g. methamphetamine [70], volatile nitrites [95]). The way in which the drug is administered may carry additional risks for acquiring HIV or blood-borne infections, as in the case of injection drug use, due to the risk of parenteral transmission through multi-person use of injection equipment.

Although club drugs may have many effects, behaviors that elevate the risk of HIV/STI acquisition include: decreased condom use; increased number of partners, increased duration of sexual contact with the same partner, or both; increased tissue damage or increased likelihood of blood to blood or semen to blood contact; and the sharing of needles or ”works” (syringes, preparation containers, kits, water). Below, we discuss each of these potential pathways in turn.

Altered Mental State

Most club drugs cause some degree of temporary mental distortion (Table 3), ranging from impaired judgment [66;90] to sedation [66;84;90;96;97], loss of muscle control [83;95;96], and even memory loss [66;83;98]. Some have such strong effects on the user’s ability to process environmental stimuli and on muscle control and memory, that they have been reported as ‘date rape’ drugs (e.g., GHB, flunitrazepam and ketamine [83;98-101;101]). These mind and/or body altering effects may compromise the user’s ability to use or negotiate condom use.

Reduced Sensation of Pain

Some types of club drugs have been described as having the ability to decrease the sensation of pain. This may be an independent effect, or may be associated with altered mental state. The effect of decreased pain may result in the ability to have greater numbers of anal sex partners in a short period of time, longer duration of sexual activity, or even more physically traumatic sexual activity (e.g., “fisting”) which may result in increased tissue damage and increased risk of HIV and STI acquisition [102-105]. Qualitative reports indicate that drugs such as methamphetamine may be used in order to sustain more physically traumatic receptive anal intercourse [70]. Volatile nitrites have also been reported to ease the pain of receptive anal intercourse through relaxation of the sphincter muscles [95]. Additionally, drugs used in the medical setting as disassociative anesthetics, such as ketamine and GHB, could also have effects of decreasing physically painful experiences [66;83;106].

Enhanced Sexual Functioning

Enhanced sexual functioning, increased libido and increased confidence in obtaining sexual partners have been reported with the use of some club drugs [107] and pharmaceutical agents misused as club drugs (e.g., sildenafil citrate). Among men in general, increased sexual desire and ability to maintain longer than normal erections have been reported with use of low doses of amphetamine and methamphetamine [85;108], but the inability to have an erection has been reported at high doses [85]. Users of methamphetamine have also reported increased feelings of confidence, helping them to recruit sexual partners in public environments, such as bars, which may not occur in the absence of the drug [70;108]. Enhanced libido, feelings of closeness, and sexual desire have also been reported with use of MDMA and LSD [85;109;110].

In recent years, pharmaceutical agents such as sildenafil citrate (Viagra®), tadalafil (Cialis®), and vardenafil hydrochloride (Levitra®) have been marketed to help men overcome mental and physical erectile dysfunction. However, recent reports examining sildenafil citrate indicate that this substance is commonly misused as a recreational drug among many populations, including MSM, to enhance sexual abilities [59;111-113], and may be used in combination with other club drugs [114]. These drugs could increase amount or duration of sexual activity [115], which may result in localized trauma, thus increasing blood-to-blood or semen-to-blood contact

Vasodilation

Some club drugs (e.g., sildenafil citrate, volatile nitrites) can cause vasodilation. Vasodilation causes pooling of blood within the lower extremities and relaxation of the smooth muscles (Table 3). Increased availability of blood in the penis and rectal region due to vasodilation may result in increased exposure to blood during sexual contact [114]. Additionally, vasodilation may also increase the duration of an erection or the relaxation of rectal muscles, which could potentially result in increased numbers of sexual partners or increased duration of sexual activity for both the insertive and receptive partners during anal sex [116].

Injection Drug Use

Club drugs that can be injected include: methamphetamine, ketamine and GHB. Sharing of needles and ‘works’ carries a high risk for HIV transmission [117-119]. Reports of injection of methamphetamine appeared as early as 1968 [120;121]. Drug injection can result in the transmission of HIV and hepatitis B or C virus if needles or “works” are shared with an infected individual.

Are Club Drugs Simply a Marker for High-Risk Behavior?

While the theoretical framework presented provides plausible biological and social pathways in which club drugs could be causal risk factors for HIV seroconversion, it is also possible that drug use could be simply a marker for a risky personality type [122;123]. Some researchers have suggested that drugs may provide an excuse for unsafe sex or a 'time out' from practicing safer sexual behavior for some MSM [124;125]. Similarly, some suggest that MSM may take club drugs to 'escape' from self-monitoring of sexual activity [126-128]. A lack of impulse control or sensation seeking has also been associated with both drug use and HIV/STI risk behaviors [129-131]. Other studies have found that depression is associated both with drug use [132;133] and increased odds of HIV/STI risk behaviors [118;134;135]. In these cases, club drugs would be considered a confounder in the pathway between impulsivity or depression and HIV/STI acquisition. On the other hand, one could argue that some club drugs, such as MDMA [136], nitrites [137], methamphetamine [138] can lead to depression; although depression did not explain associations between illicit drug use and sexual risk in one study [139]. Additionally, risk taking behaviors associated with obtaining drugs that carry greater than normal risk for HIV/STI acquisition, such as trading sex for drugs [140-142], may be confounded with the actual use of the drug.

Leigh and Stall (1993) have observed that many studies of drug use and HIV risk behaviors suffer from the inability to distinguish drugs as risk factors for HIV/STI infection as opposed to markers for risk taking. They describe a hierarchy of classifications that can be used to weight studies in terms of demonstrating causal associations from low to high levels of rigor: 1) global associations between drug use and high-risk behaviors (i.e. drugs are used and high-risk behaviors are practiced); 2) situational associations, (i.e., frequency of drug use or drug use ever with sexual activity

is associated with frequency of risky behavior or risky behavior within a given time frame); 3) event level associations (i.e., drug use at a sexual event and risky sexual behavior at that event); and 4) event level case-crossover associations (i.e., event level associations are compared at a time in which risky behaviors did and did not occur using the same individual as his/her own control). In our review of the literature, we identified only two studies of event-level associations and one study of event-level crossover associations.

Evidence for Causal Associations

In 1965, Hill [60] proposed nine criteria to help researchers to determine the existence of causal relationships between risk factors and outcomes. These criteria include: strength of association; consistency between studies; temporality (the risk should proceed the outcome); biological gradient (dose-response relationship); biological plausibility; coherence (the proposed associations should not conflict with what is currently known about the natural history and biology of the outcome); experimental evidence supports the association (including cessation); analogy (the causative model is consistent with similar models and alternative explanations have been considered); and specificity (the risk must be the only cause of the outcome and the outcome only occurs in the presence of the risk). With the exception of specificity, which is no longer considered applicable [143;144], these criteria are still applied to gauge the preponderance of evidence in support of causal associations. In the case of drug use and HIV/STI acquisition, causal risk factors would be those described in our theoretical model; non-causal relationships would include drug use as a marker for risk taking or risky personalities, which would place individuals at the same risk for HIV/STI regardless of drug use. We applied Hill's eight criteria for causation [60], Leigh and

Stall's classification of studies on drug use and HIV risk [145] and our theoretical framework (Figure 1) to the 30 studies that met our criteria to determine if a causal relationship has been established for each type of club drug listed in Table 3. Below, we discuss the body of evidence for each drug in turn.

Methamphetamine and Amphetamine

In our theoretical framework, methamphetamine could be associated with elevated risk of HIV infection through multiple causal pathways. Commonly, methamphetamine users report increased libido [70;85;108;146], increased sexual function [115;147] and more sexual confidence [70;108;115] in association with use of this drug. Studies of the action of methamphetamine on the human body indicate that it results in altered mental states among users [90;148]. Some drug users have also reported decreased sensation of pain during receptive anal sex [70;115]. Lastly, methamphetamine is sometimes administered through injection [74;149-151].

Nine studies examining methamphetamine and five examining amphetamine as independent risk factors for HIV/STI acquisition that provided a multiply controlled risk ratio measure were reviewed (Table 4). Of these 14 studies, four were longitudinal, one was a case-control and nine were cross-sectional. In three of the longitudinal studies [152-154] , amphetamine use over the follow-up period was associated with at least a two-fold increased risk of HIV seroconversion. From a methodological perspective, longitudinal studies provide the best evidence that amphetamine use is temporally associated with HIV seroconversion. The remaining longitudinal analysis [155] demonstrated associations between methamphetamine use and UAI at a particular sexual encounter. This study also provides evidence for temporality, as drug use occurred before UAI.

All but two [71;156] of the nine cross-sectional studies demonstrated that either methamphetamine or amphetamine were consistently associated with the majority of risk behaviors or disease outcomes measured. Of the two studies that showed no association, one examined HIV prevalence [156], and the other collected data during a social event [71], which may be subject to misclassification as more sensitive behaviors in such settings may be under reported. Of the seven studies demonstrating positive associations, most had risk ratios above 1.5 with confidence intervals that excluded one.

A study of 337 MSM in San Francisco [154] demonstrated some evidence of dose-response relationships. In this longitudinal study, long-term amphetamine use was associated with HIV seroconversion (RR=2.89, 95% CI: 1.36-6.16), however a similar association was not observed for recent adoption of amphetamine use, suggesting that the longer one uses the drug, the more likely they are to seroconvert. Although no quantifiable amount of amphetamine use was presented, these data suggest that further investigation into a dose-response relationship is warranted.

A number of studies demonstrate that cessation of methamphetamine use results in a reduction in risky sexual behaviors [157;158]. Although more studies are needed to establish irrefutable evidence that methamphetamine is a causative risk factor for HIV, current evidence suggests that a causative relationship is likely to exist (Table 5). However, the pathways in which methamphetamine or amphetamine may lead to HIV/STI acquisition remain unclear and warrants further investigation.

Methylendioxymethamphetamine (MDMA)

MDMA is derived from methamphetamine and has similar properties and effects [66;159]. Like methamphetamine, there is biological plausibility that MDMA may

increase the risk of HIV/STI acquisition as described by our theoretical model (Figure 1). MDMA may alter one's mental state, enhance sexual function [110] and desires [109] and may possibly decrease sensation of pain. Administration of MDMA through injection is possible, but not commonly reported.

There is a growing body of literature investigating the role of MDMA as a risk factor for HIV/STI acquisition; however, we found only five studies that met our inclusion criteria of providing adjusted risk ratios (Table 4). Of these studies, two were longitudinal and three were cross-sectional. Only two [155;160] of these studies demonstrated an association between UAI and MDMA use, which makes a poor case for consistency and strength of association. Additionally, the longitudinal study which examined MDMA use prior to HIV seroconversion [152] showed no association between MDMA use and seroconversion and therefore did not provide evidence for the most important causal criterion, temporality. None of these studies demonstrated a dose-response relationship between MDMA and HIV/STI acquisition or risk behavior. Although one could argue for coherence and analogy, there are currently too few studies of MDMA to support evidence of a causative relationship (Table 5). However, data revealing associations between MDMA use immediately prior to sexual contact and increased risk of UAI [155] suggest that further investigation of this association is warranted.

Gamma-hydroxybutyrate (GHB)

GHB could be associated with HIV/STI acquisition through three of the pathways in our theoretical framework. GHB is classified as a disassociative anesthetic [66] (Table 3) and may therefore result in a reduced ability to experience pain [99]. This in turn could increase the risk of physically traumatic sexual activity or increase duration of

activity or increase number of partners while intoxicated (Figure 1). Additionally, GHB results in an altered mental state, which can lead to decreased condom use [99]. GHB can also be administered through injection [66].

Two cross-sectional and one longitudinal study that examined associations of GHB with HIV/STI risk met our criteria for inclusion (Table 4). In a study of 564 MSM recruited from San Francisco STI clinics, GHB use in the past two weeks was not associated with incident gonorrhea [161]. Among 1169 MSM who completed questionnaires at three different circuit parties in multiple locations in the United States, GHB use in the past 12 months was only marginally associated with UAI [71]. In the only longitudinal analysis to have examined GHB as a risk factor for UAI [155], GHB was associated with any UAI or insertive UAI, but only when used at the time of the sexual encounter. These data do not provide evidence for consistency, strength of association, temporality or a dose-response relationship. Available data suggest that GHB may not be a risk factor for HIV/STI infection, however more studies are needed to determine the status of the true association.

Ketamine

Ketamine is a disassociative anesthetic (Table 3) that causes sedation and loss of muscle control [84;90]. Due to these properties, ketamine carries the risk of loss of physical control which may result in unwanted or unplanned sexual contact [83]. Ketamine could also result in increased tolerance to pain [106], which may lead to more sexual partners, longer duration of sexual contact and increased physical trauma. Both factors could result in a higher risk of HIV or STI acquisition. Additionally, ketamine may be administered through injection and therefore also carries parenteral risks for HIV acquisition.

Despite growing concern about ketamine as a substance of abuse [81;162], only two studies met our criteria for inclusion, and they provide conflicting information. In a longitudinal study of 261 MSM in Vancouver [155] where 29 (11%) reported using ketamine, ketamine was associated with UAI or insertive UAI when used during sex or at any time. In contrast, a study of 1169 MSM who completed questionnaires at three different circuit parties in the United States, ketamine use at circuit parties over 12 months (reported by 60% of participants) was not associated with UAI during the same time period [71]. The first of these two studies included both global and event level analyses, whereas the second included a situational level analysis, which may contribute to some of the differences. Due to the discrepant findings, no causal inferences can be drawn from these data and further studies are needed to clarify the role of ketamine in sexual risk behavior.

Lysergic Acid Diethylamide (LSD)

In our theoretical framework, LSD would be a risk factor for HIV/STI acquisition through only one pathway (Table 3; Figure 1). The primary effect reported by users of LSD is hallucination, which may result in altering mental thoughts and choices, such as condom use [163].

Only one study was found which examined LSD and HIV/STI risk among MSM [155], although others reported on hallucinogen use in a non-specific manner [164-166]. In this study of 261 MSM from Vancouver, LSD was not associated with increased risk of UAI when used during sex or at any other time. However, in this sample, there was very little LSD use (n=26, or 10%). Since LSD is a commonly reported drug of abuse among MSM and youth [166-168], its role in HIV/STI transmission should be further assessed.

Flunitrazepam

Flunitrazepam has been reported to cause disorientation and dizziness which can result in an altered mental state [96;169], including amnesia, hypnosis and disinhibition [170], thereby exerting a potential influence on condom use or an increased number of sexual partners. Flunitrazepam is not a known vasodilator, nor has it been reported to increase sexual functioning, nevertheless several studies and reports have considered it a club drug [68;69;96;171-174].

No studies were found which examined associations between flunitrazepam use and HIV or STI risk among MSM. Additionally, data on flunitrazepam use among MSM was not found during our review of the literature. This may be due to the lack of popularity of flunitrazepam among MSM or the failure to examine its use in this population.

Erectile dysfunction medications (EDMs)

Only a small number of studies that examine associations between erectile dysfunction medications (EDMs) and risk for HIV/STIs have been published; however growing evidence suggests that EDMs are being used as recreational drugs among MSM [59;111-113]. There has also been growing concern about the use of EDMs in combination with club drugs [114;175-178]. All of the studies on risk and EDM examined associations with sildenafil citrate (Viagra®) because the other erectile dysfunction medications (e.g. Cialis®, Levitra®) were not yet available at the time of data collection. EDMs could increase the risk of HIV/STI acquisition through vasodilation or through increased sexual functioning. Additionally, if mixed with other club drugs, the user may also experience an altered mental state or decreased

sensation of pain. However, EDMs alone do not directly affect mental functioning [179;180].

Of ten studies on sildenafil citrate, all showed significant associations between use of sildenafil and HIV/STI risk behaviors, providing evidence of both consistency and strength of association. However, only five studies met our inclusion criteria since the remainder did not report adjusted risk ratios. Four studies examined risk behaviors among MSM and one examined risk behaviors of all men who were prescribed Viagra® at an HIV clinic. Two studies were conducted on MSM in San Francisco, one [181] demonstrated associations between UAI in the past 6 months and Viagra® use during that same time period (OR=2.45); the other [182] demonstrated associations between UAI and sildenafil use at circuit parties (OR=3.8). Additionally two studies using similar data of responses from Internet-using MSM revealed that Viagra® use was associated with UAI [183] or recent STI [184]. The remaining study among men attending an HIV clinic in San Diego [185] demonstrated associations between any sildenafil prescription written by the clinic in the past 12 months and unprotected, insertive intercourse (anal, vaginal and oral; OR= 3.0).

Nine of the ten sildenafil studies were cross-sectional, which does not allow for temporal inferences to be drawn. Studies meeting inclusion criteria either demonstrated an increase in risky sexual behavior or STI incidence by self-report, which may be suggestive of an increased risk of HIV acquisition, however, it is not sufficient to determine if sildenafil use is truly a risk factor for HIV transmission; longitudinal analyses are needed. Additionally, none of the pervious studies quantified amount or duration of use; without a measure of frequency of sildenafil use, it is difficult to establish evidence for a dose-response relationship.

Volatile nitrites

Volatile nitrites have a limited effect on the user's brain (Table 3). Instead of direct disorienting effects, volatile nitrites can cause both increased blood flow to the brain and a drop in blood pressure [92], resulting in dizziness. They do not directly increase sexual functioning, although they can relax anal sphincter muscles [92] and may reduce pain, which could result in increased duration of sexual activity or number of sexual partners. Additionally, volatile nitrites are vasodilators.

Volatile nitrites have been studied as potential risk factors for HIV infection throughout the HIV epidemic due to their widespread use among MSM [166-168]. In the beginning of the epidemic, some researchers posited a causal role between volatile nitrites and Kaposi's sarcoma [186]; however, this association is now considered to be confounded [186] by HIV status.

We found 17 studies that met our inclusion criteria, 13 demonstrated associations with acquisition of HIV/STI or risky sexual behavior and four did not, indicating good consistency and strength in association. In total, there were seven longitudinal studies, three case-control studies, and seven cross-sectional studies. Six of the seven of the longitudinal studies demonstrated associations between volatile nitrite use and an elevated incidence of STIs [187], HIV seroconversion [153;154;188], UAI with a sero-discordant or unknown status partner [45] or relapse in condom use during anal sex [168]; providing evidence for temporality. Additionally, those who reported volatile nitrite use over 6 years of follow-up [154] were more likely to have HIV seroconversion (RR=2.49, 1.24-4.93) than non-users or recent nitrite user who did not have increased risk of seroconversion over non-users (RR=0.70, 0.16-3.07). This represents weak evidence of a dose-response relationship. Moreover, nitrites are used

for receptive anal intercourse, which may be more risky for HIV acquisition than insertive anal intercourse [118;153;189-193].

Although there is evidence that nitrites may be causally associated with HIV risk, this is a highly debated topic. In a study of all substance users, comparing those who always had UAI and those who always have protected sex, regardless of the influence of drugs, those who always reported protected sex were more likely to report nitrite use [194]. The strongest evidence against nitrites as a causative risk factor for HIV/STI is that they do not effect the mental functioning of the user and therefore do not affect decision making. Hence, studies which employ event-level and event-level case-crossover methodologies to examine associations between nitrite use and UAI may be helpful in determining true causal relationship between HIV/STI and nitrites.

E. Discussion

The study of drugs as causative risk factors for HIV and STI acquisition is complex. Our review indicates the need for: 1) consensus among researchers about which drugs are considered ‘club’ drugs; 2) studies which examine different drugs individually, rather than grouping them as ‘club’ drugs; 3) prospective studies that include adequate control of confounders; 4) studies which address associations between drug use and unprotected sexual activity using event-level and case-crossover methodologies; 5) studies which examine dose-response relationships between drug use and HIV/STI and 6) improved measurement of the patterns of drug use, such as polydrug use.

One of the needs identified in this review was that of a consistent list of club drugs across studies and a more universal understanding that one definition may not encompass all of these drugs. This is important in both addressing research questions and avoiding misclassification. A recent study surveyed college students about their use

of club drugs [67], but did not define ‘club drugs’ for the students on the questionnaire, thereby leaving interpretation to the respondent which in turn can lead to misclassification of exposure. We suggest studying individual drugs and in studies where drug types or names may be confused, participants should be asked to describe how the drugs look and how they are administered. Use of street names may also lead to misclassification, as the street name may be the same for two different drugs or different drug combinations may be sold under the same name [171;195;196]. A thorough understanding of how drugs are administered, including needle sharing, may also be helpful in understanding causal associations between drug use and HIV infection.

We identified a large number of articles in which club drugs were combined and others which did not provide multivariate analyses. Methodologically, both of these types of analyses are not ideal in assessing associations between drug use and HIV/STI risk. Multivariate analyses that control for possible confounding effects are necessary to avoid spurious associations between drug use and HIV/STI acquisition. Similarly, different drugs have different mechanisms of action, and may pose a differential risk for HIV/STI acquisition, therefore combining drugs may lead to confounding. Additionally, current evidence suggests that use of more than one drug simultaneously ('polydrug' use) is common [197;198], club drug users tend to be polydrug users [110;199-202], and MSM who use recreational drugs may be more likely to be polydrug users [203]. Polydrug use has been associated with HIV-risk behaviors including: higher rates of UAI [168;204] as compared to non-users or single drug users among MSM; higher odds of sharing injection drug equipment among IDU [205]; more sexual partners among MSM [206]; greater likelihood of STI [198]; HIV-positive serostatus [198;206]; and more UAI among HIV positive MSM with sero-discordant

partners [131]. Polydrug use is often reported in combination with methamphetamine use [131;204;207]. Additionally, illicit drugs may be increasingly combined with sildenafil citrate in order to create a sexual-drug experience [114;175].

A number of excellent reviews on drug use and sexual behaviors have been published [52;127;138;145;208-211], including those which review different types of methodologies that could assist in the understanding of associations between drug use and HIV/STI acquisition [145;209]. Leigh and Stall (1993) argue that global studies provide the least evidence of association, and event analyses provide the greatest. Rusch *et. al*. (2004) demonstrate the value of examining global and event level analyses within the same study and how associations may differ at each level depending on the drug used. Additionally, their study indicates that some drugs may be more likely to be associated with insertive or receptive UAI, which demonstrates the need for precise and detailed measurement and analysis.

Global, situational or event studies do not rule out drug use as a marker of risky personalities [145]. In order to establish that a high-risk sexual event is associated with drug use, within-subject analyses, that compare times in which substances have and have not been used and the type of sex that occurs, should be conducted. Colfax *et. al.* (2004) conducted such a study, in which the last sexual encounter involving UAI and the last encounter with protected anal intercourse were compared, revealing that methamphetamine use was associated with UAI (Table 4). Such studies provide more evidence for determining causal association by restricting analysis to those who report variation in UAI and drug use since they can confirm temporal associations and dose-response relationships. Even with such studies, it may be impossible to determine which behaviors are causal risk factors for HIV/STI seroconversion by examining the behavior at one point in time. While a greater number of sex partners is a well

established risk factor for HIV/STI acquisition [153;192;193;212], seroconversion typically only happens with one sexual partner and a given individual may come in contact with many HIV positive partners before seroconversion occurs.

It is also important to employ different types of methodologies among many populations when determining causation. Ethnographic techniques may be helpful in understanding why drug use occurs and how drugs affect behavior [70;86;108;209], which can help to direct questions for observational studies. Such studies could also contribute in determining if drug use among subgroups of MSM, and other populations, occurs in preparation for pre-planned UAI (e.g., 'barebacking'). Additionally, studies which examine behavior among drug-using populations [213-215], and between HIV serodiscordant couples may provide insight on the dynamics of disease spread, and may be helpful in determining how drug use may shape the sexual network. Examination of the same behaviors in different populations of MSM is also critical, as cohorts of MSM from the same urban centers may report very different risk behaviors [58]. Studies that address treatment of drug use or abuse and measure change in sexual behavior [157;158;216] may be regarded as experimental studies (for the purpose of determining causality) and are helpful in determining if sexual risk behaviors are curtailed with cessation of drug use.

In this review we identified pathways in which club drugs may be causally associated with HIV/STI and addressed the amount of causal evidence available for each of the club drugs identified. Methamphetamine and volatile nitrites are the most studied of these drugs; however, more longitudinal studies and event-level case-crossover studies which address behavior in different settings with different partner types are needed. For the remaining drugs (MDMA, GHB, ketamine, LSD, flunitrazepam, and EDMs) more longitudinal and case-control studies need to be

conducted which provide larger sample sizes and address Leigh and Stall's (1993) levels of analysis, in particular there is a need for longitudinal studies that examine situational, event level and event case-crossover associations. Further exploration into physiological changes in the body due to drug use that could increase the risk of HIV/STI acquisition also need to be explored, including depression and immune modulation. A small number of studies suggest that some club drugs, such as ketamine [217], MDMA [218], and flunitrazepam [219], may decrease immune functioning which could increase the risk of HIV/STI acquisition. For all drug types, there was a shortage of studies that quantify dose-response relationships between drug use and risky sexual behavior; such studies are needed to understand causal associations. In our review of the literature we also noted that the popularity and use of club drugs seems to be expanding from western countries to those in the east, such as China [220] and Southeast Asian countries [221-223], we therefore recommend studies which examine club drug use prevalence and HIV/STI risk factors in relation to drug use, especially methamphetamine, in all countries worldwide. Additionally, the associations between drug use and HIV/STI risk should be examined in the context of partner type, location of sexual encounter and dynamics of the partnership in which sexual contact occurs. Understanding of the associations between drug use and HIV/STI risk will be further elucidated through using many different methodologies to examine specific, detailed elements, while keeping in mind that the results will be applied to understanding causative associations and contribute to designing prevention interventions.

F. Acknowledgements: We would like to acknowledge and thank Drs. Maria Rosario Araneta, Pamina Gorbach, Susan Little, Vanessa Malcarne, Donald Slymen and Simon Frost for their support and suggestions on this manuscript.

G. Glossary

Analogy. One of Hill's nine criteria for causation. According to the criteria of analogy the causative model is consistent with similar models and alternative explanations have been considered.

Biological gradient. One of Hill's nine criteria for causation. Biological gradient is also known as dose-response relationship. As the amount of exposure to the causal risk factor increases the likelihood of the outcome occurring increases. Some biological systems are not based on monotonic trends, but on threshold effects; under this circumstance biological gradient would not be a valid assessment.

Biological plausibility. One of Hill's nine criteria for causation. Biological plausibility indicates that the association between the causal risk factor and the outcome should be plausible based on our current understanding of biology. While this criterion is important, it is based on the assumption that the current understanding of biology is correct.

Coherence. One of Hill's nine criteria for causation. Coherence states that the proposed causal associations should not conflict with what is currently known about the natural history and biology of the outcome.

Consistency. One of Hill's nine criteria for causation. Consistency refers to the consistency between studies, which also includes direction of association. The more conflicting the results (e.g., null risk ratios v. positive or negative risk ratios), the less evidence there is for a causal association; however, consistency can be affected by the quality of study methodology.

Event level association. In their 1993 manuscript Leigh and Stall (Leigh & Stall, *Am. Psych.* 48: 1035, 1993) use this term to describe studies which examine

associations between drug use at a specific sexual encounter and risky behavior at that same sexual encounter.

Event level case-crossover association. A term the authors created based on descriptions by Leigh and Stall (Leigh & Stall, *Am. Psych.* 48: 1035, 1993) for studies that compare event level associations between drug use and sexual activity within the same individual between times when the risky sexual behavior did or did not occur. This type of study has been used previously [224] and referred to as 'participant-level' analyses.

Experimental evidence. One of Hill's nine criteria for causation. Animal or human experimental models support the association; prevention or cessation of the cause results in reduction in the probability of the outcome.

Fisting. Slang term used for sexual activity in which the hand and sometimes part of the arm is inserted into the rectum. This term is also used for inserting the entire hand into the vagina, but does not apply to this review article since it focuses on sexual activity between men.

Global association. A term used by Leigh and Stall (Leigh & Stall, *Am. Psych.* 48: 1035, 1993) to describe studies which examine associations between risky behavior in general and substance use in general. Global association studies do not measure substance use at the time of sexual activity. We expanded this term to studies of general substance use and HIV/STI.

Hill's criteria for causation. Nine criteria published by Sir Bradford Hill in 1965 to help assist researchers and clinicians determine if risk factors were causes of a particular disease or outcome or merely associated. The nine criteria are defined in this glossary and include: strength of association, consistency between studies, temporality,

biological gradient, biological plausibility, coherence, specificity, experimental evidence, and analogy.

Situational association. A term used to describe studies which examine associations between substance use during sexual activity (ever or by frequency) and risky sexual behaviors (within a given time frame or by frequency) (Leigh & Stall, *Am. Psych.* 48: 1035, 1993). As with global associations, we expanded this term to include studies which examined drug use during sexual activity within the follow-up period and STI incidence or HIV seroconversion in longitudinal studies.

Specificity. One of Hill's nine criteria for causation. Specificity states that the risk factor must be the only cause for the outcome and the outcome must only occur in the presence of the causative factor. This criterion is no longer held to be true and is no longer used to assess causation.

Strength of association. One of Hill's nine criteria for causation. Strength of association refers to the size of the risk measure (e.g., relative risk, odds ratio, prevalence ratio). Associations with greater strength are more likely to be causal than those which are weaker. Strength of association may affected by the prevalence of one of multiple causal components which are required in concert to lead to the outcome [143]. If two components are required for the outcome to occur and only one is measured, associations between that which was measured and the outcome could vary between populations based on the prevalence of the unmeasured factor.

Temporality. One of Hill's nine criteria for causation. Temporality refers to the risk factor preceding the outcome. Temporal order is the only criterion which absolutely must be met in order to establish cause; it can be viewed as a part of the definition of a causative agent.

Works. Slang term for all other equipment necessary to inject drugs.

H. Chapter Acknowledgement

This chapter been accepted in its entirety as a manuscript for publication in Substance Use and Misuse and is in press as of the completion of this dissertation. The author of this dissertation, Lydia N. Drumright, will appear as the primary author on this manuscript in publication; Dr. Thomas L. Patterson from the Department of Psychiatry at the University of California, San Diego (UCSD) will appear as the second author; and Dr. Steffanie A. Strathdee of the Department of Family and Preventive Medicine at UCSD, Head of the Division of Cross-Cultural Medicine, Harold Simon Chair, and Chair of this dissertation, will appear as the senior author.

Table 2-1: Definitions of 'club' drugs in current scientific literature

Definition	Drugs Included	Focus of Paper	Year	References
"a loosely defined category of drugs from different classes.. grouped due to their use at dance clubs and raves"	MDMA, methamphetamine, ketamine	Predictors of club drug use among college students.	2005	[67]
Drugs that have been "associated with the club scene"	cocaine, crystal methamphetamine, amyl nitrites, MDMA, GHB, ketamine, Viagra®	Drug use and UAI among Internet using MSM.	2005	[225]
"a group of drugs used primarily by young adults often at all night dance parties called "raves"…"	MDMA, GHB, ketamine, Flunitrazepam (Rohypnol®)	Overview of club drug pharmacology	2005	[101]
"a broad array of legal and illegal substances with varying effects…"	MDMA, GHB, ketamine, flunitrazepam (Rohypnol®), LSD, research chemicals ("2C T7", "Foxy Methoxy")	Epidemiology of club drugs in Seattle	2005	[226]
None provided	Cocaine, MDMA, GHB, crystal methamphetamine, amyl nitrites, Viagra®	Epidemiology of club drug use among Hispanic MSM in Miami, Florida	2005	[227]
"The substances NIDA was referring to include LSD, ecstasy, GHB, Ketamine, Rohypnol, methamphetamine, and psilocybin mushrooms and are collectively known as 'club drugs'"	LSD, MDMA, ketamine, flunitrazepam, methamphetamine, psilocybin mushrooms	Demographic, risk behavior, home environment, and rave attendance differences among club drug and non-club drug using delinquent youth in Oregon	2005	[228]
"a wide range of substances, from stimulants to depressants to hallucinogens. The unifying classificatory principle is that these substances proliferated with a perceived association with club subcultures."	MDMA, ketamine, methamphetamine, GHB	Club drug using youths' perceptions of club drug risks	2005	[229]
"a relatively new classification of drugs that have been receiving a great deal of attention recently." "The term 'club drugs' derives from the setting in which these substances are typically used… rater than any pharmacological properties.."	MDMA, GHB, ketamine, methamphetamine	Marijuana, alcohol and tobacco as predictors of club drug use among middle school children	2005	[230]
None provided	MDMA, flunitrazepam, GHB, ketamine, LSD, methamphetamine, PCP	Club drug use among ethnic minority populations in New York City.	2004	[173]
Drugs used in late night dance clubs	GHB, ketamine, MDMA, Rohypnol	Toxic effects of club drugs.	2004	[65]
None provided	MDMA, ketamine, cocaine, crystal methamphetamine, GHB, marijuana, amyl nitrites	Motivations for circuit party attendance.	2003	[129]
"substances used in a recreational fashion to enhance social experience"	MDMA, GHB, ketamine	Review of club drugs and HIV risk behaviors among MSM.	2003	[54]
Drugs consumed in the "context of gay bars, dance clubs, sex parties, and bathhouses." A distinct pattern of substance use among gay men who are "out".	cocaine, MDMA, methamphetamine, ketamine, GHB	Reasons for club drug use among MSM.	2003	[70]
No definition provided, but the settings of use are described as raves and circuit parties	MDMA, GHB, ketamine, smart/power drinks (which contain caffeine or ephedrine)	To describe "settings, demographic groups, and types of drugs that make up the 'club scene'".	2002	[231]
"chemical substances used recreationally in an attempt to enhance social experiences".	MDMA, flunitrazepam, ketamine, GHB	Review of effects of club drugs.	2002	[96]
"the drugs commonly taken to enhance the whole experience (circuit party)"	alcohol, cocaine, MDMA, ketamine, methamphetamine, GHB, cocaine, marijuana, nitrites	Drug use and unsafe sex among MSM attending circuit parties.	2001	[71]
Drugs "used most often at all-night dance parties known as raves."	MDMA, GHB, flunitrazepam, ketamine, methamphetamine, LSD	Review of MDMA and GHB as club drugs.	2001	[66]
Drugs used by teens and young adults at all night dance parties (raves). Synthetic drugs used at raves. "Club drug list" referred to.	LSD, MDMA, GHB, ketamine and other drugs, flunitrazepam, amphetamines, ephedrine	Hearing on trafficking of club drugs before the United States House of Representatives.	2000	[69]
"a wide variety of drugs being used by young people at dance clubs, bars and all-night dance parties".	MDMA, flunitrazepam, ketamine, GHB, LSD	Community information on club drugs provided by NIDA.	2000	[68]

Table 2-1: Definitions of 'club' drugs in current scientific literature (continued)

Referred to as party drugs, "a group of substances that have become increasingly associated with high-risk sexual and drug taking behaviors".	MDMA and other hallucinogens; ketamine; GHB; cocaine; amphetamines; methamphetamine	Drug use and HIV among MSM, education for nurses.	2000	[232]
Referred to as 'dance drugs'; defined as drugs used at raves.	MDMA, amphetamines, LSD, ketamine, cocaine, nitrites	Examination of patterns of drug use at a rave in Perth, Australia.	1997	[64]

UAI= unprotected anal intercourse MSM= men who have sex with men NIDA= National Institutes on Drug Abuse MDMA= Methylendioxy-methamphetamine
GHB= Gamma-hydroxybutyrate LSD= Lysergic acid diethylamide

Table 2-2: Potential criteria for grouping of drugs

Criteria	**Examples**
Drug Class	Psychomotor stimulant, opiate, etc.
Physiological Effects	Stimulant, depressant, hallucinogen, analgesic, etc.
Method of administration	Inhalant, injection, etc.
Method of production	Synthetic manufacturing, naturally occurring and chemically modified, naturally occurring
Legal status	Legal (medically controlled or freely distributed) or illicit
Situation of use	Party, club, rave, etc.
Population using	Teens, men who have sex with men, etc.
Social effects	Withdrawn, socially confident, sexually stimulated, etc.
Myths/ perceptions	Drug safety, drug effects, etc.
Periodicity	Drugs which are popular during certain time periods or eras

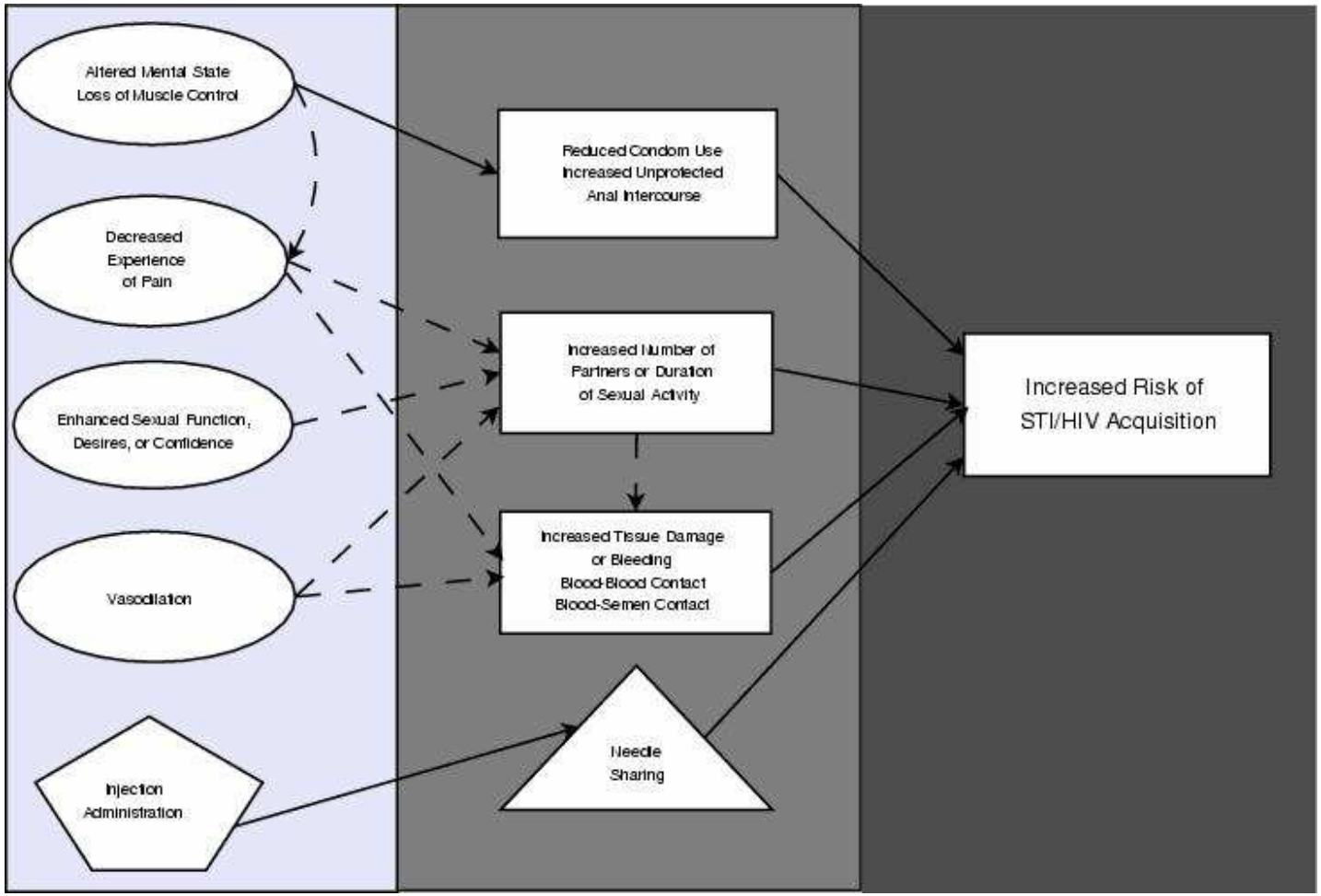


Figure 2-1: Theoretical model proposing drug use as a causative risk factor for HIV and STIs among MSM. Different club drugs can cause a range of effects (altered mental state, reduction of pain, enhancement of sexual function, vasodilation) on the human body that may result in: tissue damage or increased bleeding; reduction of condom use; increased number of partners or duration of sexual episode. Additionally, injecting drugs can result in needle or equipment sharing. The text in the circles on the light background in the 'first layer' represents the effects that club drugs can have on the user; the pentagon represents a risky mode of administration. The 'second layer' represented by boxes on the medium colored background are behaviors that may occur as a response to drug effects or routes of administration. Dashed lines represent theoretically plausible pathways which are likely to result in the next step but have yet to be confirmed. Solid lines represent well established pathways.

Table 2-3: Biological and social effects of 'club' drugs and pharmaceutical agents sometimes used as club drugs

Drug	Alternative Names	Class	Pharmacological Effects	External Effects
Methamphetamine	Meth, Speed, Chalk, Crystal, Glass, Ice, Crank, Bennies, Black beauties, Dexies, Tina, Fire	Stimulant	Increases the release, blocks reuptake, and causes synaptic leak of serotonin	Increased motor activity; anorexia; increased feeling of confidence and well-being; agitation; decreased fatigue; euphoria; increased respiration; hyperthermia; increased libido (at moderate doses); erectile dysfunction (at high doses)
Methylendioxy-methamphetamine (MDMA)	Ecstasy, 'E', 'X', XTC, STP, Peace, Adam, Clarity, Eve, Lover's speed, eccie	Hallucinogen/ Stimulant.	Increases the release and blocks reuptake of serotonin and possibly dopamine	Increased feelings of euphoria and well-being; increased derealization and depersonalization; increased anxiety; increased blood pressure and pulse; sexual arousal; increased awareness of emotions; tachycardia; bruxism; trismus; anorexia; hyperthermia
Ketamine	Special K, 'K', Kit kat, Cat valium, Vitamin K, Lady K, Ketaject	Disassociative anesthetic	Causes CNS depression through binding with the following receptors: NDMA, non-NDMA glutamate; nicotinic; muscarinic cholinergic; monoaminergic; opioid	Analgesia; amnesia; immobility; sedation; complete dissociation from environment
Gamma-hydroxybutyrate (GHB)	Blue nitro, Liquid ecstasy, Liquid X, Liquid E, Georgia home boy, Grievous bodily harm, G-Riffick, Soap, Salty water, Somatomax, Organic qualude, Fantasy, cherry meth, soap, Growth Hormone Boosters, Gamma OH	Disassociative anesthetic	Exact action on CNS undetermined; likely to act on the cerebral cortex rather than the reticular activating system; anesthetic and hypnotic properties, no analgesic effects.	Bradycardia; reduced respiratory rate; amnesia; drowsiness; euphoria; hypotonia
Flunitrazepam	Roofies, Rohypnol, Rophies, Rope, Roche, Circles, R2, Wolfies, Mexican valium, Forget me pill	Sedative	Facilitates the functioning of GABA by binding to the receptor, causing an ion channel cascade which results in reducing the ability for the neuron to fire.	Muscle relaxation; hypnotic effects; amnesia; dizziness; confusion; hypotension
Lysergic acid diethylamide (LSD)	Acid, Alice, Tabs, Trips, Blotter, Boomers, Microdot, Yellow sunshine	Hallucinogen	Incompletely understood; LSD binds to serotonin receptors and effects the raphe nuclei and reticular activating area of the brain which controls sensory input	Synaesthesia; intensification of sensory input; loss of depth perception; intensification of thoughts and value of thoughts; hallucination; paranoia
Volatile nitrites	Poppers, Snappers, Aroma of men, Rush, Stud, Hardware, Locker room, Liquid gold, Climax	Inhalant	No CNS effects; possible dizziness experienced from shortage of oxygen to the brain.	Relaxation of smooth muscles; vasodilation; pooling of blood in lower extremities; lower blood pressure
Sildenafil citrate	Viagra, sildenafil	Prescription Drug.	Acts by inhibiting cyclic guanosine monophosphate (cGMP) in all body tissue	Increased blood accumulation in the penis during sexual arousal and slower relaxation of the corpus cavernosum muscles post ejaculation

Table 2-4: Studies examining 'club' drug use and HIV/STI risk

Drug	Reference	Design	n	Location	Inclusion/Exclusion	Associations	Association Type
Methamphetamine	[105]	Cross-sectional	4943	Pittsburgh; Baltimore; Los Angeles; Chicago; (USA)	Multi-center AIDS Cohort Study (MACS) participants	Methamphetamine use in the last 2 years and prevalent HIV sero-positivity: OR=1.53 (1.23, 1.91)	Global
	[233]	Cross-sectional	258,567	California (USA)	HIV testers at funded sites between July 1, 1994 and December 31, 1995; ~13% MSM	Used methamphetamine during sex and: • Condom use during insertive anal sex: OR=0.5 (0.3, 0.6) • Condom use during receptive anal sex: OR=0.5 (0.4, 0.7) • Paid for sex: OR=3.3 (2.1, 5.0) • Were paid for sex: OR= 4.3 (3.3, 4.9) • Sex with known IDU: OR=5.0 (3.6, 6.9) • HIV positive: OR=1.9 (1.3, 2.9)	Situational
	[234]	Cross-sectional	908	Los Angeles (USA)	MSM in West Hollywood who agreed to participate in street outreach	Current methamphetamine use and: • Recent sexual contact with IDU: OR=2.75 (1.62-4.65) • Recently selling sex: OR=1.48 (0.93-2.35) • Recently Injecting drugs: OR=57.0 (28.3-114.2)	Global
	[182]	Cross-sectional	295	San Francisco (USA)	Adult men who self-identified as gay or bi-sexual; worked or lived in San Francisco; attended at least one circuit party past 12 months	Had UAI with sero-discordant or unknown status partner and used crystal methamphetamine during circuit party weekend: OR= 2.4 (1.1-4.9);p=0.021	Global
	[71]	Cross-sectional	1169	United States	Men attending any of three circuit parties	UAI and crystal methamphetamine use during sexual activity past 12 months: OR=1.40 (0.87-2.24) p=0.085	Situational
	[235]	Cross-sectional	564	Seattle (USA)	HIV negative STD clinic patients	HIV negative MSM were 2.3 (1.2-4.4) more likely to report methamphetamine use during sex if they had an HIV positive partner in the past 2 months	Situational
	[224]	Cross-sectional	4295	Boston; Chicago; Denver; New York; San Francisco; Seattle (USA)	HIV negative MSM participating in EXPLORE	UAI with sero-discordant partner last sex and: • used methamphetamine just before last sex: OR=1.5 (1.1-2.0) • partner used drugs before sex OR=1.5 (1.2-2.0) • used methamphetamine in last 6 months < 1/week: OR=1.4 (1.2-1.7) • used methamphetamine in last 6 months 1/week +: OR=2.0 (1.3-3.1)	Global Event Cross-over
	[184]	Case-control	2643	United States	Self-selected Internet sample of MSM	Methamphetamine use before or during sex past 6 months and self-reported incident STD: OR=2.0 (1.1, 3.8)	Situational

Table 2-4: Studies examining 'club' drug use and HIV/STI risk (continued)

Drug	Author	Design	n	Location	Inclusion/Exclusion	Associations	Association Type
Methamphetamine	[155]	Longitudinal (6 years)	261	Vancouver (Canada)	HIV negative MSM 18-30 in Vanguard study; who attended at least one study visit for each 2 year study period for 6 years	• Crystal MA use during sex and UAI: OR=1.75 (1.0, 3.05) • Crystal MA use anytime and UAI: OR=1.57 (1.12,2.19) • Crystal MA use during sex and IUAI: OR=1.74 (1.05,2.91)	Global Event
Amphetamine	[161]	Cross-sectional	564	San Francisco (USA)	Any MSM screened for rectal gonorrhea at the San Francisco City STD clinic from February to October 2000	Rectal gonorrhea by culture associated with amphetamine use during sex past 2 weeks: • HIV-: PR=3.7 (1.1, 9.4) • HIV+: PR=1.8 (0.5, 4.9)	Situational
	[156]	Cross-sectional	3316	San Francisco; Los Angeles; Seattle; Dallas; Miami; Baltimore; New York; (USA)	Participants of the Young Men's Survey	HIV prevalence and amphetamine use during sex past 6 months: OR=0.83 (0.46, 1.5)	Global
	[152]	Longitudinal (1 year)	492	Sydney, Australia	MSM from Sydney general medical practices and outpatient clinics participating in the Sydney AIDS Project	Amphetamine use during the 1 year follow-up HIV seroconversion: RR= 4.8 (2.2-10.5) p<0.001	Global
	[153]	Longitudinal	378	Amsterdam San Francisco Vancouver Sydney	All MSM who seroconverted in the Tricontinental Seroconverter Study between 1982 and 1994	HIV seroconversion and amphetamine use during seroconversion using participant as own control: RR=2.50 (1.24, 5.04)	Global
	[154]	Longitudinal (6 years)	337	San Francisco (USA)	In SFMHS Cohort; HIV negative at baseline; Data from at least 2/3 of interviews	HIV seroconversion associated with • Amphetamine use over follow-up RR= 2.89 (1.36, 6.16) • New amphetamine users RR= 1.02 (0.24, 4.41)	Global
MDMA	[71]	Cross-sectional	1169	San Diego (USA)	Men attending any of 3 circuit parties	UAI and MDMA use during sex past 12 months: OR=0.68 (0.41-1.15) p=0.075	Situational
	[160]	Cross-sectional	733	New York City (USA)	Sampling from zipcodes with high MSM residency based on businesses, etc; 18 years or older, report sex with a man since age 14 or self-identify as gay or bisexual	UAI in past and: • MDMA use ever: OR=2.34 (1.3, 4.2)	Global
	[161]	Cross-sectional	564	San Francisco (USA)	Any MSM screened for rectal GC at the San Francisco City STD clinic from February to October 2000	Ecstasy during sex use past 2 weeks and rectal gonorrhea among HIV-: OR=1.2 (0.1, 4.6)	Situational
	[152]	Longitudinal (1 year)	492	Sydney, Australia	MSM from Sydney AIDS Project	MDMA use during the 1 year follow-up and HIV seroconversion: RR= 2.6 (0.8-8.4) p=0.11	Global

Table 2-4: Studies examining 'club' drug use and HIV/STI risk (continued)

Drug	Author	Design	n	Location	Inclusion/Exclusion	Associations	Association Type
MDMA	[155]	Longitudinal	261	Vancouver, Canada	MSM 18-30 in Vanguard study; HIV-; attended at least one study visit for each 2 year study period for 6 years	MDMA use during sex and: • UAI OR=1.88 (1.2, 2.95) • RUAI OR=1.85 (1.22,2.79) • IUAI OR=1.53 (1.01,2.33) MDMA use any use time and: • UAI OR=1.57 (1.12,2.19) • RUAI OR=1.69 (1.23,2.32)	Global Event
GHB	[71]	Cross-sectional	1169	San Diego (USA)	Men attending any of 3 circuit parties	UAI and GHB use during sex past 12 months: OR= 1.45 (0.90-2.32) p=0.064	Situational
	[161]	Cross-sectional	564	San Francisco (USA)	MSM screened for rectal gonorrhea at City STD clinic February to October 2000	Rectal gonorrhea by culture and GHB use during sex past 2 weeks: HIV- PR= 0.9 (0.02, 5.4); HIV+ PR=1.8 (0.04, 18.3)	Situational
	[155]	Longitudinal	261	Vancouver, Canada	MSM 18-30 in Vanguard study; HIV-; attended at least one study visit for each 2 year study period for 6 years	GHB use during sex and: • UAI OR=1.98 (1.01, 3.87) • IUAI OR=2.14 (1.13, 4.03)	Global Event
Ketamine	[71]	Cross-sectional	1169	San Diego (USA)	Men attending any of 3 circuit parties	UAI and ketamine use during sex past 12 months: OR= 0.76 (0.45, 1.29) p=0.157	Situational
	[155]	Longitudinal	261	Vancouver, Canada	MSM 18-30 in Vanguard study; HIV-; attended at least one study visit for each 2 year study period for 6 years	Ketamine use during sex and: • UAI OR= 2.17 (1.08,4.33) • IUAI OR=2.05 (1.09,3.87) Any ketamine use and: • UAI OR=1.80 (1.06,3.08) • IUAI OR=1.76 (1.06,2.90)	Global Event
Flunitrazepam	NO STUDIES CONDUCTED						
LSD	[155]	Longitudinal	261	Vancouver, Canada	MSM 18-30 in Vanguard study; HIV-; attended at least one study visit for each 2 year study period for 6 years	LSD use during sex or any time was not associated with any type of UAI by any type of partner	Global Event
Sildenafil	[182]	Cross-sectional	305	San Francisco (USA)	Community recruited MSM who reported attending a circuit party previous 12 months	UAI with sero-status unknown partner and used sildenafil at a circuit party OR=3.8 (2.0, 7.3)	Situational
	[185]	Cross-sectional	439	San Diego (USA)	Male HIV clinic patients	Sildenafil prescription from the clinic past 12 months and • Unprotected insertive sex (vaginal, anal or oral) OR=3.0 • More than one sex partner OR=4.5	Global
	[181]	Cross-sectional	837	San Francisco (USA)	Community recruited MSM	UAI with serostatus unknown partner and sildenafil use past 6 mo OR= 2.45 (1.4,4.3)	Situational

Table 2-4: Studies examining 'club' drug use and HIV/STI risk (continued)

Drug	Author	Design	n	Location	Inclusion/Exclusion	Associations	Association Type
Sildenafil	[183]	Cross-sectional	2,916	United States	Self-selected Internet sample of MSM	UAI within the prior 6 months was associated with Viagra use during that time period: OR=1.5 (1.1-2.2)	Situational
	[184]	Case-control	2643	United States	Self-selected Internet sample of MSM	STD within the prior 6 months was associated with Viagra use during that time period: OR=2.1 (1.2-3.7)	Situational
Volatile Nitrites	[236]	Cross-sectional	106	Milwaukee; Wisconsin; (USA)	Recruitment strategies unspecified	UAI in past 3 months was associated with nitrite use prior to sex in the past year OR=22.76 (p=0.003)	Situational
	[119]	Cross-sectional	439	Vancouver, Canada	MSM recruited from medical services who had not received a positive HIV test (Vanguard)	UAI with casual male sex partners in the pervious year associated with use of nitrite inhalants during that time OR=2.30 (1.53-3.45)	Global
	[164]	Cross-section	3220	Boston; New York;Chicago; Denver; San Francisco; Seattle (USA)	HIV negative MSM in VPS study	UAI with more than 1 partner in the past 6 months was associated with: • Some vs. none nitrite use past 6 mo: OR=1.61 (1.35-1.92) • Heavy vs. none nitrite use past 6 mo: OR=2.18 (1.48-3.20)	Global
	[237]	Cross-sectional	466	Edinburgh, United Kingdom	MSM in gay oriented venues.	UAI with sero-discordant or status unknown partner was associated with nitrite use: • At last sex OR=2.40 (1.42-4.05) • Over past 3 mo.: OR=3.56 (1.7, 7.1)	Event Global
	[235]	Cross-sectional	564	Seattle (USA)	STD clinic patients; all HIV statuses, 564-HIV negative	HIV negative MSM were not significantly more likely to report sex with a positive partner in the past 2 months if using nitrites OR=1.5 (0.9-2.6)	Situational
	[161]	Cross-sectional	564	San Francisco (USA)	Any MSM screened for rectal gonorrhea at the San Francisco City STD clinic from February to October 2000	Rectal gonorrhea by culture not associated with nitrite use past 2 weeks: • HIV-: PR=2.5 (0.8-6.2) • HIV+: PR=1.3 (0.3-3.7)	Situational
	[156]	Cross-sectional	3316	San Francisco; Los Angeles; Seattle; Dallas; Miami; Baltimore; New York; (USA)	Participants of the Young Men's Survey	HIV prevalence and nitrate use during sex past 6 months: OR=1.5 (0.71, 3.0)	Global
	[238]	Case-control	459	San Francisco (USA)	Any MSM resident of San Francisco who were diagnosed with AIDS prior to April 1984, and neighborhood and clinic controls who were HIV negative.	Number of nitrite inhalant 'hits' per month and prevalent HIV infection: • Neighborhood controls: OR=2.2 (p=0.16) none vs. 1-65 'hits' per month; OR=5.7 (p=0.04) none vs. >65 'hits' • Clinic controls: OR=1.4 (p=0.57) none vs. 1-65 'hits' per month; OR=9.1 (p=0.09) none vs. >65 'hits'.	Global

Table 2-4: Studies examining 'club' drug use and HIV/STI risk (continued)

Drug	Author	Design	n	Location	Inclusion/Exclusion	Associations	Association Type
Volatile Nitrites	[239]	Nested case-control	481	Boston (USA)	MSM with and without an AIDS diagnosis seen at Deaconess Hospital or Fenway Community Health Center between May 1985 and December 1988 and their sexual partners	Associations between AIDS diagnosis and receptive UAI within the past 5 years with: • No simultaneous nitrite use: OR= 9.0 (2.5-32.1) • Some simultaneous nitrite use: OR=7.1 (2.1-23.6) • 100% simultaneous nitrite use: OR=31.8 (12.9-76.7)	Situational
	[240]	Nested case-control	456	Chicago (USA)	MACS Cohort seroconverters and randomly selected controls	Use of amyl nitrites in the 6 months prior to the sero-conversion visit: OR=2.89 (1.37, 6.08)	Situational
	[241]	Longitudinal	125	Boston (USA)	HIV negative, sexually active MSM attending a Boston health center and completed 7 visits	Higher risk sexual practices was not associated with continuation of nitrite use: RR=1.24 (0.83, 1.84)	Global
	[168]	Longitudinal	1005	Chicago (USA)	MACS Cohort	Relapsing from using condoms for all anal intercourse to not using condoms was associated with nitrite use: OR=5.64 (2.07, 15.35)	Global
	[153]	Longitudinal	378	Amsterdam San Francisco Vancouver Sydney	All MSM who seroconverted in the Tricontinental Seroconverter Study between 1982 and 1994	HIV seroconversion and nitrite use: OR=2.55 (1.26, 5.15)	Global
	[154]	Longitudinal (6 years)	337	San Francisco (USA)	In SFMHS Cohort; HIV negative at baseline; Data from at least 2/3 of interviews	HIV seroconversion associated with • Nitrite use over follow-up RR= 2.49 (1.24, 4.93) • But not new nitrite users RR= 0.70 (0.16, 3.07)	Global
	[187]	Longitudinal	578	Seattle (USA)	Community recruited HIV negative MSM who engaged in anal sex in previous 12 mo	Those who reported nitrite use during follow-up were 3.1 (1.4-6.6) times more likely to incident STD in 12 month follow-up.	Global
	[45]	Longitudinal	510	San Francisco (USA)	San Francisco Young Men's Health Study	UAI with serodiscordant or unknown status partner was associated with use of nitrites past 12 mo: OR=5.16 (1.58-16.84)	Global
	[188]	Longitudinal	3257	Boston; Chicago; Denver; New York; San Francisco; Seattle (USA)	MSM enrolled in the HIVNET Vaccine Preparedness Study	HIV Seroconversion was associated with nitrate inhalant use during sex in the 6 months prior to seroconversion: OR=2.2 (1.4-3.7)	Situational

OR=odds ratio RR=relative risk PR=prevalence ratio MSM= men who have sex with men
UAI= unprotected anal intercourse IUA= insertive unprotected anal intercourse RUAI=receptive anal intercourse MDMA= Methylendioxy-methamphetamine
GHB= gamma-hydroxybutyrate LSD= lysergic acid diethylamide

Table 2-5: Evidence for meeting Hill's criteria for causation by drug type

Drug	Causal Criteria								
	Strength	**Consistency**	**Temporality**	**Biological Gradient**	**Plausibility**	**Coherence**	**Specificity**	**Experimental Evidence**	**Analogy**
Methamphetamine	+++	+++	++++	++	++++	++++	0	++++	++++
MDMA	+	+	0	0	+++	+++	0	0	++++
Ketamine	+	+	0	0	+++	++	0	0	++
GHB	+	+	0	0	+++	++	0	0	++++
LSD	0	0	0	0	++	+	0	0	0
Flunitrazepam	0	0	0	0	++	+	0	0	0
Sildenafil	+++	++++	0	0	+++	+++	0	0	0
Volatile Nitrites	+++	+++	+++	+++	++	++	0	0	0

*0= no evidence to meet criterion
+ = very poor evidence to meet criterion ++ = some evidence to meet criterion +++ = good evidence to meet criterion ++++ = very strong evidence available to meet criterion

I. References

(1) Hamouda O. HIV/AIDS surveillance in Germany. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S49-S54.

(2) Smith E. HIV/AIDS surveillance in Denmark: The challenges ahead. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S33-S38.

(3) Archibald CP, Sutherland J, Geduld J *et al*. Combining data sources to monitor the HIV epidemic in Canada. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S24-S32.

(4) Kaldor J, McDonald A. HIV/AIDS surveillance systems in Australia. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S18-S23.

(5) Centers for Disease Control and Prevention. Increases in HIV diagnoses- 29 states, 1999-2002. *Morbidity and Mortality Weekly Report*. 2003; 52:1145-1148.

(6) Murphy G, Charlett A, Jordan LF *et al*. HIV incidence appears constant in men who have sex with men despite widespread use of effective antiretroviral therapy. *AIDS*. 2004; 18:265-272.

(7) Quan VM, Steketee RW, Valleroy L *et al*. HIV incidence in the United States, 1978-1999. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 31:188-201.

(8) Winkelstein W, Wiley JA, Padian NS *et al*. The San Francisco men's health study: continued decline in HIV seroconversion rates among homosexual/bisexual men. *American Journal of Public Health*. 1988; 78:1472-1474.

(9) Weinstock H, Dale M, Gwinn M *et al*. HIV seroincidence among patients at clinics for sexually transmitted diseases in nine cities in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2002; 29:478-483.

(10) Kingsley LA, Zhou SY, Bacellar H *et al*. Temporal trends in human immunodeficiency virus type 1 seroconversion 1984-1989. A report from the Multicenter AIDS Cohort Study (MACS). *Am J Epidemiol*. 1991; 134:331-339.

(11) Hamers FF, Downs AM. HIV in central and eastern Europe. *Lancet*. 2003; 361:1035-1044.

(12) van der Bij AK, Stolte IG, Coutinho RA *et al*. Increase of sexually transmitted infections, but not HIV, among young homosexual men in Amsterdam: are STIs still reliable markers for HIV transmission? *Sexually Transmitted Infections*. 2005; 81:34-37.

(13) Moatti JP, Dab W, Abenham L *et al*. Modifications of sexual-behavior related to AIDS - a survey in the Paris region. *Health Policy*. 1989; 11:15-30.

(14) Becker MH, Joseph JG. AIDS and behavioral change to reduce risk: a review. *American Journal of Public Health*. 1988; 78:394-410.

(15) Chesson HW, Dee TS, Aral SO. AIDS mortality may have contributed to the decline in syphilis rates in the United States in the 1990s. *Sexually Transmitted Diseases*. 2003; 30:419-424.

(16) Winkelstein W, Samuel M, Padian NS *et al*. The San Francisco mens health study 3: reduction in human-immunodeficiency-virus transmission among homosexual and bisexual men, 1982-86. *American Journal of Public Health*. 1987; 77:685-689.

(17) Blower SM, van Griensven GJP. Effect of differential mortality on risk-behavior change in cohort studies. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1993; 6:1364-1367.

(18) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *Journal of Acquired Immune Deficiency Syndromes*. 2001; 28:59-64.

(19) Bluthenthal RN, Kral AH, Gee L *et al*. Trends in HIV seroprevalence and risk among gay and bisexual men who inject drugs in San Francisco, 1988 to 2000. *Journal of Acquired Immune Deficiency Syndromes*. 2001; 28:264-269.

(20) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(21) Dukers NHTM, Spaargaren J, Geskus RB *et al*. HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. *AIDS*. 2002; 16:F19-F24.

(22) del Romero J, Castilla J, Garcia S. *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988-2000. *AIDS*. 2001; 15:1319-1321.

(23) Centers for Disease Control and Prevention. HIV transmission among Black college students and non-student men who have sex with men- North Carolina, 2003. *Morbidity and Mortality Weekly Report*. 2004; 53:731-734.

(24) Kihara M, Ono-Kihara M, Feldman MD *et al*. HIV/AIDS surveillance in Japan, 1984-2000. *J Acquir Immune Defic Syndr*. 2003; 32 Suppl 1:S55-S62.

(25) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(26) Centers for Disease Control and Prevention. Outbreak of primary and secondary syphilis- Gilford County, North Carolina, 1996-1997. *Morbidity and Mortality Weekly Report*. 1998; 47:1070-1073.

(27) Centers for Disease Control and Prevention. Resurgence of bacterial sexually transmitted diseases among men who have sex with men- King County, Washington, 1997-1999. *Morbidity and Mortality Weekly Report*. 2004; 48:773-777.

(28) Centers for Disease Control and Prevention. Increases in unsafe sex and rectal gonorrhea among men who have sex with men- San Francisco, California, 1994-1997. *Morbidity and Mortality Weekly Report*. 1999; 48:45-48.

(29) Centers for Disease Control and Prevention. Primary and secondary syphilis among men who have sex with men - New York City, 2001. *Morbidity and Mortality Weekly Report*. 2002; 51:853-856.

(30) Centers for Disease Control and Prevention. Primary and secondary syphilis-United States, 2002. *Morbidity and Mortality Weekly Report*. 2003; 52:1117-1120.

(31) Centers for Disease Control and Prevention. Internet use and early syphilis infection among men who have sex with men - San Fransisco, California, 1999-2003. *Morbidity and Mortality Weekly Report*. 2003; 52:1229-1233.

(32) Centers for Disease Control and Prevention. Increase in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men- United States, 2003. *Morbidity and Mortality Weekly Report*. 2004; 53:335-338.

(33) Centers for Disease Control and Prevention. Trends in primary and secondary syphilis and HIV infections in men who have sex with men-San Fransisco and Los Angeles, California, 1998-2002. *Morbidity and Mortality Weekly Report*. 2004; 53:575-578.

(34) Williams LA, Klausner JD, Whittington WLH *et al*. Elimination and reintroduction of primary and secondary syphilis. *American Journal of Public Health*. 1999; 89:1093-1097.

(35) Stolte IG, Dukers NHTM, De Wit JBF *et al*. Increase in sexually transmitted infections among homosexual men in Amsterdam in relation to HAART. *Sexually Transmitted Infections*. 2001; 77:184-186.

(36) D'Souza G, Lee JH, Paffel JM. Outbreak of syphilis among men who have sex with men in Houstin, Texas. *Sex Transm Dis*. 2003; 30:872-873.

(37) Hopkins S, Lyons F, Coleman C *et al*. Resurgence in infectious syphilis in Ireland - An epidemiological study. *Sexually Transmitted Diseases*. 2004; 31:317-321.

(38) Fox KK, del Rio C, Holmes KK *et al*. Gonorrhea in the HIV era: A reversal in trends among men who have sex with men. *American Journal of Public Health*. 2001; 91:959-964.

(39) Rietmeijer CA, Patnaik JL, Judson FN *et al*. Increases in gonorrhea and sexual risk behaviors among men who have sex with men: A 12-year trend analysis at the Denver Metro Health Clinic. *Sexually Transmitted Diseases*. 2003; 30:562-567.

(40) Elford J, Bolding G, Sherr L. High-risk sexual behaviour increases among London gay men between 1998 and 2001: what is the role of HIV optimism? *AIDS*. 2002; 16:1537-1544.

(41) Chen SY, Gibson S, Weide D *et al*. Unprotected anal intercourse between potentially HIV-serodiscordant men who have sex with men, San Francisco. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:166-170.

(42) Wohl AR, Johnson DF, Lu S *et al*. Recent increase in high-risk sexual behaviors among sexually active men who have sex with men living with AIDS in Los Angeles County. *Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:209-211.

(43) Stolte IG, Dukers NHTM, Geskus RB *et al*. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. *AIDS*. 2004; 18:303-309.

(44) Van de Ven P, Rawstorne P, Crawford J *et al*. Increasing proportions of Australian gay and homosexually active men engage in unprotected anal intercourse with regular and casual partners. *AIDS Care*. 2002; 14:335-341.

(45) Ekstrand ML, Stall RD, Paul JP *et al*. Gay men report high rates of unprotected anal sex with partners of unknown or discordant HIV status. *AIDS*. 1999; 13:1525-1533.

(46) Katz MH, Schwarcz SK, Kellogg TA *et al*. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *American Journal of Public Health*. 2002; 92:388-394.

(47) Dodds JP, Mercey DE, Parry JV *et al*. Increasing risk behaviour and high levels of undiagnosed HIV infection in a community sample of homosexual men. *Sexually Transmitted Infections*. 2004; 80:236-240.

(48) Ostrow DE, Fox KJ, Chmiel JS *et al*. Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men. *AIDS*. 2002; 16:775-780.

(49) Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA*. 2004; 292:224-236.

(50) Dewit JBF, Vandenhoek JAR, Sandfort TGM *et al*. Increase in Unprotected Anogenital Intercourse Among Homosexual Men. *American Journal of Public Health*. 1993; 83:1451-1453.

(51) Slavin S. Crystal methamphetamine use and HIV risk. *Social Research Briefs*. 2004; 4:1-4.

(52) Halkitis PN, Parsons JT, Stirratt MJ. A double epidemic: crystal methamphetamine drug use in relation to HIV transmission among gay men. *J Homosex*. 2001; 41:17-35.

(53) Gorman M, Halkitis P. Methamphetamine and club drug use and HIV. *Focus*. 2003; 18:5-6.

(54) Romanelli F, Smith KM, Pomeroy C. Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Top HIV Med*. 2003; 11:25-32.

(55) Swanson J, Cooper A. Dangerous liaison: club drugs and HIV. *Posit Aware*. 2003; 14:32-36.

(56) Anonymous. Special report: club drugs & HIV. Drug treatment best hope for meth-using MSMs. Researchers want to get word out about problem. *AIDS Alert*. 2002; 17:137-8, 143.

(57) Anonymous. Research shows 'poppers' use in connected with infection among MSM. Little is done to address problem. *AIDS Alert*. 2004; 19:61, 63-61, 64.

(58) Craib KJ, Weber AC, Cornelisse PG *et al*. Comparison of sexual behaviors, unprotected sex, and substance use between two independent cohorts of gay and bisexual men. *AIDS*. 2000; 14:303-311.

(59) Sherr L, Bolding G, Maguire M. Viagra use and sexual risk behavior among gay men in London. *AIDS*. 2000; 14:2051-2052.

(60) HILL AB. The environment and disease: associations or causation? *Proceedings of the Royal Society of Medicine*. 1965; 58:295-300.

(61) Fendrich M, Johnson T. Editors' introduction to this special issue on club drug epidemiology. *Substance Use & Misuse*. 2005; 40:1179-1184.

(62) Maxwell JC. Party drugs: Properties, prevalence, patterns, and problems. *Substance Use & Misuse*. 2005; 40:1203-1240.

(63) Degenhardt L, Copeland J, Dillon P. Recent trends in the use of "club drugs": An Australian review. *Substance Use & Misuse*. 2005; 40:1241-1256.

(64) Lenton S, Boys A, Norcross K. Raves, drugs and experience: drug use by a sample of people who attend raves in Western Australia. *Addiction*. 1997; 92:1327-1337.

(65) Gable RS. Acute toxic effects of club drugs. *J Psychoactive Drugs*. 2004; 36:303-313.

(66) Teter CJ, Guthrie SK. A comprehansive review of MDMA and GHB: two common club drugs. *Pharmacotherapy*. 2001; 21:1486-1513.

(67) Simons JS, Gaher RM, Correia CJ *et al*. Club drug use among college students. *Addict Behav*. 2005; In press.

(68) National Institutes on Drug Abuse. Club drugs: what are they? NIDA Notes 14[6]. 2000. 2-2-2005. (Electronic Citation)

(69) United States Government Printing Office. Threat posed by the illegal importation, trafficking, and use of ecstasy and other "club" drugs. 101. 2000. Judiciary House of Representatives, Crime. (Hearing)

(70) Green AI. "Chem friendly": the institutional basis of "club drug" use in a sample of urban gay men. *Deviant Behavior*. 2003; 24:427-447.

(71) Mattison AM, Ross MW, Wolfson T *et al*. Circuit party attendance, club drug use, and unsafe sex in gay men. *J Subst Abuse*. 2001; 13:119-126.

(72) Leshner AI. Club drugs aren't "fun drugs". NIDA Reports on Science of Drug Abuse and Addiction . 2005. National Institute on Drug Abuse. (Electronic Citation)

(73) NIDA community drug alert bulletin- club drugs. National Institutes of Health Website . 2005. (Electronic Citation)

(74) Brecht M, O'Brien A, von Mayrhauser C *et al*. Methamphetmaine use and gender differences. *Addictive Behaviors*. 2004; 29:89-106.

(75) Abramson HA, Evans LT. Lysergic acid diethylamide (LSD 25): II. Psychobiological effects on the Siamese fighting fish. *Science*. 1954; 120:990-991.

(76) National Institute of Drug Abuse. Nationwide drug trends. September 2004. 2004. National Institutes of Health. NIDA InfoFacts. (Report)

(77) Roxburgh A, Degenhardt L, Breen C. Changes in patterns of drug use among injecting drug users following changes in the availability of heroin in New South Wales, Australia. *Drug Alcohol Rev*. 2004; 23:287-294.

(78) Topp L, Day C, Degenhardt L. Changes in patterns of drug injection concurrent with a sustained reduction in the availability of heroin in Australia. *Drug Alcohol Depend*. 2003; 70:275-286.

(79) NIDA Community Epidemiology Work Group. Epidemiologic trends in drug abuse: advanced report. December 2003. 2003. (Report)

(80) Thiede H, Valleroy LA, MacKellar DA *et al*. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health*. 2003; 93:1915-1921.

(81) Maxwell JC. Patterns of club drug use in the U.S., 2004. 2004. Austin, Texas, The Center for Excellence in Drug Epidemiology: The Gulf Coast Addiction Technology Transfer Center: University of Texas. (Report)

(82) Fendrich M, Wislar JS, Johnson TP *et al*. A contextual profile of club drug use among adults in Chicago. *Addiction*. 2003; 98:1693-1703.

(83) Freese TE, Miotto K, Reback CJ. The effects and consequences of selected club drugs. *Journal of Substance Abuse Treatment*. 2002; 23:151-156.

(84) Kohrrs R, Duriex ME. Ketamine: teaching an old drug new tricks. *Anethesia and Analgesia*. 1998; 87:1186-1193.

(85) Buffum J. Pharmacosexology; the effects of drugs on sexual function a review. *Journal of Psychoactive Drugs*. 1982; 14:5-41.

(86) Kurtz SP. Post-circuit blues: motivations and consequences of cystal meth use among gay men in Miami. *AIDS and Behavior*. 2005; 9:63-72.

(87) Ekmekcioglu O, Inci M, Demirci D *et al*. Effects of sildenafil citrate on ejaculation latency, detumescence time, and refractory period: Placebo-controlled, double-blind, crossover laboratory setting study. *Urology*. 2005; 65:347-352.

(88) Boyce EG, Umland EM. Sildenafil citrate: a therapeutic update. *Clinical Therapeutics*. 2001; 23:2-23.

(89) Eid JF. Sildenafil citrate: current clinical experience. *International Journal of Impotence Research*. 2000; 12:S62-S66.

(90) McKim WA. Drugs and behavior. 5th ed. Upper Saddle River: Prentice Hall, 2003.

(91) National Institute of Drug Abuse. Ecstasy: what we know and don't know about MDMA: a scientific review. 2001. (Report)

(92) French RS, Power R. Self-reported effects of alkyl nitrate use : a qualitative study amongst targeted groups. *Addiction Research*. 2001; 5:519-548.

(93) Gillies HC, Roblin D, Jackson G. Coronary and systemic hemodynamic effects of sildenafil citrate: from basic science to clinical studies in patients with cardiovascular disease. *International Journal of Cardiology*. 2002; 86:131-141.

(94) Ishikura F, Beppu S, Hamada T *et al*. Effects of sildenafil citrate (Viagra) combined with nitrate on the heart. *Circulation*. 2000; 102:2516-2521.

(95) Romanelli F, Smith KM, Thornton AC *et al*. Poppers: Epidemiology and clinical management of inhaled nitrite abuse. *Pharmacotherapy*. 2004; 24:69-78.

(96) Smith KM, Larive LL, Romanelli F. Club drugs: methylenedioxymethampetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate. *American Journal of Health-Systems Pharmocology*. 2002; 59:1067-1076.

(97) Farre M, Teran MT, Cami J. A comparison of the acute behavioral effects of flunitrazepam and triazolam in healthy volunteers. *Psychopharmacology*. 1996; 125:1-12.

(98) Dowd SM, Strong MJ, Janicak PG *et al*. The Behavioral and cognitive effects of two benzodiazepines associated with drug-facilitated sexual assault. *Journal of Forensic Sciences*. 2002; 47:1101-1107.

(99) Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. *Drug and Alcohol Dependence*. 2001; 63:1-22.

(100) Anglin D, Spears KL, Hutson HR. Flunitrazepam and its involvement in date or acquaintance rape. *Academic Emergency Medicine*. 1997; 4:323-326.

(101) Britt GC, McCance-Katz EF. A brief overview of the clinical pharmacology of "club drugs". *Substance Use & Misuse*. 2005; 40:1189-1201.

(102) Figueroa JP, Brathwaite A, Morris J *et al*. Rising HIV-1 prevalence among sexually transmitted disease clinic attendees in Jamacia: traumatic sex and genital ulcers as risk factors. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology*. 1994; 7:310-316.

(103) Blattner WA, O'Brien TR, Mueller NE. Retroviruses: Human Immunodeficiency virus. In: Evans AS, Kaslow RA, editors. Viral Infections of Humans. New York: Plenum Medical Book Company, 1997: 713-783.

(104) Ambroziak J, Levy JA. Epidemiology, natural history, and pathogenesis of HIV infection. In: Holmes KK, Sparling PF, Mardh P, Lemon SM, Stamm WE, Piot P *et al*., editors. Sexually Transmitted Diseases. New York: McGraw-Hill, 1999: 251-258.

(105) Chmiel J, Detels R, Kaslow RA *et al*. Factors associated with prevalent HIV infection in the multicenter AIDS cohort. *American Journal of Epidemiology*. 1997; 126:568-577.

(106) Kvarnstrom A, Karlsten R, Quiding H *et al*. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. *Acta Anaesthesiologica Scandinavica*. 2003; 47:868-877.

(107) Myers T, Aguinaldo JP, Dakers D *et al*. How drug using men who have sex with men account for substance use during sexual behaviours: Questioning

assumptions of HIV prevention and research. *Addiction Research & Theory*. 2004; 12:213-229.

(108) Semple SJ, Patterson TL, Grant I. Motivations associated with methamphetamine use among HIV+ men who have sex with men. *J Subst Abuse Treat*. 2002; 22:149-156.

(109) McElrath K. MDMA and sexual behavior: Ecstasy users' perceptions about sexuality and sexual risk. *Substance Use & Misuse*. 2005; 40:1461-1477.

(110) Levy KB, O'Grady KE, Wish ED *et al*. An in-depth qualitative examination of the ecstasy experience: Results of a focus group with ecstasy-using college students. *Substance Use & Misuse*. 2005; 40:1427-1441.

(111) Delate T, Simmons VA, Motheral BR. Patterns of sildenafil among commercially insured adults in the United States: 1998-2002. *International Journal of Impotence Research*. 2004; 16:313-318.

(112) Romanelli F, Smith KM. Recreational use of sildenafil by HIV-positive and -negative homosexual/bisexual males. *Ann Pharmacother*. 2004; 38:1024-1030.

(113) Aldridge J, Measham F. Sildenafil (Viagra) is used as a recreational drug in England. *British Medical Journal*. 1999; 318:669.

(114) Crosby R, Diclemente RJ. Use of recreational Viagra among men having sex with men. *Sex Transm Infect*. 2004; 80:466-468.

(115) Halkitis PN, Fischgrund BN, Parsons JT. Explanations for methamphetamine use among gay and bisexual men in New York City. *Substance Use & Misuse*. 2005; 40:1331-1345.

(116) French R, Power R. A qualitative study of the social contextual use of alkyl nitrites (poppers) among targeted groups. *Journal of Drug Issues*. 1998; 28:57-76.

(117) Strathdee SA, Martindale SL, Cornelisse PG *et al*. HIV infection and risk behaviours among young gay and bisexual men in Vancouver. *CMAJ*. 2000; 162:21-25.

(118) Weber AE, Craib KJ, Chan K *et al*. Determinants of HIV serconversion in an era of increasing HIV infection among young gay and bisexual men. *AIDS*. 2003; 17:774-777.

(119) Strathdee SA, Hogg RS, Martindale SL *et al*. Determinants of sexual risk-taking among young HIV-negative gay and bisexual men. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998; 19:61-66.

(120) James IP. A methylamphetamine epidemic? *Lancet*. 1968; 1:916.

(121) Anonymous. Abuse of methylamphetamine. *Lancet*. 1968; 2:818.

(122) Kokkevi A, Stefanis N, Anastasopoulou E *et al*. Personality disorders in drug abusers: Prevalence and their association with AXIS I disorders as predictors of treatment retention. *Addictive Behaviors*. 1998; 23:841-853.

(123) Semple SJ, Patterson TL, Grant I. Psychosocial predictors of unprotected anal intercourse in a sample of HIV positive gay men who volunteer for a sexual risk reduction intervention. *AIDS Education and Prevention*. 2000; 12:416-430.

(124) Rhodes T, Stimson GV. What is the relationship between drug taking and sexual risk? social realtions and social research. *Sociology of Health and Illness*. 1994; 16:209-228.

(125) Rhodes T. Culture, drugs and unsafe sex: confusion about casuation. *Addiction*. 1996; 91:753-758.

(126) McKirnan DJ, Ostrow DG, Hope B. Sex, drugs and escape: a psychological model of HIV-risk sexual behaviours. *AIDS Care*. 1996; 8:655-669.

(127) Ostrow D, McKirnan D. Prevention of substance-related high-risk sexual behavior among gay men: critical review of the literature and proposed harm reduction approach. *Journal of the Gay and Lesbian Medical Association*. 1997; 1:97-110.

(128) McKirnan DJ, Vanable PA, Ostrow DG *et al*. Expectancies of sexual "escape" and sexual risk among drug and alcohol-involved gay and bisexual men. *Journal of Substance Abuse*. 2001; 13:137-154.

(129) Ross MW, Mattison AM, Franklin DR, Jr. Club drugs and sex on drugs are associated with different motivations for gay circuit party attendance in men. *Subst Use Misuse*. 2003; 38:1173-1183.

(130) Mccoul MD, Haslam N. Predicting high risk sexual behaviour in heterosexual and homosexual men: the roles of impulsivity and sensation seeking. *Personality and Individual Differences*. 2001; 31:1303-1310.

(131) Patterson TL, Semple SJ, Zians JK *et al*. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:I120-I126.

(132) Windle RC, Windle M. An investigation of adolescents' substance use behaviors, depressed affect, and suicidal behaviors. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 1997; 38:921-929.

(133) Parker G, Roy K. Adolescent depression: a review. *Australian and New Zealand Journal of Psychiatry*. 2001; 35:572-580.

(134) Kim MT, Han HR, Hill MN *et al*. Depression, substance use, adherence behaviors, and blood pressure in urban hypertensive black men. *Annals of Behavioral Medicine*. 2003; 26:24-31.

(135) Bing EG, Burnam A, Longshore D *et al*. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*. 2001; 58:721-728.

(136) Roiser JP, Sahakian BJ. Relationship between ecstasy use and depression: a study controlling for poly-drug use. *Psychopharmacology*. 2004; 173:411-417.

(137) Botnick MR, Heath KV, Cornelisse PGA *et al*. Correlates of suicide attempts in an open cohort of young men who have sex with men. *Canadian Journal of Public Health-Revue Canadienne de Sante Publique*. 2002; 93:59-62.

(138) Urbina A, Jones K. Crystal methamphetamine, its analogues, and HIV infection: medical and psychiatric aspects of a new epidemic. *Clin Infect Dis*. 2004; 38:890-894.

(139) Morrill AC, Kasten L, Urato M *et al*. Abuse, addiction, and depression as pathways to sexual risk in women and men with a history of substance abuse. *Journal of Substance Abuse*. 2001; 13:169-184.

(140) Doll LS, Beeker C. Male bisexual behavior and HIV risk in the United States: Synthesis of research with implications for behavioral interventions. *AIDS Education and Prevention*. 1996; 8:205-225.

(141) Inciardi JA. Crack, Crack House Sex, and HIV Risk. *Archives of Sexual Behavior*. 1995; 24:249-269.

(142) Kunawararak P, Beyrer C, Natpratan C *et al*. The Epidemiology of HIV and Syphilis Among Male Commercial Sex Workers in Northern Thailand. *AIDS*. 1995; 9:517-521.

(143) Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 1998.

(144) Gordis L. Epidemiology. 1st ed. Philadelphia: W.B.Saunders Company, 1996.

(145) Leigh BC, Stall R. Substance use and risky sexual behavior for exposure to HIV: Issues in methodology, interpretation, and prevention. *American Psychologist*. 1993; 48:1035-1045.

(146) Gorman EM, Barr BD, Hansen A *et al*. Speed, sex, gay men, and HIV: ecological and community perspectives. *Medical Anthropology Quarterly*. 1997; 11:505-515.

(147) Diaz RM, Heckert AL, Sanchez J. Reasons for stimulant use among latino gay men in san francisco: a comparison between methamphetamine and cocaine users. *J Urban Health*. 2005; 82:i71-i78.

(148) National Institutes on Drug Abuse. Methamphetamine: abuse and addiction. *NIDA Research Report Series*. 2002; 02-4210.

(149) Gleghorn AA, Marx R, Vittinghoff E *et al*. Associations between drug use patterns and HIV risks among homeless, runaway, and street youth in Northern California. *Drug and Alcohol Dependence*. 1998; 51:219-227.

(150) Bull SS, Piper P, Rietmeijer C. Men who have sex with men and also inject drugs-profiles of risk related to the synergy of sex and drug injection behaviors. *J Homosex*. 2002; 42:31-51.

(151) Semple SJ, Patterson TL, Grant I. A comparison of injection and non-injection methamphetamine-using HIV positive men who have sex with men. *Drug Alcohol Depend*. 2004; 76:203-212.

(152) Burcham JL, Tindall B, Marmor M *et al*. Incidence and risk factors for human immunodeficiency virus seroconversion in a cohort of Sydney homosexual men. *The Medical Journal of Australia*. 1989; 150:634-639.

(153) Page-Shafer K, Veugelers PJ, Moss AR *et al*. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994. *Am J Epidemiol*. 1997; 146:531-542.

(154) Chesney MA, Barrett DC, Stall R. Histories of substance use and risk behavior: Precursors to HIV seroconversion in homosexual men. *American Journal of Public Health*. 1998; 88:113-116.

(155) Rusch M, Lampinen TM, Schilder A *et al*. Unprotected anal intercourse associated with recreational drug use among young men who have sex with men depends on partner type and intercourse role. *Sex Transm Dis*. 2004; 31:492-498.

(156) Harawa NT, Greenland S, Bingham TA *et al*. Associations of race/ethnicity with HIV prevalence and HIV-related behaviors among young men who have sex with men in 7 urban centers in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:526-536.

(157) Shoptaw S, Reback CJ, Peck JA *et al*. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug and Alcohol Dependence*. 2004.

(158) Shoptaw S, Reback CJ, Frosch DL *et al*. Stimulant abuse treatment as HIV prevention. *J Addict Dis*. 1998; 17:19-32.

(159) de la Torre R, Farre M, Roset PN *et al*. Human pharmacology of MDMA - Pharmacokinetics, metabolism, and disposition. *Therapeutic Drug Monitoring*. 2004; 26:137-144.

(160) Klitzman RL, Greenberg JD, Pollack LM *et al*. MDMA ('ecstasy') use, and its association with high risk behaviors, mental health, and other factors among gay/bisexual men in New York City. *Drug and Alcohol Dependence*. 2002; 66:115-125.

(161) Kim AA, Kent C, Klausner J. Risk facors for rectal gonococcal infection amidst resurgence in HIV transmission. *Sex Transm Dis*. 2003; 30:813-817.

(162) Morgan CJA, Riccelli M, Maitland CH *et al*. Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug and Alcohol Dependence*. 2004; 75:301-308.

(163) Parrott A, Morinan A, Moss M, Scholey A. Understanding drugs and behaviour. Chichester: John Wiley & Sons Inc., 2004.

(164) Woody GE, Donnell D, Seage GR *et al*. Non-injection substance use correlates with risky sex among men having sex with men: data from HIVNET. *Drug Alcohol Depend*. 1999; 53:197-205.

(165) Purcell DW, Parsons JT, Halkitis PN *et al*. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse*. 2001; 13:185-200.

(166) Koblin BA, Chesney MA, Husnik MJ *et al*. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. *Am J Public Health*. 2003; 93:926-932.

(167) Stall R, Wiley J. A comparison of alcohol and drug use patterns of homosexual and heterosexual men: the San Francisco Men's Health Study. *Drug and Alcohol Dependence*. 1998; 22:63-73.

(168) Ostrow DG, Beltran ED, Joseph JG *et al*. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. *J Subst Abuse*. 1993; 5:311-325.

(169) United States Drug Enforcement Administration (DEA). Flunitrazepam (Rohypnol) "roofies". www.dea.gov . 2005. (Electronic Citation)

(170) Simmons MM, Cupp MJ. Use and abuse of flunitrazepam. *Ann Pharmacother*. 1998; 32:117-119.

(171) Gahlinger PM. Club drugs: MDMA, gamma-hydroxybutyrate (GHB), Rohypnol, and ketamine. *Am Fam Physician*. 2004; 69:2619-2626.

(172) Klein M, Kramer F. Rave drugs: pharmacological considerations. *AANA J*. 2004; 72:61-67.

(173) Ompad DC, Galea S, Fuller CM *et al*. Club drug use among minority substance users in New York City. *J Psychoactive Drugs*. 2004; 36:397-399.

(174) Parks KA, Kennedy CL. Club drugs: reasons for and consequences of use. *J Psychoactive Drugs*. 2004; 36:295-302.

(175) Breslau K. The 'sextasy' craze. Clubland's dangerous party mix: Viagra and ecstasy. *Newsweek*. 2002; 139:30.

(176) Loeb L. Viagra: the science and politics of drugs, sex, and risk. *Focus*. 2004; 19:4-7.

(177) James JS. Viagra warning re "poppers" and notice re protease inhibitors. *AIDS Treat News*. 1998;1.

(178) Anonymous. HIV-STD synergy worries public health officials. Drugs, Viagra play role in problem. *AIDS Alert*. 2004; 19:81-83.

(179) Glossmann H, Petrischor G, Bartsch G. Molecular mechanisms of the effects of sildenafil (VIAGRA (R)). *Experimental Gerontology*. 1999; 34:305-318.

(180) Padma-Nathan H, Eardley I, Kloner RA *et al*. A 4-year update on the safety of sildenafil citrate (Viagra((R))). *Urology*. 2002; 60:67-90.

(181) Chu PL, McFarland W, Gibson S *et al*. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr*. 2003; 33:191-193.

(182) Colfax GN, Mansergh G, Guzman R *et al*. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr*. 2001; 28:373-379.

(183) Hirshfield S, Remien RH, Humberstone M *et al*. Substance use and high-risk sex among men who have sex with men: a national online study in the USA. *AIDS Care*. 2004; 16:1036-1047.

(184) Hirshfield S, Remien RH, Walavalkar I *et al*. Crystal methamphetamine use predicts incident STD infection among men who have sex with men recruited online: a nested case-control study. *J Med Internet Res*. 2004; 6:e41.

(185) Cachay E, Mar-Tang M, Mathews WC. Screening for potentially transmitting sexual risk behaviors, urethral sexually transmitted infection, and sildenafil use among males entering care for HIV infection. *AIDS Patient Care STDS*. 2004; 18:349-354.

(186) Morabia A. Poppers, Kaposi's sarcoma, and HIV infection: empirical example of a strong confounding effect? *Prev Med*. 1995; 24:90-95.

(187) Tabet SR, Krone MR, Paradise MA *et al*. Incidence of HIV and sexually transmitted diseases (STD) in a cohort of HIV-negative men who have sex with men (MSM). *AIDS*. 1998; 12:2041-2048.

(188) Buchbinder S, Vittinghoff E, Heagerty P *et al*. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 39:82-89.

(189) Detels R, English P, Visscher BR *et al*. Seroconversion, sexual activity, and condom use among 2915 HIV seronegative men followed for up to 2 years. *J Acquir Immune Defic Syndr*. 1989; 2:77-83.

(190) Winkelstein W, Lyman DM, Padian N *et al*. Sexual practices and risk of infection by the human immunodeficiency virus: the San Francisco Men's Health Study. *Journal of the American Medical Association*. 1987; 257:321-325.

(191) Difranceisco W, Ostrow DG, Chmiel JS. Sexual adventurism, high-risk behavior, and human immunodeficiency virus-1 seroconversion among the Chicago MACS-CCS cohort, 1984 to 1992. A case-control study. *Sex Transm Dis*. 1996; 23:453-460.

(192) Kuiken CL, van Griensven GJ, de Vroome EM *et al*. Risk factors and changes in sexual behavior in male homosexuals who seroconverted for human immunodeficiency virus antibodies. *Am J Epidemiol*. 1990; 132:523-530.

(193) Kingsley LA, Detels R, Kaslow R *et al*. Risk factors for seroconversion to human immunodeficiency virus among male homosexuals. Results from the Multicenter AIDS Cohort Study. *Lancet*. 1987; 1:345-349.

(194) Crosby GM, Stall RD, Paul JP *et al*. Condom use among gay/bisexual male substance abusers using the timeline follow-back method. *Addictive Behaviors*. 1996; 21:249-257.

(195) Lampinen TM, Schilder AJ, McErlane K, Miller ML, Chan K, Schechter MT *et al*. Inadvertent consumption of crystal methamphetamine sold as ecstasy in Vancouver, British Columbia and relation to sexual risk behaviors of young gay men. 15th International Conference on the Reduction of Drug Related Harm Melbourne, Australia[Abstract # 998]. 2004. 4-20-2004.

(196) Clatts MC, Goldsamt LA, Yi H. Club drug use among young men who have sex with men in NYC: A preliminary epidemiological profile. *Substance Use & Misuse*. 2005; 40:1317-1330.

(197) Lee SJ, Galanter M, Dermatis H *et al*. Circuit parties and patterns of drug use in a subset of gay men. *J Addict Dis*. 2003; 22:47-60.

(198) Greenwood GL, White EW, Page-Shafer K *et al*. Correlates of heavy substance use among young gay and bisexual men: The San Francisco Young Men's Health Study. *Drug and Alcohol Dependence*. 2001; 61:105-112.

(199) Lankenau SE, Clatts MC. Patterns of polydrug use among ketamme injectors in New York City. *Substance Use & Misuse*. 2005; 40:1381-1397.

(200) Ter Bogt TFM, Engels RCME. "Partying" hard: Party style, motives for and effects of MDMA use at rave parties. *Substance Use & Misuse*. 2005; 40:1479-1502.

(201) Maxwell JC, Spence RT. Profiles of club drug users in treatment. *Substance Use & Misuse*. 2005; 40:1409-1426.

(202) Barrett SP, Gross SR, Garand I *et al*. Patterns of simultaneous polysubstance use in Canadian rave attendees. *Substance Use & Misuse*. 2005; 40:1525-1537.

(203) Halkitis PN, Green KA, Mourgues P. Longitudinal Investigation of Methamphetamine Use Among Gay and Bisexual Men in New York City: Findings from Project BUMPS. *J Urban Health*. 2005; 82:i18-i25.

(204) Colfax G, Coates TJ, Husnik MJ *et al*. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health*. 2005; 82:i62-i70.

(205) Klee H, Faugier J, Hayes C *et al*. AIDS-related risk behaviour, polydrug use and temazepam. *Brittish Journal of Addiction*. 1990; 85:1125-1132.

(206) Stall RD, Paul JP, Greenwood GL *et al*. Alcohol use, drug use and alcohol-realted problems among men who have sex with men: the Urban Men's Health Study. *Addiction*. 2001; 96:1589-1601.

(207) Degenhardt L, Topp L. 'Crystal meth' use among polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. *International Journal of Drug Policy*. 2003; 14:17-24.

(208) Stall R, Purcell DW. Intertwining epidemics: a review of research on substance use among men who have sex with men and its connection to the AIDS epidemic. *AIDS and Behavior*. 2000; 4:181-192.

(209) Clatts MC, Sothern JL. Challenges in research on drug and sexual risk practices of men who have sex with men: applications of ethnography in HIV epidemiology and prevention. *AIDS and Behavior*. 1999; 4:169-179.

(210) Stall RD, Hays RB, Waldo CR *et al*. The Gay '90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. *AIDS*. 2000; 14:S101-S114.

(211) Ostrow DG. The role of drugs in the sexual lives of men who have sex with men: continuing barriers to researching this question. *AIDS and Behavior*. 1999; 4:205-219.

(212) Finer LB, Darroch JE, Singh S. Sexual partnership patterns as a behavioral risk factor for sexually transmitted diseases. *Family Planning Perspectives*. 1999; 31:228-236.

(213) Frosch D, Shoptaw S, Huber A *et al*. Sexual HIV risk among gay and bisexual male methamphetamine abusers. *J Subst Abuse Treat*. 1996; 13:483-486.

(214) Shoptaw S, Peck J, Reback CJ *et al*. Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment. *J Psychoactive Drugs*. 2003; 35 Suppl 1:161-168.

(215) Patterson TL, Semple SJ. Sexual risk reduction among HIV-positive drug-using men who have sex with men. *J Urban Health*. 2003; 80:iii77-iii87.

(216) Reback CJ, Larkins S, Shoptaw S. Changes in the meaning of sexual risk behaviors among gay and bisexual male methamphetamine abusers before and after drug treatment. *AIDS Behav*. 2004; 8:87-98.

(217) Chang Y, Chen TL, Sheu JR *et al*. Suppressive effects of ketamine on macrophage functions. *Toxicology and Applied Pharmacology*. 2005; 204:27-35.

(218) Connor TJ. Methylenedioxymethamphetamine (MDMA, 'Ecstasy'): a stressor on the immune system. *Immunology*. 2004; 111:357-367.

(219) Maravelias C, Dona A, Athanaselis S *et al*. Cytotoxic and immunomodulative effects of flunitrazepam, zipeprol and trihexyphenidyl on human peripheral blood lymphocytes. *Veterinary and Human Toxicology*. 2000; 42:205-208.

(220) Laidler KAJ. The rise of club drugs in a heroin society: The case of Hong Kong. *Substance Use & Misuse*. 2005; 40:1257-1278.

(221) Kulsudjarit K. Drug problem in southeast and southwest Asia. *Ann N Y Acad Sci*. 2004; 1025:446-457.

(222) Beyrer C, Razak MH, Jittiwutikarn J *et al*. Methamphetamine users in northern Thailand: changing demographics and risks for HIV and STD among treatment-seeking substance abusers. *Int J STD AIDS*. 2004; 15:697-704.

(223) Sattah MV, Supawitkul S, Dondero TJ *et al*. Prevalence of and risk factors for methamphetamine use in northern Thai youth: results of an audio-computer-assisted self-interviewing survey with urine testing. *Addiction*. 2002; 97:801-808.

(224) Colfax G, Vittinghoff E, Husnik MJ *et al*. Substance use and sexual risk: A participant- and episode-level analysis among a cohort of men who have sex with men. *American Journal of Epidemiology*. 2004; 159:1002-1012.

(225) Fernandez MI, Perrino T, Collazo JB *et al*. Surfing new territory: club-drug use and risky sex among Hispanic men who have sex with men recruited on the internet. *J Urban Health*. 2005; 82:i79-i88.

(226) Banta-Green C, Goldbaum G, Kingston S *et al*. Epidemiology of MDMA and associated club drugs in the Seattle area. *Substance Use & Misuse*. 2005; 40:1295-1315.

(227) Fernandez MI, Bowen GS, Varga LM *et al*. High rates of club drug use and risky sexual practices among Hispanic men who have sex with men in Miami, Florida. *Substance Use & Misuse*. 2005; 40:1347-1362.

(228) Krebs CP, Steffey DM. Club drug use among delinquent youth. *Substance Use & Misuse*. 2005; 40:1363-1379.

(229) Kelly BC. Conceptions of risk in the lives of club drug-using youth. *Substance Use & Misuse*. 2005; 40:1443-1459.

(230) Goldsamt LA, O'Brien J, Clatts MC *et al*. The relationship between club drug use and other drug use: A survey of New York City middle school students. *Substance Use & Misuse*. 2005; 40:1539-1555.

(231) Tong T, Boyer EW. Club drugs, smart drugs, raves, and circuit parties: an overview of the club scene. *Pediatr Emerg Care*. 2002; 18:216-218.

(232) Gorman EM, Carroll RT. Substance abuse and HIV: considerations with regard to methamphetamines and other recreational drugs for nursing practice and research. *J Assoc Nurses AIDS Care*. 2000; 11:51-62.

(233) Molitor F, Truax SR, Ruiz JD *et al*. Associations with methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. *Western Journal of Medicine*. 1998; 168:93-97.

(234) Reback CJ, Grella CE. HIV risk behaviors of gay and bisexual male methamphetamine users contacted through street outreach. *Journal of Drug Issues*. 1999; 29:155-166.

(235) Whittington WL, Collis T, Dithmer-Schreck D *et al*. Sexually transmitted diseases and human immunodeficiency virus-discordant partnerships among men who have sex with men. *Clin Infect Dis*. 2002; 35:1010-1017.

(236) Mulry G, Kalichman SC, Kelly JA. Substance Use and Unsafe Sex Among Gay Men - Global Versus Situational Use of Substances. *Journal of Sex Education & Therapy*. 1994; 20:175-184.

(237) Clutterbuck DJ, Gorman D, McMillan A *et al*. Substance use and unsafe sex amongst homosexual men in Edinburgh. *AIDS Care*. 2001; 13:527-535.

(238) Moss AR, Osmond D, Bacchetti P *et al*. Risk factors for AIDS and HIV seropositivity in homosexual men. *Am J Epidemiol*. 1987; 125:1035-1047.

(239) Seage GR, III, Mayer KH, Horsburgh CR, Jr. *et al*. The relation between nitrite inhalants, unprotected receptive anal intercourse, and the risk of human immunodeficiency virus infection. *Am J Epidemiol*. 1992; 135:1-11.

(240) Ostrow DG, DiFranceisco WJ, Chmiel JS *et al*. A case-control study of human immunodeficiency virus type 1 seroconversion and risk-related behaviors in the

Chicago MACS/CCS Cohort, 1984-1992. Multicenter AIDS Cohort Study. Coping and Change Study. *Am J Epidemiol*. 1995; 142:875-883.

(241) McCusker J, Westenhouse J, Stoddard AM *et al*. Use of drugs and alcohol by homosexually active men in relation to sexual practices. *J Acquir Immune Defic Syndr*. 1990; 3:729-736.

III. METHODS

The methods described in this chapter were applied to manuscripts 2 and 3. All of the data for these two studies came from the Acute Infection and Early Disease Research Program (AIEDRP). Data were derived from a baseline computer assisted survey instrument (CASI) that was implemented in May of 2002. These data represent a cross-sectional study design, but incorporate repeated measures. The study protocol for data collection was approved by the institutional review boards (IRB) of University of California, San Diego (UCSD), University of California, Los Angeles (UCLA), Harbor UCLA Hospital, and Cedar-Sinai Hospital. All participants completed informed consent prior to study participation. Additionally, analysis of data for manuscripts 2 and 3 was approved by the San Diego State University IRB in accordance with joint doctoral program regulations.

A. The Acute Infection and Early Disease Research Program (AIEDRP)

AIEDRP is a multi-site research network funded by the Division of AIDS (DAIDS) and the National Institutes of Allergy and Infectious Diseases (NIAID) [1]. Established in 1997, the primary research goal of AIEDRP was to increase the understanding of the natural history of HIV disease through identifying people with acute (0-30 days) and early (1-12 months) HIV infection and monitoring their disease progression through periodic collection of biological samples. Currently, the AIEDRP network consists of nine independent sites, eight funded by NIAID and one additional site that receives funding from other sources. Each site may have satellite sites in other cities in the United States or other countries throughout the world.

Currently, AIEDRP investigators conduct both local research studies at their individual sites and cooperative research studies that share data between sites. The data for this dissertation comes from an independent project conducted at the UCSD AIEDRP site and its satellite site at UCLA. All participants and individuals screening for potential participation in San Diego are seen at the Antiviral Research Center (AVRC) and in Los Angeles are seen either at Harbor Hospital UCLA or Cedar-Sinai, Culver City.

B. Recruitment of Participants

Recruitment of potential participants is conducted in a similar manner in San Diego and Los Angeles. The methods employed are used to identify the largest possible number of individuals who are experiencing acute or early HIV infection. Due to longer duration of data collection, smaller county size, and greater financial feasibility, the San Diego site conducts more intensive recruitment than Los Angeles.

In San Diego, recruitment for AIEDRP is conducted under the study name, “First Choice”. Brochures and business cards are distributed in multiple locations and connections are made with community organizations, medical and psychological providers, substance abuse programs, clinics, and hospitals. First Choice brochures (Figure 3-1) and business cards (Figure 3-2) are distributed to bars, bathhouses, gay oriented events, and community organizations that cater to gay identified men and MSM in order to establish recognition in the community for self-referral or friend-referral to the AVRC. Additionally, brochures and business cards are displayed at San Diego County (SDC) HIV testing sites, SDC sexually transmitted disease (STD) clinics, substance abuse programs, emergency rooms and other medical locations and physician’s offices

where individuals may potentially be diagnosed with HIV. In addition to providing recruitment materials, seminars, informational dinners, and trainings are arranged for HIV test site counselors, STD clinic staff, and physicians who may diagnose or treat people who become infected with HIV. AVRC researchers and staff also provide community education and raise awareness through presentations and organization and management of community support and advisory groups. These efforts have created effective community ties that provide multiple avenues of recruitment for the AIEDRP/First Choice study in San Diego.

Individuals who are referred to the First Choice study most often initiate contact with the AVRC. Those who contact the AVRC (usually by telephone) are screened by an AIEDRP nurse, outreach staff, or physician to determine if they are a good candidate to receive HIV RNA screening to determine if they are eligible for AIEDRP enrollment. Candidates who are selected for HIV RNA screening are those who are deemed likely to have acute or early HIV infection. These individuals meet one of the following conditions: 1) they exhibit primary HIV symptoms (Table 3-1) and report high-risk sexual behavior; 2) they report unprotected sexual contact with either a partner who is known to have HIV or a partner of unknown status who has a high probability of having HIV; 3) they have tested positive for the first time outside of the AVRC and had a negative HIV test within the last year; or 4) they are asymptomatic, but report an “extreme” high risk exposure, such as physically traumatic penetrative anal contact during non-consensual sex. If the individual is eligible, a RNA PCR screening appointment is made.

In Los Angeles, a smaller number of individuals are referred to AIEDRP annually. Participants are recruited in much the same way as San Diego; however there is less physician referral. Additionally, the site in Los Angeles experiences competition with other investigators that recruit recently HIV infected individuals for their research

studies. Similar procedures to San Diego are followed in Los Angeles. Interested participants contact the study by telephone and are screened for HIV infection using HIV RNA PCR.

When potential participants contact the San Diego site a screening form is generated by the screen coordinator. When this form is filled in completely, information on how the individual was referred to the AVRC, age, sex, ethnicity, and employment is obtained. Between May 2002, when the CASI questionnaire was added to the San Diego AIEDRP site, and November 2005, the date at which collection of data for manuscripts 2 and 3 ceased, 575 individuals who contacted the First Choice study were considered eligible for HIV RNA screening. During the second half of 2002, either no information on how patients were referred was collected or the screening form was not available (Table 4-2). Data were collected on referral source for more than half of the individuals who contacted the first choice study and were eligible for screening in 2003 (62.3%), 2004 (59.7%), and 2005 (54.6%). For all years that data were collected, the largest proportion of referrals came from one of the San Diego County Health and Human Services public HIV and STD screening sites (16.7 % in 2003, 17.5% in 2004, 19.3% in 2005). Most people were referred from the HIV screening site located closest to the AVRC in the region of San Diego known as Hillcrest, an area of San Diego that is historically a gay and lesbian community. The second largest proportion of referrals came from community physicians and health care facilities, such as hospitals, in 2003 (14.8%) and 2004 (16.1%), but not in 2005 (8.4%). In 2005, the second largest proportion of referrals came from other patients who were enrolled in the study, friends, or sexual partners (12.6%), which was also a common referral source in 2003 (13.0%) and 2004 (10.1%). Fewer people were referred by community organizations, such as Being Alive and the Lesbian, Gay, Bisexual, and Transgendered Center, or those who

are affiliated with the UCSD AVRC in all years. The least common referral source reported for any year was self-referral (4.2% in 2003, 2.0% in 2004, 2.5% in 2005). Data on referral source of participants in Los Angeles was not collected.

C. Screening of Participants

Study appointments are scheduled for all individuals who are considered from their telephone screen to be at risk for acute or early HIV infection and are therefore eligible for HIV RNA screening. At their first visit, potential AIEDRP participants are consented, counseled by a nurse or screening staff, and their blood is drawn for HIV testing. The consent form for study screening is the full consent form to participate in the AIEDRP study and includes HIV serology testing, regular future visits, blood-draws, and all interviews (including CASI). The consent explains that patients will only continue on the study if they are diagnosed with acute or early HIV infection.

After patients are consented, they receive standard pre-test counseling for HIV testing according to Centers for Disease Control and Prevention (CDC) guidelines [2] and their HIV acquisition risks are discussed. Blood is drawn for HIV ribonucleic acid (RNA) testing by polymerase chain reaction (PCR), HIV antibody testing by Western Blot, HIV antibody testing by sensitive and less sensitive (detuned) enzyme-linked immunoassay (EIA), and other HIV related tests, such as CD4 T-cell count. Participants are scheduled for an appointment to receive their test results the following week. The HIV RNA, Western Blot, and EIA tests are used in conjunction with any previously documented test results to determine eligibility of the participants for AIEDRP.

At their second visit, patients receive their HIV test results and post-test counseling. Patients who are HIV negative by RNA PCR testing and have negative EIA and Western Blot are not eligible for enrollment into AIEDRP since they are not HIV

infected. These subjects are counseled on safer sexual practices and may be referred to other study protocols. Patients whose test results reveal that they have had HIV infection for more than 12 months are not eligible for AIEDRP because they have prevalent HIV infection rather than acute or early infection. These patients are informed of their diagnosis, provided post test counseling, and are referred to HIV organizations, support groups, physicians, and other studies for which they may be eligible.

Patients who have acute or early HIV infection (defined in section E) are told of their diagnosis, assigned an AIEDRP nurse, and are scheduled for a series of follow-up appointments. During this visit or one of the next three follow up visits at weekly intervals, AIEDRP participants are asked to complete the CASI. In San Diego, all English speaking participants were invited to complete the CASI, however in Los Angeles about one third of AIEDRP participants were not asked to complete CASI due limitations of space or time (for comparisons of non-participants to participants see section F: Study Population). All patients on the AIEDRP study are followed up indefinitely, every week for the first four weeks, then every four weeks for the next 20 weeks, and every eight to 12 weeks there after.

D. Laboratory HIV Tests used for Inclusion and Exclusion

As mentioned in the previous section, blood is drawn on potential participants for HIV testing by the following methods: HIV RNA testing by PCR, HIV antibody testing by Western Blot, and HIV antibody testing by sensitive and less sensitive (detuned) EIA. Each of these methods is used to provide unique information that allows for confirmation of HIV infection and determination of estimated date of infection.

HIV RNA testing is used to detect HIV viral RNA sequences in the plasma from patients. HIV RNA PCR has the highest specificity of all HIV tests and the sensitivity is

high for HIV subtypes A-G of group M. HIV RNA testing for the San Diego and Los Angeles AIEDRP cohorts was conducted using the commercially available Amplicor Assay (Roche Molecular Systems). According to Amplicor kit instructions, PCR is used to amplify HIV RNA in plasma, which is then quantified to determine HIV copy number.

Western Blots were conducted using a commercially available test kit (Cambridge Biotech). Western Blot is used to detect host antibody proteins against HIV [3]. This is accomplished by standard Western Blot technique wherein HIV antibody proteins are separated on a cellulose membrane by molecular weight and is probed by a solution that is made from the patients' blood sample. Binding to the membrane will occur at each HIV antibody protein site if that antibody is present within the patient's serum. Western Blot has been historically used as a confirmatory test for EIA positive tests. This is because Western Blot has a higher specificity than EIA, but a lower sensitivity.

There were two classes of EIA used to detect HIV, the commercially available HIV EIA and the less sensitive "detuned" EIA. The commercially available HIV EIA used in this study was manufactured by Abbott Laboratories. This EIA was developed to detect IgG and IgM antibodies against HIV-1 and HIV-2 [4]. This class of EIA is the standard test used to detect HIV in typical HIV testing and counseling sites. HIV EIA, like Western Blot, tests for host antibodies against HIV, however EIA detects simple binding of antibody in general and does not help to specify which antibody proteins have been activated. The less sensitive or detuned EIA was developed as a method for detecting incident HIV infection [5]. The detuned EIA is not a commercially available test kit. Detuned EIA is conducted by modifying the procedures for the commercially available HIV EIA to make detection of antibodies less sensitive as previously described [5].

E. Inclusion and Exclusion Criteria, Definition of Acute and Early Infection, and Estimated Date of Infection

Inclusion and exclusion criteria for the San Diego AIEDRP site (and the partner site in Los Angeles) apply to the entire AIEDRP network, as the overall goal is to identify people within their first 12 months of infection in order to study the natural history of HIV infection. However, other criteria, such as estimated date of HIV infection and definition of stage (acute versus early HIV infection) are established by individual site and may vary between sites. In this section inclusion/ exclusion criteria for the AIEDRP network and estimated date of infection and infection stage for the San Diego and Los Angeles sites are discussed.

Inclusion and Exclusion Criteria

To be eligible for AIEDRP individuals must be thirteen years of age or older, complete informed consent, assent if younger than 18 years of age with a parent or guardian completing informed consent, and have documented HIV infection within the previous 12 months [see Appendix B: AIEDRP Eligibility Form]. Potential participants must have acute or early HIV infection, and therefore meet one of the following criteria with regard to HIV testing and documentation: 1) a negative test results on an HIV EIA test and a Western Blot, but a detectable HIV viral load on the PCR test; 2) a positive HIV EIA and an indeterminate Western Blot; 3) a positive test result on an HIV EIA, and a negative test result on a less sensitive (detuned) EIA (i.e., a detuned EIA consistent with recent HIV infection); or 4) a positive EIA test with a documented HIV EIA negative test in the previous 12 months.

Individuals are excluded from participating in AIEDRP if they do not meet the inclusion criteria (i.e., being younger than 13 years of age; being unable to provide

documentation of recent infection, such as a negative EIA test result from the previous 12 months; and test results that are inconsistent with acute or early infection). Additionally, individuals are not eligible, regardless of the previous criteria, if they received more than seven days of anti-retroviral medication prior to study enrollment. However, individuals who receive post-exposure HIV treatment, but become infected with HIV are not excluded from enrollment.

Estimated Date of Infection and Stage of Infection

Acute infection is considered by the AIEDRP network as the first 30 days after HIV infection occurs and early infection is considered to be the next 11 months [see Appendix B: Estimated Date of Infection Rules]. According to diagnostic criteria for inclusion into AIEDRP, a patient is considered to be acutely infected if s/he has "positive plasma RNA (≥2000 copies/mL) or detectable serum p24 antigen within 14 days of study entry and one of the following:" 1) negative HIV EIA; 2) positive HIV EIA and negative or intermediate Western Blot; or 3) positive HIV EIA and Western Blot, but from the previous 30 days the patient had documented negative EIA, plasma HIV RNA, and Western Blot or a Western Blot lacking the p31 band. Patients with early HIV infection that have detectable plasma HIV RNA, test positive on both Western Blot and an HIV EIA, and either 1) test negative on a less sensitive detuned EIA; or 2) have a documented negative HIV EIA test within the 12 months prior.

Estimated date of infection is based on HIV and CD4 testing results from plasma. At the San Diego and Los Angeles AIEDRP locations, acutely HIV infected patients are assigned an estimated date of infection 21or 28 days before their initial screening blood draw [See Appendix B: Estimated Date of Infection Rules]. If the patient has detectable plasma HIV RNA, but all other HIV test results are negative, their

estimated date of infection is assigned as the date 21 days prior to when their plasma sample was obtained and they are classified as acute 1 (A1) (Table 3-3). If the patient has detectable plasma HIV RNA and an indeterminate Western Blot, their estimated date of infection is 28 days prior to the date of study entry (usually their screening visit) and they are classified as acute 2 (A2). When the viral plasma RNA is detectable, and the HIV EIA is positive, and the Western Blot has five or fewer bands or there is a documented negative HIV EIA or negative/indeterminate Western Blot within the previous 30 days, and the less sensitive detuned EIA is negative, the estimated date of infection is 45 days prior to enrollment; this is considered acute 3 (A3). An estimated date of infection of 85 days prior to enrollment is assigned when all criteria for early infection 1 are met, except there are more than five bands on the Western Blot, this is considered early infection 1 (E1). Finally, if all HIV tests (RNA, Western Blot, HIV EIA, and less sensitive detuned EIA) are positive then the estimated date of infection is the midpoint date between the last negative EIA and the first positive EIA (early infection 2, E2).

F. Study Population

Since the CASI was implemented in May 2002 until the data collection for manuscript 3 was completed in November 2005, there were 575 people eligible for screening in San Diego (Table 3-4) and 102 in Los Angeles (Table 3-5). Of these, 195 were recently infected and 181 became AIEDRP participants in San Diego. In Los Angeles, 70 were recently infected and 67 became AIEDRP participants (reasons for not enrolling are described in this section and Table 3-6).

In San Diego, of the 575 people eligible for screening, 40 (6.9%) did not attend their screening visit, 139 (24.2%) were determined to be chronically infected, 201

(34.9%) were uninfected, and 195 (33.9%) had acute or early infection (Table 3-4). There were some differences with regard to recruitment site; however data were too sparse to determine if such differences were statistically significant. A slightly higher percentage of the recently HIV infected individuals (9.2%) were referred by those who are affiliated with the AVRC than chronically infected (6.5%) or uninfected (3.5%) individuals. Additionally, fewer HIV negative individuals (4.5%) were referred by community physicians or healthcare facilities when compared to recently (14.9%) and chronically (15.6%) HIV infected individuals.

Most of the people who screened for AIEDRP at the AVRC were men (92.7%). A significantly larger proportion of women where HIV negative (11.9%) than recently HIV-infected (1.6%), chronically infected (4.4%), or untested (7.5%) (p=0.001). Over half of the screeners reported white ethnicity (66.4%), followed by Hispanic (18.4%), Black or African American (6.6%), and Asian (3.7%). When ethnic group was collapsed into white ethnicity versus all others, there were statistically significant differences in the proportion reporting white ethnicity by HIV status (p=0.01). Those who did not screen were least likely to report white ethnicity (45%), followed by chronically infected individuals (61.2%), followed by recently HIV infected individuals (67.7%), and finally, uninfected individuals (73.1); this trend was significant (p=0.01). The average age of those screening for AIEDRP was 34.5 years old and those who missed their screening appointment were younger (31.8 years) than the other groups, but this difference was not statistically significant (p=0.13).

In Los Angeles, data was not available on referral source. However, similar trends to San Diego were observed for demographic characteristics (Table 3-5). Most (97.1%) screeners were men. Over half (64.7%) reported white ethnicity, followed by Hispanic (25.5%), Black or African American (3.9%), and Asian (2.9%). The average

age of screeners in Los Angeles was 36.4 years. There were no significant differences in sex, ethnicity (white versus all others), or age by categories of HIV status. Additionally, there were no significant differences between screeners from Los Angeles and San Diego by age (p=0.47), ethnicity (white versus other) (p=0.39), or sex (p=0.99).

Of those who screened for AIEDRP and received a diagnosis of recent HIV infection, 20 in San Diego and 30 in Los Angeles did not completed the CASI (Table 3-6). In San Diego, four either declined to enroll in AIEDRP (n=2) or were determined to be ineligible (n=2) due to anti-retroviral medication use. Of the remaining 10, six could not complete the CASI because they were monolingual Spanish speakers (the CASI was only in English), one declined to complete the CASI, and three moved away from Southern California before completing CASI. In Los Angeles, participants did not completed CASI because three did not continue on AIEDRP, one was ineligible for AIEDRP due to anti-retroviral medication use, two were monolingual Spanish speakers, and there was no available space or not enough time while the nurse was at a satellite site for 24 of the AIEDRP participants to complete the questionnaire. There were no significant differences in sex, age, or ethnicity between those who were interviewed with CASI versus those who were not in San Diego or Los Angeles (Table 3-7).

Among the AIEDRP participants who completed a baseline CASI, there were no significant differences in demographics or sexual history by enrollment site (San Diego vs. Los Angeles) for those enrolled by study 2 (Table 3-8) or study 3 (Table 3-9). Additionally, participant characteristics were similar between those enrolled by studies 2 and 3, although there were an additional 13 participants by the time data were analyzed for study 3. At the time of data analysis for study 3 (Table 3-9), most participants who completed CASI were men (98.6%) and most were men who report exclusive sexual contact with men in the past 12 months (88.6%). Over half reported white ethnicity

(67.7%) and working at least part-time (67.3%). Participants were well educated, with 41.4% completing some college and 46.4% completing college or a higher degree. The average age was about 35 years old and the average age of sexual debut was about 16 years old. There was a large variation in the number of male sexual partners reported. Just over half (55%) reported greater than 95 life-time male sexual partners. The mean number of male sexual partners was 42.4 (median 20) in the past 12 months, 9.1 (median 4) in the past 3 months, and 3.6 (median 1) in the past month. Over half (66.8%) reported having sexual contact with more than one person at one time (i.e., group sex) in the previous 12 months, but few reported buying (21.5%) or selling (20.1%) sex. A history of non-consensual sexual contact was reported by 36.5% and injection drug use over the past 12 months was reported by 6.8% of participants. These characteristics are similar to the characteristics of the MSM included in the data analyses for studies 2 and 3.

G. Behavioral Data Collection

Behavioral data was collected on all participants using a 60-minute, IRB-Human Subjects approved CASI questionnaire. The CASI style questionnaire was chosen over face-to-face interview or self-administered paper and pencil because several studies [6-10] indicate that CASI increases reporting of sensitive information, such as sexual behaviors and drug use. The CASI interview contains 595 questions and the same interview was used for all participants regardless of sex or sexual orientation. Due to skip patterns, the average participant answered about 100 questions, which took an average 60 minutes (range 30-120 minutes).

The questionnaire was designed to address many different research questions. General demographic and sexual history information was asked to gather background

information on all participants. Data were collected on types of partners in the previous 12 months in order to assess how common certain partner types were. Data were collected on sexual, social, and demographic characteristics of the participant's last three partners to examine partner dynamics by partner type. Detailed information on erectile dysfunction medication use (EDM) was collected in order to describe EDM misuse among MSM and to conduct a case control study on EDM use and risk for HIV acquisition. Questions pertaining to use of the Internet to recruit sexual partners were asked to assess sexual risk behaviors associated with Internet use. Data were collected on the number of partners that the participants engaged in specific sexual behaviors with over the course of the previous 12 months in order to assess general HIV risk behavior. Information pertaining to venue type, name, and number of partners recruited from each venue was collected in order to estimate social and sexual networks of recently infected individuals. Finally, data were collected on traumatic events, such as non-consensual sexual activity and domestic violence to assess these traumas as risk factors for risky sexual behavior. The data for manuscripts 2 and 3 were derived from questions pertaining to the last three sexual partners that the participant reported sexual contact with. The specific questions that were used for these studies, as well as data presented in other chapters of this dissertation, can be found in Appendix A.

Some questions were recoded for use in specific analyses. All recoding was conducted using STATA SE 8.2. The participants' date of birth was recoded to age by calculating their age from the dates of their CASI interviews. Education was recoded into high school, which included people who had completed 10-12 grade; some college; and completed college or higher, including post-graduate training, masters degree, doctorate degree, or other professional degree. Ethnicity was collapsed into white versus all other groups, as most participants reported white ethnicity. Partner type was

collapsed into main versus other. Meeting location was collapsed into bathhouse versus other. How long ago participants met their last partner, duration of time between meeting and sexual activity, and time since last sexual encounter were recoded so that time frames were in days. Time frames that were recorded in minutes or hours were counted as a single day. Sexual activity was collapsed into unprotected anal intercourse or not. Illicit substances used with the last three partners were collapsed for manuscript 3, but not manuscript 2 into a single variable that included the following categories: no substance use, methamphetamine only, other substances only, or a combination of methamphetamine and other substances. The HIV serostatus of each of the participants' last three sexual partners were coded as positive, negative, or unknown if participants reported not talking to their partner about his status or they could not report his status.

H. Data Analyses

Outcomes and Predictors

For both manuscripts 2 and 3 the outcome was unprotected anal intercourse (UAI) with each of the last three partners. For each study, UAI was coded as a dichotomous variable (i.e., reporting UAI with each partner or not). This variable was used because the purpose of both studies was to determine if the participants were engaging in risk behaviors that could result in HIV transmission. Additionally, for one analysis in manuscript 2, UAI was categorized into three ordinal categories, UAI with none, some, or all of the last three partners. This new variable was created in order to determine if there was a trend in proportion reporting substance use with any of the last three partners increased across ordered categories of UAI.

UAI was selected as the primary outcome because it is likely to carry a greater risk of transmission than other activities, including anal intercourse with a condom or oral intercourse [11-14]. It would have been ideal to examine insertive and receptive UAI in separate analyses, as insertive UAI may carry a higher risk of transmitting HIV and receptive UAI may carry a higher risk of acquiring HIV [15]. However, these data were not collected for the first 100 participants due to an oversight in questionnaire programming (i.e., data on anal intercourse, but not position were collected).

The primary predictor for both manuscripts 2 and 3 was illicit substance use with each of the last three partners. Additionally, for the trend analysis in manuscript 2, illicit substance use was categorized as used of a specific substance with any of the last three partners. Following recommendations which were made in manuscript 1, substance use was kept as specific substances and collapsed only when necessary (i.e., the data became too sparse). For manuscript 2 the primary predictors were use of methamphetamine, volatile nitrites, marijuana, and erectile dysfunction medications (EDMs). Other categories of substance use were not considered because too few respondents reported use of them with their last three partners. All predictors were dichotomized into used or did not use with each partner. For manuscript 3, the predictor of interest included a substance use variable that encoded four levels, no substance use, methamphetamine only, substances other than methamphetamine, and a combination of methamphetamine and other substances. This combination was selected for two reasons. Firstly, overlap of different types of substances with the same partner was very common, therefore all substances could not be examined without causing the data to become very sparse. Secondly, the other substances which were most commonly reported, marijuana, nitrites, and gamma hydroxyl-butyrate (GHB), had a similar effect to one another, but an opposite effect to methamphetamine with regard

to UAI and it therefore made more sense to group substances other than methamphetamine.

Analyses

For both manuscripts summary statistics and univariate analyses were used to summarize the cohort characteristics. Chi-square analysis or Fisher's exact test were used to compare proportions among data that did not contain repeated measures. Chi-square analysis was used unless a cross-tabulation cell had less than five observations, then Fisher's exact test was used. T-tests were used for any continuous variables that were compared between two groups and one way analysis of variance (ANOVA) was used if a continuous variable was being compared across more than two groups. For all tests (univariate and multivariate) in both studies, and alpha level of 0.05 was used as the cut point for statistical significance using two-sided tests.

In manuscript 2, Cuzick's test for trend was used to examine trends of substance use across UAI groups. This test was designed by Cuzick [16] in order to examine categorical trend across ordered groups. UAI was ordered as UAI with none, some, or all of the last three partners. Cuzick's test for trend uses a Wilcoxon-type test to calculate the probability.

For both manuscripts, analyses of all partner data (i.e., repeated measures) were completed using a repeated measures analysis. For manuscript 2, both generalized estimating equations and conditional logistic regression were used. Additionally, generalized linear latent mixed models (GLLAMM) were used and results were compared to GEE, however GEE was selected over GLLAMM (see GEE section below for explanation). For manuscript 3, GEE models were used to adjust for repeated measures.

Generalized Estimating Equations (GEE)

Generalized estimating equations are used when inferences about the population-level average are the focus, and when there are repeated measurements [17]. By obtaining a non-parametric estimate of the variance based on a working correlation matrix, GEEs correct “naïve” estimates to generate robust estimates of parameters and their associated variances [18].

In manuscript 2, GEE was used to examine associations between UAI and substance use across the entire sample. Conditional logistic regression (CLR) was used for a subset, which will be discussed further, but was not appropriate for the entire sample because not all individuals reported variation (protected anal intercourse vs. UAI) in the outcome (some reported UAI with all of their last three partners and some reported UAI with none of their last three partners). GEE was used to determine if an association between UAI and substance use was present across the sample when taking into account all participants and all of the partners that they reported on. This information was valuable because it provided associations in behavior among all participants, not just those who vary their UAI practice.

The use of GEE was compared to GLLAMM in manuscripts 2 and 3 (see Appendix C, Tables C-1 and C-2 for GLLAMM analyses). The primary difference between GEE and GLLAMM is that GEEs only provide population level estimates, and make few assumptions regarding within-subject correlations [18], whereas GLLAMMs also provide individual-level estimates, by making explicit assumptions about within-subject correlations [19]. As results for GEE and GLLAMM models were similar (See GLLAMM Tables Appendix C), GEE was selected as the analysis of choice, as population-level effects were the primary focus, and fewer assumptions regarding subject-specific patterns had to be introduced into the model.

In manuscript 3, GEE was also selected as the most appropriate statistical analysis because it allowed for simple examination of the interactions of interest while examining the effects of all other variables on the outcome. In this analysis repeated measures were assessed and therefore a repeated measures analysis, such as GEE was warranted. Additionally, as in manuscript 2, we were more interested in population level effects, than both population and individual effects.

For both manuscripts 2 and 3 the same family and link function were used for GEE. A binomial family was specified because the outcome measure, UAI, was a dichotomous measure. The logit link was specified, as it is the canonical link function for the binomial; alternative links include the probit and the complementary log-log [18]. An unstructured correlation matrix was specified, as it was believed that individuals' behaviors with different partners were likely to be highly correlated, but the structure of this correlation could not easily be expressed a priori. In addition, with only three repeated measures, it was not necessary to try to limit the number of estimated parameters in the correlation matrix structure.

Conditional Logistic Regression (CLR)

Conditional logistic regression (CLR) is another method for controlling for repeated measures. CLR differs from GEE and logistic regression in that it conditions on a particular factor. CLR is most often used when a study design included matching, such as a matched case-control study, or when an individual is being compared to him/herself, such as in a pre/post-test situation [20]. In the later situation, CLR controls for all individual factors and those are essentially removed from their effect on the outcome. Therefore, CLR is especially effective when examining the effect of substance

use on UAI, as it removes unmeasured characteristics that are constant within the individual, but allows for the dynamic characteristics of the partnership to be examined.

CLR was used for manuscript 2 to examine behavior changes within the individual in the presence and absence of illicit substances. It was only appropriate for those who reported variation in the outcome and was therefore used only with a subset of the sample. However, CLR provided different information than GEE in this analysis. The CLR models examined the effect of substance use on the change in behavior, therefore looking at a within-subjects association. CLR did not provide information on people who reported no variation in UAI.

Confounding

Confounding has been described in epidemiology as the effect of a third variable that results in a distortion of the association between the outcome and the main predictor of interest [21]. Statistically confounding has been described as a factor that helps to explain or distort the association between two other variables [22]. A confounder can either mask a true association or give the impression that an association exists when it is actually spurious [23]. Confounding is common in observational studies [24] and it is therefore critical to control for it either in study design or analysis.

For both manuscript 2 and 3 a number of variables were examined statistically to determine if they confounded the associations between UAI and substance use (Table 3-10). Variables that were likely to be associated with both the outcome and the predictors were selected. Demographic factors that were considered as potential confounders included: age, partner's age, ethnicity, partner's ethnicity, and education level. Variables that captured partner dynamics were also examined, including: age

discordance, ethnic discordance, partner type, partner HIV status, timing between meeting and first sexual contact, meeting location, and sexual contact prior to or after HIV diagnosis. Each of these variables could be associated with the outcome and the main predictor in different ways. Previous studies have demonstrated that those who use illicit substances tend to be younger [25], and younger MSM may be more likely to participate in UAI [26]. Lower education and ethnic identification other than White/Caucasian may be associated with an increase in risk for HIV [27-30], while White/Caucasian ethnic identification may be associated with substance use [27;31] and UAI with sero-discordant partners [32] among MSM.

It was also important to determine if the association between substance use and UAI was independent from other factors that may increase the risk of UAI. Among some ethnic groups, UAI was reported more commonly among MSM who were concordant by ethnicity [33]. Additionally, UAI appears to be more common among main partners than other partner types [34]. Some studies that indicate that UAI may be more common if MSM are sero-concordant for HIV [34;35], even when MSM used illicit substances [36]. On the other hand, some studies indicate that HIV positive [37;38] and HIV negative [39] MSM are likely to have known sero-discordant UAI while using illicit substances.

For both manuscripts confounding was assessed by examining the odds ratio for the association between outcome and predictor (crude odds ratio) and comparing it to the odds ratio in the presence of the potential confounder [22]. Each variable that was considered a potential confounder was added to the model separately, so that there were only three variables total in the model at once. After each potential confounder was added the newly adjusted odds ratio was compared to the crude odds ratio. A variable was considered a confounder of the association if the odds ratio changed by greater than 15 percent after adjustment. If the change in odds ratio was 15 percent or

less the variable was not be considered a confounder and was left out of the model. Variables that were not confounders by statistical assessment, but were significantly associated with the outcome ($p<0.05$), were left in the model as covariates.

Statistical Interactions

Interaction, also known as effect modification, occurs when the association between a predictor and an outcome differ by different strata of a third variable [22]. Interaction effects may be present when the relationship of predictors to the outcome is complex, for example with partner dynamics, sexual risk behavior and substance use. Therefore, careful attention was given to the potential of interactions in manuscripts 2 and 3.

In the analyses for manuscripts 2 and 3, statistical interactions were assessed by “multiplying” the predictors that were believed to interact and examining the effect of the association on the outcome. This was done because interactions at the odds ratio (or relative risk) level are multiplicative because risk ratios are measured on a multiplicative scale. Unlike confounding, the significance of the interaction was determined by examining the p-value of the interaction terms for values less than 0.05.

For both manuscripts interactions to be tested were decided upon a priori based on previous studies. In manuscript 2, interactions were examined between partner type and substance use because previous studies demonstrate that UAI may be more likely to occur among main partners than other partnership types [40;41]. Therefore it was hypothesized that substance use with a main partner may increase the risk of UAI more than additively. Additionally, interactions between recreational substances and EDMs were tested because previous literature suggests that a combination of EDM and illicit substance use may be associated with increased risk taking [42-44]. Interactions were

included separately for each substance and partner type in four different models. If an interaction was not present ($p<0.05$) or probable ($p<0.10$), it was removed from the model. Significant interactions were included in the final model.

In manuscript 3, interaction terms were used to test the hypothesis that different substances were associated with UAI before and after diagnosis. One interaction was examined between timing of sexual activity (before or after HIV diagnosis) and a multi-strata variable for substance use, no substance use, methamphetamine only, substances other than methamphetamine, or methamphetamine and other substances combined. This interaction term was retained in the model because it provided the support for or against the hypothesis. Results of data analyses are presented as two different manuscripts in chapters 4 and 5.

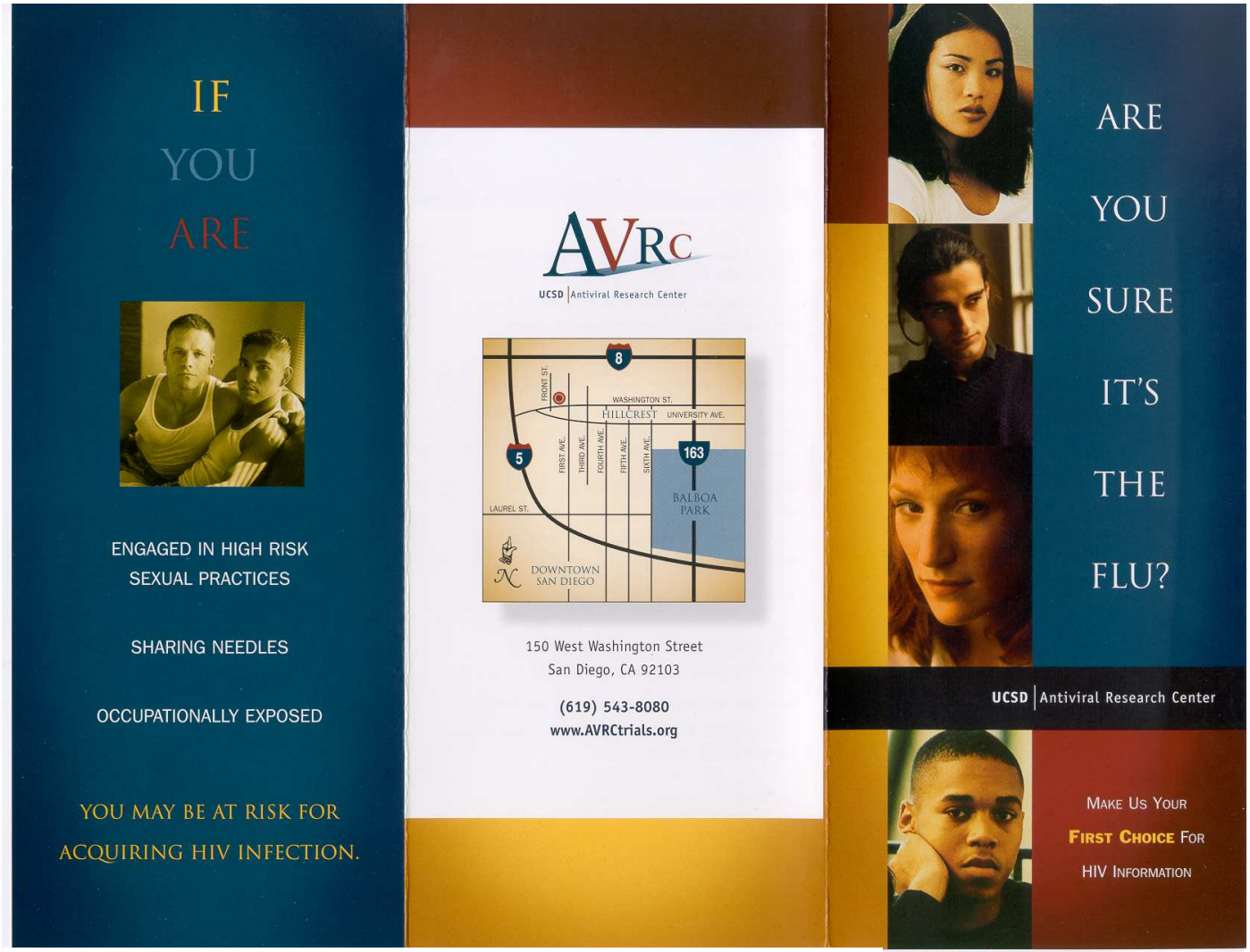


Figure 3-1: First Choice brochure for recruitment in San Diego (Outside)

Figure 3-2: First Choice brochure for recruitment in San Diego (Inside)

Figure 3-3: First Choice business card

Table 3-1: Possible primary HIV symptoms. When screening for primary HIV symptoms at telephone interview research staff are looking for combinations of the following that present as acute viral infection. Due to the non-specific nature of acute HIV symptoms, there is not a clear definition of what constitutes primary HIV symptoms.

Symptoms:
• Mononucleosis- or influenza-like symptoms • Fever (low or high grade) • Rash • Fatigue • Headache • Myalgia • Night sweats • Arthralgia • Lymphadenopathy • Pharyngitis • Oral ulcers

Table 3-2: Referral locations of individuals screening at the AVRC by year (May 2002 through November 2005)

	2002*	**2003**	**2004**	**2005**	**Total**
	% (n)	**% (n)**	**% (n)**	**% (n)**	**% (n)**
	n=92	**n=215**	**n=149**	**n=119**	**n=575**
San Diego County HIV testing services	0	16.7 (36)	17.5 (26)	19.3 (23)	14.8 (85)
Advertisement/ self referral	0	4.2 (9)	2.0 (3)	2.5 (3)	2.6 (15)
AVRC / HNRC/ Owen Clinic‡	0	7.9 (17)	6.0 (9)	7.6 (9)	6.1 (35)
Community organization	0	5.6 (12)	8.1 (12)	4.2 (5)	5.0 (29)
Patient on study/ friend/ partner	0	13.0 (28)	10.1 (15)	12.6 (15)	10.1 (58)
Community physician/ health care facility	0	14.8 (32)	16.1 (24)	8.4 (10)	11.5 (66)
Unknown	100 (92)	37.7 (81)	40.3 (60)	45.4 (54)	50.0 (288)

* Recruitment began May 2002

‡ AVRC= Antiviral Research Center; HNRC= HIV Neurobehavioral Research Center; The Owen Clinic is a UCSD affiliated clinic that provides medical care to HIV positive people

Table 3-3: Acute and Early HIV infection criteria and estimated days of infection based on HIV testing

Stage	HIV RNA	Western Blot	HIV EIA	Less Sensitive Detuned EIA	Documented Negative EIA (≤ 12 months)	Estimated Days of Infection
Acute 1	+	-	-	N/A	N/A	21
Acute 2	+	I[ŧ]	+/-	N/A	N/A	28
Acute 3	+	+ ≤ 5 bands[†]	+/-	N/A	N/A	45
Early 1	+/-	+ > 5 bands	+	_	N/A	85
Early 2	+/-	+	+	+	+	Midpoint*

*midpoint between last negative EIA and first positive EIA

[ŧ] "I" indicates intermediate western blot

[†] or a negative EIA or negative/indeterminate Western Blot within the previous 30 days

Table 3-4: Referral locations and demographic information by HIV status of participants screening for AIEDRP at the AVRC in San Diego

	Did not attend screen % (n) n=40	**Chronic Patients % (n) n=139**	**Primary HIV Patient % (n) n=195**	**HIV Negative Patient % (n) n=201**	**Total % (n) n=575**
Referral Source					
San Diego County HIV testing	12.5 (5)	17.3 (24)	17.4 (34)	11.0 (22)	14.8 (85)
Advertisement/ self referral	2.5 (1)	2.2 (3)	1.5 (3)	4.0 (8)	2.6 (15)
AVRC / HNRC/ Owen Clinic	2.5 (1)	6.5 (9)	9.2 (18)	3.5 (7)	6.1 (35)
Community organization	2.5 (1)	5.0 (7)	4.6 (9)	6.0 (12)	5.0 (29)
Patient on study/ friend/ partner	15.0 (6)	5.8 (8)	9.7 (19)	12.4 (25)	10.1 (58)
Community physician/ health facility	12.5 (5)	15.6 (23)	14.9 (29)	4.5 (9)	11.5 (66)
Unknown	52.5 (21)	46.8 (65)	42.6 (83)	58.7 (118)	49.9 (287)
Sex					
Men	82.5 (33)	95.7 (133)	98.5 (192)	88.1 (177)	92.7 (533)
Women	7.5 (3)	4.4 (6)	1.5 (3)	11.9 (24)	6.3 (36)
Unknown	10.0 (4)	0	0	0	0.7 (4)
Ethnicity					
Asian	0	5.8 (8)	3.1 (6)	3.5 (7)	3.7 (21)
Black/ African American	7.5 (3)	10.8 (15)	5.3 (10)	5.0 (10)	6.6 (38)
White	45.0 (18)	61.2 (85)	67.7 (132)	73.1 (147)	66.4 (382)
Hispanic	22.5 (9)	17.3 (24)	22.1 (43)	14.9 (30)	18.4 (106)
Other	5.0 (2)	2.9 (4)	1.5 (3)	3.0 (6)	2.6 (15)
Unknown	20.0 (8)	2.2 (3)	0.5 (1)	0.5 (1)	2.3 (13)
Age	31.8 (31)	35.5 (36)	35.0 (34.5)	33.8 (40.5)	34.5 (34)

Table 3-5: Demographics by HIV status of participants screening for AIEDRP in Los Angeles

	Chronic Patients	**Primary HIV Patient**	**HIV Negative Patient**	**Total**
	% (n) mean (median) n=21	**% (n) mean (median) n=70**	**% (n) mean (median) n=11**	**% (n) mean (median) n=102**
Sex				
Men	100 (21)	95.7 (67)	100 (11)	97.1 (97)
Women	0	4.3 (3)	0	2.9 (3)
Ethnicity				
Asian	9.5 (2)	1.4 (1)	0	2.9 (3)
Black/ African American	0	5.7 (4)	0	3.9 (4)
White	52.4 (11)	68.6 (48)	63.6 (7)	64.7 (66)
Hispanic	28.6 (6)	22.7 (16)	36.4 (4)	25.5 (26)
Other	0	1.4 (1)	0	1.0 (1)
Unknown	9.5 (2)	0	0	2.0 (2)
Age	38.2 (39)	36.3 (36)	33.6 (30)	36.4 (37)

Table 3-6: Reasons for not completing CASI among recently infected individuals screening for AIEDRP by site

	San Diego n=14	Los Angeles n=33
Did not continue AIEDRP	2	3
Ineligible for AIEDRP	2	1
No space or time for CASI	0	27
Not English Speaking	6	2
Declined CASI	1	0
Moved away before CASI	3	0

Table 3-7: Demographics and differences between recently infected AIEDRP participants who did and did not complete CASI by recruitment location and study

	San Diego			Los Angeles		
	No CASI	**CASI**	**p-value**	**No CASI**	**CASI**	**p-value**
	n=14	**n=181**		**n=33**	**n=37**	
Women	7.7 (1)	1.1 (2)	0.19	9.9 (3)	5.6 (2)	0.67
Age	35.9	35.0	0.75	35.6	36.9	0.61
Ethnicity (white vs. other)	42.9 (6)	69.6 (126)	0.07	63.6 (21)	73.0 (27)	0.40
Referral Source			0.34	N/A	N/A	N/A
San Diego County	7.1 (1)	18.2 (33)				
Advertisement/ self	7.1 (1)	1.1 (2)				
AVRC / HNRC/ Owen Clinic	0	9.9 (18)				
Community organization	0	5.0 (9)				
Patient / friend/ partner	14.3 (2)	9.4 (17)				
Community physician/	14.3 (2)	14.9 (27)				
Unknown	57.4 (8)	41.4 (75)				

Table 3-8: Demographics and sexual history of AIEDRP participants who completed CASI before analysis of data for manuscript 2

	San Diego **% (n)** **mean** **(median)** **n=174**	**Los Angeles** **% (n)** **mean** **(median)** **n=33**	**Total** **% (n)** **mean** **(median)** **n=207**
Women	0.6 (1)	6.6 (2)	1.5 (3)
Age	34.5 (34)	37.3 (38)	34.9 (35)
White Ethnicity	66.1 (115)	72.7 (24)	67.2 (139)
Education			
High school	12.6 (22)	15.2 (5)	13.0 (27)
Completed some college	41.4 (72)	30.3 (10)	39.6 (82)
Completed college or higher	46.0 (80)	54.6 (18)	47.3 (98)
Employed	69.0 (120)	63.6 (21)	68.1 (141)
Sexual situation past 12 months			
MSM	88.5 (154)	87.9 (29)	88.4 (183)
MSMW	6.3 (11)	3.0 (1)	5.8 (12)
MSW	4.0 (7)	3.0 (1)	3.9 (8)
WSM	0.6 (1)	0	0.4 (1)
WSMW	0	6.1 (2)	1.0 (2)
No Sexual Contact	0.6 (1)	0	0.4 (1)
Age at sexual debut	16.0 (16)	16.5 (16)	16.1 (16)
>95 Male Lifetime Partners	54.6 (95)	60.6 (20)	55.6 (115)
Number of Male Partners			
Past 12 months	39.0 (20)	63.5 (27.5)	42.9 (20.5)
Past 3 months	9.4 (4)	7.7 (4)	9.2 (4)
Past month	3.7 (1)	3.2 (1.5)	3.6 (1)
Group Sex Past 12 Months	64.9 (113)	78.8 (26)	67.2 (139)
Ever Bought Sex	22.0 (38)	21.2 (7)	21.8 (45)
Ever Sold Sex	21.4 (37)	12.1 (4)	19.9 (41)
Injected Drugs Past 12 Months	7.5 (13)	6.1 (2)	7.3 (15)
Ever had non-consensual sex	36.8 (64)	36.4 (12)	36.7 (76)

* no significant differences between San Diego and LA for all variables (p>0.05)

Table 3-9: Demographics and sexual history of AIEDRP participants who completed CASI before analysis of data for manuscript 3

	San Diego **% (n) mean (median) n=186**	**Los Angeles** **% (n) mean (median) n=34**	**Total** **% (n) mean (median) n=220**
Women	0.5 (1)	5.9 (2)	1.4 (3)
Age	34.4 (34)	37.4 (39)	34.9 (35)
White Ethnicity	67.2 (125)	70.6 (24)	67.7 (149)
Education			
High school	11.8 (22)	14.7 (5)	12.3 (27)
Completed some college	43.0 (80)	32.4 (11)	41.4 (91)
Completed college or higher	45.2 (84)	52.9 (18)	46.4 (102)
Employed	68.3 (127)	61.8 (21)	67.3 (148)
Sexual situation past 12 months			
MSM	88.7 (165)	88.2 (30)	88.6 (195)
MSMW	3.8 (7)	2.9 (1)	3.6 (8)
MSW	6.5 (12)	2.9 (1)	5.9 (13)
WSM	0.5 (1)	0	0.5 (1)
WSMW	0	5.9 (2)	0.9 (2)
No Sexual Contact	0.5 (1)	0	0.5 (1)
Age at sexual debut	16.0 (16)	16.5 (16)	16.1 (16)
>95 Male Lifetime Partners	53.8 (100)	61.8 (21)	55.0 (121)
Number of Male Partners			
Past 12 months	38.7 (20)	63.3 (25)	42.4 (20)
Past 3 months	9.4 (4)	7.6 (4)	9.1 (4)
Past month	3.7 (1)	3.2 (2)	3.6 (1)
Group Sex Past 12 Months	65.1 (121)	76.5 (26)	66.8 (147)
Ever Bought Sex	21.6 (40)	20.6 (7)	21.5 (47)
Ever Sold Sex	21.6 (4)	11.8 (4)	20.1 (44)
Injected Drugs Past 12 Months	7.0 (13)	5.9 (2)	6.8 (15)
Ever had non-consensual sex	36.8 (68)	35.3 (12)	36.5 (80)

Table 3-10: Variables that were examined as potential confounders

Variable	Study	Included	Format	Reason for Format
Age	2 and 3	No	Continuous (years)	Collected as a continuous variable, only uses one degree of freedom, provides more information
Partner's age	2 and 3	Study 2	Continuous (years)	Collected as a continuous variable, only uses one degree of freedom, provides more information
Age discordance	2 and 3	No	Dichotomous	Only two strata, discordant or concordant
Ethnicity	2 and 3	No	Dichotomous: White vs. all other ethnicities	60% or more of participants reported white ethnicity, other strata were too thin
Partner's ethnicity	2 and 3	No	Dichotomous: White vs. all other ethnicities	60% or more of partners were reported to be white, other strata were too thin
Ethnic discordance	2 and 3	No	Dichotomous	Only two strata, discordant or concordant
Education	2 and 3	No	Categorical: High School, college, more than college	Collected as categorical data; Categories collapsed to: save degrees of freedom, represent educational levels (no one less than high school, most college or above).
Time between meeting and first sexual contact	2	Study 2	Continuous (days)	Collected as a continuous variable, only uses one degree of freedom, provides more information
Meeting location	3	Study 3	Dichotomous: Bathhouse vs. all other locations	Multiple categories, strata thin, bathhouse most likely to be associated with UAI and substance use
Partner type	3	Study 3	Dichotomous: Main vs. all other types	Behavior differs most between main and other partner types, strata thin for some partner types
Timing of sexual activity in respect to HIV diagnosis	2	Study 2	Dichotomous: Before or after diagnosis	Behavior change may be different before and after diagnosis, only two strata
Partner's HIV status	2 and 3	Studies 2 & 3	Categorical: Negative, positive, unknown	Collected as categorical, all categories represented

I. References

(1) AIEDRP Statistical and Coordinating Center. Acute Infection and Early Disease Research Program website. http://www.aiedrp.org. (Electronic Citation) Accessed 1 January 2006.

(2) Centers for Disease Control and Prevention. Revised Guidelines for HIV Counseling, Testing, and Referral. *Morbidity and Mortality Weekly Report*. 2001; 50:1-46.

(3) Cambridge Biotech. Human immunodeficiency virus type 1 Western Blot Kit. 2000. Rockville, MD, Calypte Biomedical.

(4) Abbott Laboratories. Human immunodeficiency virus types 1 and 2: (E. coli, B. megaterium, recombinant antigen) HIVAB HIV-1/HIV-2 (rDNA) EIA. 2004. Abbott Park, IL, Abbott Laboratories Diagnostic Division.

(5) Janssen RS, Satten GA, Stramer SL *et al*. New Testing Strategy to Detect Early HIV-1 Infection for Use in Incidence Estimates and for Clinical and Prevention Purposes. *JAMA*. 1998; 280:42-48.

(6) Macalino GE, Celentano DD, Latkin C *et al*. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. *AIDS Education and Prevention*. 2002; 14:367-378.

(7) Newman JC, Jarlais D, Turner CF *et al*. The differential effects of face-to-face and computer interview modes. *American Journal of Public Health*. 2002; 92:294-297.

(8) Kurth AE, Martin DP, Golden MR *et al*. A comparison between audio computer-assisted self-interviews and clinician interviews for obtaining the sexual history. *Sexually Transmitted Diseases*. 2004; 31:719-726.

(9) Perlis TE, Des Jarlais DC, Friedman SR *et al*. Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. *Addiction*. 2004; 99:885-896.

(10) Ghanem KG, Hutton HE, Zenilman JM *et al*. Audio computer assisted self interview and face to face interview modes in assessing response bias among STD clinic patients. *Sexually Transmitted Infections*. 2005; 81:421-425.

(11) Keet IPM, Vanlent NA, Sandfort TGM *et al*. Orogenital Sex and the Transmission of HIV Among Homosexual Men. *AIDS*. 1992; 6:223-226.

(12) Samuel MC, Hessol N, Shiboski S *et al*. Factors Associated with Human-Immunodeficiency-Virus Seroconversion in Homosexual Men in 3 San-Francisco Cohort Studies, 1984-1989. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1993; 6:303-312.

(13) Pinkerton SD, Abramson PR. Effectiveness of condoms in preventing HIV transmission. *Social Science & Medicine*. 1997; 44:1303-1312.

(14) PageShafer K, Veugelers PJ, Moss AR *et al*. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the tricontinental seroconverter study, 1982-1994. *American Journal of Epidemiology*. 1997; 146:531-542.

(15) Varghese B, Maher JE, Peterman TA *et al*. Reducing the risk of sexual HIV transmission - Quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. *Sexually Transmitted Diseases*. 2002; 29:38-43.

(16) Cuzick J. A Wilcoxon-Type Test for Trend. *Statistics in Medicine*. 1985; 4:87-90.

(17) Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biomterics*. 1986; 42:121-130.

(18) Diggle PJ, Heagerty P, Liang K, Zeger SL. Analysis of Longitudinal Data. 2nd ed. Oxford: Oxford University Press, 2002.

(19) Rabe-Hesketh S, Skrondal A, Pickles A. GLLAMM Manual. U.C. Berkeley Division of Biostatistics Working Paper Series Paper 160. 2004. The Berkeley Electronic Press. (Electronic Citation) Accessed 28 April 2005.

(20) Breslow NE, Day NE. The Analysis of Case-Control Studies. Statistical Methods in Cancer Research: Vol. 1. Lyon, France: IARC Scientific Publications, 1980.

(21) Szklo M, Nieto FJ. Epidemiology: beyond the basics. Gaithersberg: 2000.

(22) Woodward M. Confounding and interaction. Epidemiology: study design and data analysis. Boca Raton: Chapman and Hall/CRC, 1999: 146-189.

(23) Gordis L. Epidemiology. 1st ed. Philadelphia: W.B. Saunders Company, 1996.

(24) Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 1998.

(25) Colfax G, Coates TJ, Husnik MJ *et al*. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of San Francisco men who have sex with men. *J Urban Health*. 2005; 82:i62-i70.

(26) Crepaz N, Marks G, Mansergh G *et al*. Age-related risk for HIV infection in men who have sex with men: Examination of behavioral, relationship, and serostatus variables. *AIDS Education and Prevention*. 2000; 12:405-415.

(27) Harawa NT, Greenland S, Bingham TA *et al*. Associations of race/ethnicity with HIV prevalence and HIV-related behaviors among young men who have sex

with men in 7 urban centers in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:526-536.

(28) Valleroy LA, MacKellar DA, Karon JM *et al*. HIV prevalence and associated risks in young men who have sex with men. *JAMA-Journal of the American Medical Association*. 2000; 284:198-204.

(29) Celentano DD, Sifakis F, Hylton J *et al*. Race/ethnic differences in HIV prevalence and risks among adolescent and young adult men who have sex with men. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:610-621.

(30) Hickson F, Reid D, Weatherburn P *et al*. HIV, sexual risk, and ethnicity among men in England who have sex with men. *Sexually Transmitted Infections*. 2004; 80:443-450.

(31) Thiede H, Valleroy LA, MacKellar DA *et al*. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health*. 2003; 93:1915-1921.

(32) Chen SY, Gibson S, Weide D *et al*. Unprotected anal intercourse between potentially HIV-serodiscordant men who have sex with men, San Francisco. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:166-170.

(33) Choi KH, Operario D, Gregorich SE *et al*. Age and race mixing patterns of sexual partnerships among Asian men who have sex with men: Implications for HIV transmission and prevention. *AIDS Education and Prevention*. 2003; 15:53-65.

(34) Poppen PJ, Relsen CA, Zea MC *et al*. Serostatus disclosure, seroconcordance, partner relationship, and unprotected anal intercourse among HIV-positive Latino men who have sex with men. *AIDS Education and Prevention*. 2005; 17:227-237.

(35) Clatts MC, Goldsamt LA, Yi H. An emerging HIV risk environment: a preliminary epidemiological profile of an MSM POZ party in New York City. *Sexually Transmitted Infections*. 2005; 81:373-376.

(36) Purcell DW, Moss S, Remien RH *et al*. Illicit substance use, sexual risk, and HIV-positive gay and bisexual men: differences by serostatus of casual partners. *AIDS*. 2005; 19:S37-S47.

(37) Halkitis PN, Green KA, Remien RH *et al*. Seroconcordant sexual partnering of HIV-seropositive men who have sex with men. *AIDS*. 2005; 19:S77-S86.

(38) Halkitis PN, Wilton L, Wolitski RJ *et al*. Barebacking identity among HIV-positive gay and bisexual men: demographic, psychological, and behavioral correlates. *AIDS*. 2005; 19:S27-S35.

(39) Colfax G, Vittinghoff E, Husnik MJ *et al*. Substance use and sexual risk: A participant- and episode-level analysis among a cohort of men who have sex with men. *American Journal of Epidemiology*. 2004; 159:1002-1012.

(40) Xiridou M, Geskus R, De Wit J *et al*. The contribution of steady and casual partnerships to the incidence of HIV infection among homosexual men in Amsterdam. *AIDS*. 2003; 17:1029-1038.

(41) Gorbach PM, Drumright LN, Daar ES, Little SJ. Transmission behaviors of recently HIV-infected men who have sex with men. *Journal of Acquired Immune Deficiency Syndromes*. 2006 *in press*.

(42) Chu PL, McFarland W, Gibson S *et al*. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. -*Journal of Acquired Immune Deficiency Syndromes*. 2003; 33:191-193.

(43) Crosby R, DiClemente RJ. Use of recreational Viagra among men having sex with men. *Sexually Transmitted Infections*. 2004; 80:466-468.

(44) Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS*. 2002; 16:1425-1428.

IV. MANUSCRIPT 2

Unprotected anal intercourse and substance use among men who have sex with men with recent HIV infection

A. Abstract

Objectives: To examine cross-sectional trends, within-subjects, and overall associations between substance use and unprotected anal intercourse (UAI) among men who have sex with men (MSM) with recent HIV infection.

Methods: 194 MSM, who were recently infected with HIV, completed a computer-assisted questionnaire regarding sexual behaviors and substance use with their last three partners. Associations between UAI and substance use were assessed using: Cuzick's test for trend for substance use across UAI categories (UAI with none, some, or all of the partners); conditional logistic regression (CLR) to assess associations among the 116 MSM reporting UAI with some, but not all, partners; and generalized estimating equations (GEE) to examine associations within the entire sample (n=194).

Results: Increasing substance use was reported with UAI ranging from none to some to all of the last three partners. In multivariate CLR and GEE models, UAI was associated with use of methamphetamine (OR: 4.9 and 2.7 respectively), marijuana (OR: 4.0 and 1.9 respectively) and erectile dysfunction medications when used with a main partner (OR: 26.0 and 17.1 respectively).

Conclusions: Results indicate that a direct association may exist between specific substances and UAI and provide evidence that use of methamphetamine and EDM may contribute to HIV transmission.

B. Introduction

Previous studies have demonstrated associations between amphetamine, methamphetamine, or nitrite use and human immunodeficiency virus type 1 (HIV) seroconversion [1-5], incident sexually transmitted infections (STI) [6-8] or unprotected anal intercourse (UAI) [9-16] among men who have sex with men (MSM). However, the meaning and significance of these associations is unclear. It has been suggested that substance use and sexual risk are markers for risky personality types [17], lack of impulse control [18-20], or desire to escape concern about HIV risk [21-25]. In contrast, some studies indicate that substance use may have a direct causal effect on sexual behavior. Intoxication with alcohol or illicit substances has been shown to compromise one's ability to negotiate or use condoms [26-30]. Additionally, after completion of methamphetamine treatment, MSM have reported significant decreases in their number of sexual partners and an increase in their ability to use condoms [31;32] as compared to just before initiating treatment, suggesting that methamphetamine had impaired their ability to practice safer sex. Higher rates of substance use among MSM compared to the general population [33;34] coupled with high HIV incidence [35] and prevalence [36] highlight the need to better understand associations between substance use and UAI.

Leigh and Stall have proposed that *event* and *within-subjects* analyses provide better understanding of the true associations between drug use and HIV/STI risk than studies of *global* or *situational* associations [37]. Event and within-subject analyses examine one instance of sexual behavior and measure occurrence of substance use at that instance, which provides evidence of a direct association. Within-subjects analyses differ from event analyses by controlling for individual characteristics that are difficult to measure, through using individuals as their own control while comparing instances when risky sexual activity did and did not occur. In contrast, situational association studies

measure the frequency of substance use before sexual activity in relation to the occurrence or frequency of high-risk sexual activity. Global association studies examine substance use and high-risk sexual activity in general. These studies are unable to establish temporality (i.e., that substance use occurred during or immediately prior to the high-risk sexual situation).

Few studies that examine event or within-subjects analyses in the context of substance use and HIV have been published, and some provide conflicting evidence. Among HIV-negative MSM, event level associations between UAI and use of alcohol, methamphetamine, ecstasy, gamma hydroxyl-butyrate (GHB), or ketamine during sex, but not when used outside of sexual activity [10] have been demonstrated. Additionally, substance use, collapsed across amyl nitrites, cocaine and amphetamine, has been associated with sero-discordant UAI in within-subjects analyses among HIV negative MSM [38]. In contrast, an earlier study of MSM with unknown HIV status revealed no within-subjects associations between substance use and UAI [39]. Although a growing number of cross-sectional studies have demonstrated global associations between Viagra® (sildenafil) use and UAI [9;40-44], to our knowledge no within-subjects or event studies have taken into account erectile dysfunction medications (EDM) (i.e.,Viagra®, Cialis®, and Levitra®), which represent an emerging class of abused substances [44-46].

To further elucidate the relationship between substance use and UAI, we studied a unique cohort of MSM with recent HIV infection. Occurrence of UAI within this cohort is of particular interest because recent risk behaviors coincide with acquisition of HIV, and at each episode of UAI following infection, further HIV transmission is likely, due to the high viral loads observed during early infection [47-50]. The objectives of this study were: 1) to examine cross-sectional trends in UAI and substance use; 2) to estimate

associations between use of specific recreational substances and EDM on UAI while using individuals as their own control in within-subjects analyses; and 3) to determine if recreational substance use was associated with UAI when considering all participants, including those with no variation in UAI between partners.

C. Methods

Between May 2002 and July 2005, 211 people enrolled in the Acute Infection and Early Disease Research Program (AIEDRP) in San Diego and Los Angeles and provided informed consent. Of those, 207 (98%) completed a computer-assisted self interview (CASI). All participants had recent HIV infection as determined by one of the following: 1) HIV seroconversion within the previous 12 months (negative HIV enzyme immunoassay (EIA) followed by positive EIA); 2) presence of HIV RNA in plasma, but a negative EIA; or 3) results on a detuned EIA that are consistent with early infection. Estimated date of infection for all participants was based on last HIV negative test result and serology as previously described [51].

This study includes data from 194 of the 207 subjects who were men that reported sexual contact with other men in the previous 12 months. The remaining 13 subjects, four women, eight men who reported sexual contact with only women and one man who reported no sexual activity in the previous 12 months, were excluded since the focus of this study was sexual risk behaviors among MSM. Interview data were collected using Ci3 (Sawtooth Software, Northbrook, IL). The protocol for this study was approved by the Institutional Review Boards of the University of California in San Diego and Los Angeles; Harbor/UCLA Hospital; and Cedar Sinai Hospital, Los Angeles.

Participants were asked to provide detailed information about the last three people with whom they had had sexual contact. Questions were asked for each partner

regarding types of sexual activities that occurred, substances used just prior to or during sexual activity, partner demographic information, timing of sexual activity with regard to meeting the partner, partner HIV status, and partner type (e.g. main, anonymous, etc.). Date of HIV diagnosis was established through reviewing medical records and assigned as the first positive HIV test that was reported to the participant.

For trend analyses, participant responses regarding UAI with the last three partners were grouped by those who reported UAI with none of the last three partners, UAI with one or two (i.e., some) of the last three partners, and UAI with all of the last three partners. These three groups were compared by demographics, sexual history and type of substance use using analysis of variance (ANOVA), chi-square analyses, or Fisher's exact tests. For proportions of substance use across categories of UAI (from UAI with none to UAI with all of the last three partners), Cuzick's test was used to identify specific trends across UAI categories.

Repeated measures analyses were used to assess UAI and drug use for each of the last 3 partners individually. Univariate and multivariate conditional logistic regression (CLR) models were used to examine associations between substances used and UAI among the 116 MSM reporting UAI with some of their last three partners in within-subjects analyses. CLR enables one to examine change from one time point to the next at the individual level while conditioning on individual characteristics; thus allowing examination of individual behavior in the presence and absence of substance use while controlling for unmeasured individual characteristics [52], such as personality type.

Analyses that examined associations between UAI and substance use prior to sexual activity across all 194 participants were conducted using univariate and multivariate generalized estimating equations (GEE). GEE models correct variance estimates for repeated measures on the same individual, but do not require that all

subjects have variation in UAI because they provide information on the association between two variables regardless of individual change [53]. Interactions between EDM use and partner type were examined in both GEE and CLR models and were considered statistically significant at a p-value of 0.1. Analyses were performed using STATA version 8.2 SE (STATA Corporation, College Station, TX).

D. Results

Patients were interviewed on average 16 (median 14) weeks after their estimated date of HIV infection, and on average 5 (median 3) weeks after receiving an HIV-positive diagnosis. Respondents had a mean age of 35 years (range 18-65) and were mostly white (69.6%). Almost half (47.9%) reported completing college or higher education and over two thirds (71.6%) were employed (Table 1). Twelve subjects (6.2%) reported sexual activity with both men and women in the past 12 months; the remaining 93.8% reported sexual contact exclusively with men. The median reported number of male partners was: 99 for lifetime (range 2-1000); 20.5 in the previous 12 months (range 1-750); and 4 in the previous 3 months (range 0-100).

Use of any substance with any of the last three partners was reported by 58% of participants. Use of specific substance types with any of the last three partners were reported as follows: methamphetamine 31%; volatile nitrites 33%; marijuana 25%; GHB 13%; methylenedioxymethamphetamine (MDMA) 7%; cocaine 5%; ketamine 3%; other drugs 6%; EDM 23%; polydrug use (a combination of two or more substances except EDM) 35%.

All but six participants reported having sexual contact with three or more partners in the previous 12 months. When categorized by how many of the last three partners participants had UAI with, 16% (31) reported no UAI; 60% (116) reported UAI with some,

but not all of the last three partners; and 24% (47) reported UAI will all of their last three partners. By ANOVA, chi-square or Fisher's exact test, participants did not differ by demographic or sexual history characteristics across these three categories of UAI (Table 1).

There were, however, significant differences by chi-square or Fisher's exact tests between these three groups by proportion of substance use (Figure 1). Proportions of drug use increased across categories of UAI from none of the last three partners, to some, to all respectively for methamphetamine (16.1% v. 27.6% v. 51.1%, p=0.002); nitrites (12.9% v. 32.8% v.44.7%, p=0.011); polydrug use (16.1% v. 31.9% v. 53.2%, p=0.002); and GHB (3.2% v. 11.2% v. 23.4%, p=0.031). MDMA approached statistical significance (0 v. 6.9% v. 12.8%, p=0.088); however, few participants reported MDMA use with their last three partners (n=14, 7.2%). By Cuzick's test, statistically significant trends of increasing use were seen with methamphetamine (p<0.01), nitrites (p<0.01), GHB (p=0.01), MDMA (p=0.03), and polydrug use (p<0.01) from reporting UAI with none, to some, to all of the last three partners (Figure 1). No significant associations were seen for cocaine, marijuana, or all substances combined. Interestingly, the frequency of EDM use across categories of UAI was the same, 22.6%, 23.3%, 21.3% for no UAI, UAI with some, and UAI with all respectively.

Within-subjects analyses*:* Among the 116 MSM who reported UAI with some (but not all) partners, UAI was more commonly reported with partners whom participants had used methamphetamine (OR=5.28), volatile nitrites (OR=2.55), marijuana (OR=5.74), multiple classes of substances ("polydrug" use, OR=4.18), or any substance (OR=3.83) when compared to their partners in which drug use did not occur using CLR (Table 2).

Similar associations were seen in multivariate CLR models, which included methamphetamine, nitrites, marijuana, and EDM and controlled for partner type (main v. all other types), partner age, days between meeting the partner and sexual intercourse, partner HIV status and whether sexual contact occurred before or after HIV diagnosis (Table 3). In the CLR model, which controls for underlying characteristics of the participants, methamphetamine use was the strongest predictor of UAI (OR=4.86), followed by marijuana use (OR=4.01). In addition, a significant interaction between EDM use and partner type was present in which EDM use with the main partner (e.g., boyfriend, life partner) greatly increased the likelihood of UAI (OR=26.0). Partner's age and HIV status, partner type, and timing of first sexual contact or sexual contact with regard to HIV diagnosis were not associated with UAI.

Situational analyses*:* In univariate GEE models which included the entire sample (n=194) regardless of variation in UAI between partners, methamphetamine (OR=3.13), volatile nitrites (OR=2.27), GHB (OR=4.22), marijuana (OR=3.09), polydrug use (OR=3.39), or use of any substance (OR=2.24) were associated with UAI (Table 2). In multivariate GEE models, which included methamphetamine, nitrites, marijuana, and EDM and controlled for partner type, partner age, days between meeting the partner and sexual intercourse, partner HIV status and whether sexual contact occurred before or after HIV diagnosis, methamphetamine use was the strongest predictor of UAI (OR=2.71), followed by marijuana use (OR=1.94) (Table 3). The significant interaction between the main partner type and EDM use was also present in the GEE model (OR=17.1). In addition, having a main partner (OR=2.2), an HIV positive partner (OR=1.92) or sexual contact occurring before HIV diagnosis (OR=1.62) were also

associated with UAI and volatile nitrite use was marginally associated with UAI (OR=1.64, p=0.062). No additional variables were associated with UAI.

Due to possible differences in associations between substance use and UAI by partner type, as observed by the interaction between EDM use and partner type, we constructed two additional multivariate GEE models that examined these associations among only main partners (e.g. boyfriend) or only non-main partners (Figure 2). In the main partner model (n=105 partners), associations between UAI and EDM use (OR=6.94, p=0.09) or having an HIV positive partner (OR=5.67, p=0.06) approached statistical significance; no other controlling variables or substances were associated with UAI (p>0.05). However, in models which examined only non-main partners (n=477 partners), UAI was significantly associated with methamphetamine use (OR=2.87, p=0.001), nitrite use (OR=1.76, p=0.05), marijuana use (OR=2.22, p=0.03) and sexual contact occurring before HIV diagnosis (OR=1.77, p=0.01). EDM use did not approach statistical significance in this model (p=0.79).

E. Discussion

In this study of MSM with recent HIV infection, methamphetamine, marijuana, nitrites and EDM use were associated with UAI. Methamphetamine, marijuana and EDM use with main partners were associated with UAI in within-subjects analyses, suggesting that use of these substances may increase UAI independent of individual characteristics and that this association might not be confounded by personality for these drugs as has been previously suggested [17-19]. Additionally, in analyses of situational associations that included the entire sample (GEE), use of methamphetamine, marijuana, and EDM with a main partner were associated with UAI, suggesting that the results seen in within-subjects analyses also exist in the larger sample. The current study contributes to the

overall understanding of drug use and UAI by: 1) providing support to prior studies which demonstrate associations between methamphetamine or EDM and sexual risk behavior [9;10;38;54;55]; 2) clarifying that a direct association is likely to exist between specific drugs and UAI; and 3) providing evidence that use of methamphetamine, EDM and possibly other illicit drugs, may contribute to HIV transmission.

In all analyses, the most important predictor of UAI among the last three sexual partners was methamphetamine use, suggesting that methamphetamine is an independent predictor of HIV transmission. To our knowledge, our study is the first to demonstrate that methamphetamine is associated with UAI among recently HIV infected MSM while controlling for individual factors using within-subjects analyses. Additionally, the most dramatic trends of increasing use by category of UAI were demonstrated with methamphetamine. Considering the transmissibility of HIV during early infection, these analyses suggest that methamphetamine may contribute significantly to HIV transmission from newly infected MSM to others.

There are many plausible pathways in which methamphetamine could increase the risk of UAI. Methamphetamine could impair judgment or reduce ability to negotiate condom use through direct effects on mental functioning [56]. Additionally, methamphetamine has been reported to increase individuals' desire for sexual activity [57-60], which independently, or in combination with modified mental functioning, could result in increased likelihood of UAI.

Of interest was our finding that the association between UAI and EDM use differed by partner type. EDM use was only associated with UAI when used with main partners, but not other partner types. To our knowledge, no study has documented a differential effect of EDM use on UAI in relation to partner type. However, studies examining nitrites, marijuana, and GHB [10] or alcohol [26;27] use have demonstrated

differences in sexual behavior by partner type. It is possible that the association we observed reflects the differential use of EDM according to the specific type of anal intercourse (insertive or receptive). EDM are more likely to be used by the insertive rather than the receptive partner during UAI and most participants in our sample reported being the latter. Among the 102 participants for whom type of UAI (insertive versus receptive) was measured, only 30% reported being the insertive partner with their last three partners. Additionally, participants were more likely to report insertive UAI with main partners than other types (OR=1.98, p=0.02) by GEE, suggesting that the interaction between EDM use and main partners could be due to sexual positioning. However, data were too sparse to determine if EDM use was independently associated with insertive UAI. Regardless of sexual positioning, the relatively high use of EDM among MSM who do not have erectile dysfunction, as demonstrated here and in previous studies [41;44], does raise concern about EDM misuse.

Conversely, use of methamphetamine was more common with other partner types than the main partner. We found that methamphetamine, nitrites, or marijuana did not predict UAI with the main partner, suggesting that significant interactions between partner dynamics and drug use may affect UAI. We recommend that future studies explore associations between drug use and UAI in the context of partner type. For example, EDM may be used in the context of planned UAI, while other substances such as methamphetamine may lead to unplanned UAI due to physiological drug effects. Our results should be interpreted cautiously since they are based on a very small proportion of EDM users with main partners, as indicated by the large confidence intervals.

The association between nitrite use and UAI ranged between statistically significant to marginally significant in GEE and CLR analyses, which is consistent with previous studies examining nitrite use and UAI [11-15] or HIV seroconversion [2;4;5;61].

In our study, the association was not as strong as for methamphetamine, even though the prevalence of use was similar, suggesting that nitrites may be less likely to contribute directly to UAI than other substances. Lack of association between UAI and nitrite use has been demonstrated previously [10] and frequent use of nitrites (once per week or more) was not associated with increased risk of UAI with a serodiscordant partner [38]. However, we did observe a significant trend in nitrite use by UAI category. The ambiguity of the association between nitrite use and UAI may be a result of use of nitrites for preplanned UAI, as nitrites do not appear to alter mental functioning [62].

Significant associations were also observed between marijuana use and UAI among those who reported variation in UAI and the overall sample, suggesting that marijuana is an independent risk factor for UAI, but no trend of increasing use with UAI category was observed. In contrast to our study, a previous event analysis study demonstrated that marijuana use in general was associated with UAI, but not when marijuana was used during sexual activity [10], suggesting that marijuana use is more likely to be a marker of high risk behaviors in general than a risk factor for UAI. Although the associations between marijuana use and UAI in our study may be valid, over half of marijuana users also used methamphetamine, suggesting that associations between UAI and marijuana may be an artifact of the overlap in use of methamphetamine. Overlap between marijuana or nitrite use and methamphetamine is not uncommon among MSM [63], therefore future studies could benefit from examining marijuana and nitrite use in within-subjects analyses and take into account polydrug use.

As with all studies, our study has some inherent limitations. Many studies have suggested that alcohol use is associated with increased UAI among HIV infected [64-66] and uninfected MSM [10;13;67;68]; however, since alcohol use was not measured in our study interactions between alcohol and substance use could not be examined and

alcohol could not be considered as a confounder. Additionally, significant associations between GHB and MDMA were observed in univariate, but not multivariate, analyses, which may have been due to lack of power. Our sample may not be representative of all MSM who are at risk for HIV as they were only sampled from Southern California, the majority self-reported white ethnicity, and they were well educated. Additionally, substance use may vary by region, and MSM on the east coast of the United States may be more likely to use substances such as heroin or cocaine, whereas those on the west coast may be more likely to use substances such as methamphetamine [33;69]. Therefore these data should not be extrapolated to all types of substance use.

These analyses provide new evidence that supports a growing body of literature demonstrating that use of methamphetamine just prior to or during sexual activity increases the likelihood of UAI among MSM. Additionally, our study demonstrates that this is occurring among recently infected MSM, suggesting that methamphetamine use may be helping to propagate the current HIV epidemic among MSM in the United States. We also confirm that EDM use has become a stable drug of misuse among some MSM and demonstrate that it may increase the risk of UAI, and therefore increase the risk of HIV transmission, with particular types of partners. Interventions that focus on methamphetamine abuse prevention or rehabilitation and help prevent adoption of emerging substances of abuse among recently HIV infected MSM may help to reduce HIV incidence among MSM.

F. Acknowledgements:

The authors would like to acknowledge and thank W. Susan Cheng for her assistance in data collection and management; and Tari Gilbert, Jacqui Pitt, Paula Potter, Joanne Santangelo, and the University of California, San Diego Antiviral Research Center staff for their support in data collection. We would also like to thank Dr. Simon Frost for his suggestions and assistance in developing and writing this manuscript. Most of all we would like to thank our participants for the time and effort they have contributed to this study; without their willingness to participate and share their personal information with us this research would not be possible. Funding for this study was provided by: the National Institutes of Allergy and Infectious Diseases, grant # AI43638 (The Southern California Primary Infections Program); and the Universitywide AIDS Research Program, grant # ID01-SDSU-056; grant # IS02-SD-701; and grant # D03-SD-400.

G. Chapter Acknowledgements

This chapter was submitted in it's entirety as a manuscript for publication in the Journal of Acquired Immune Deficiency Syndromes and is under review as of the completion of this dissertation. The author of this dissertation, Lydia N. Drumright, will appear as the primary author on this manuscript in publication. The following are the contributing authors and their affiliations in the order in which they appear on the submitted manuscript: Susan J. Little, M.D., University of California, San Diego (UCSD), Department of Medicine, Antiviral Research Center; Steffanie A. Strathdee, Ph.D., UCSD, Department of Family and Preventive Medicine, Head of the Division of Cross-Cultural Medicine and Harold Simon Chair; Donald J. Slymen, Ph.D., San Diego State University (SDSU), Graduate School of Public Health; Maria Rosario G. Aaraneta, Ph.D., UCSD, Department of Family and Preventive Medicine; Vanessa L. Malcarne, Ph.D., SDSU, Department of Psychology; Eric S. Daar, M.D., University of California, Los Angeles (UCLA), David Geffen School of Medicine and Harbor-UCLA Hospital, Biomedical Research Institute; and Pamina M. Gorbach, DrPH, UCLA, School of Public Health and David Geffen School of Medicine, Division of Infectious Diseases.

Table 4-1: Unprotected anal intercourse (UAI) among the last three partners by demographics and sexual history (n=194)

	UAI with Last Three Partners			
	No UAI % (n) mean (median) n=31	**Variation in UAI** % (n) mean (median) n=116	**UAI with All** % (n) mean (median) n=47	**Total** % (n) mean (median) n=194
Age*	33.8 (34)	35.1 (36)	35.6 (37)	35.0 (35)
White ethnicity*	61.3 (19)	68.1 (79)	78.7 (37)	69.6 (135)
Unemployed*	38.7 (12)	28.5 (33)	25.5 (12)	29.4 (57)
Completed college or higher*	38.7 (12)	52.6 (61)	42.6 (20)	47.9 (93)
Recruited from main site*	87.1 (27)	87.1 (101)	76.6 (36)	84.5 (164)
Lifetime male sexual partners*	156 (75)	229 (99)	242 (100)	220 (99)
Male sexual partners in past 12 mo*	52 (14)	36 (20)	34 (25)	38 (20.5)
Male sexual partners in past 3 mo*	8 (3)	8 (4.5)	9 (5)	9 (4)
Sex with men & women past 12 mo†	3.2 (1)	6.0 (7)	8.5 (4)	6.2 (12)

* p>0.05 between UAI groups by chi-square analysis or ANOVA

† p>0.05 between UAI groups by Fisher's exact test

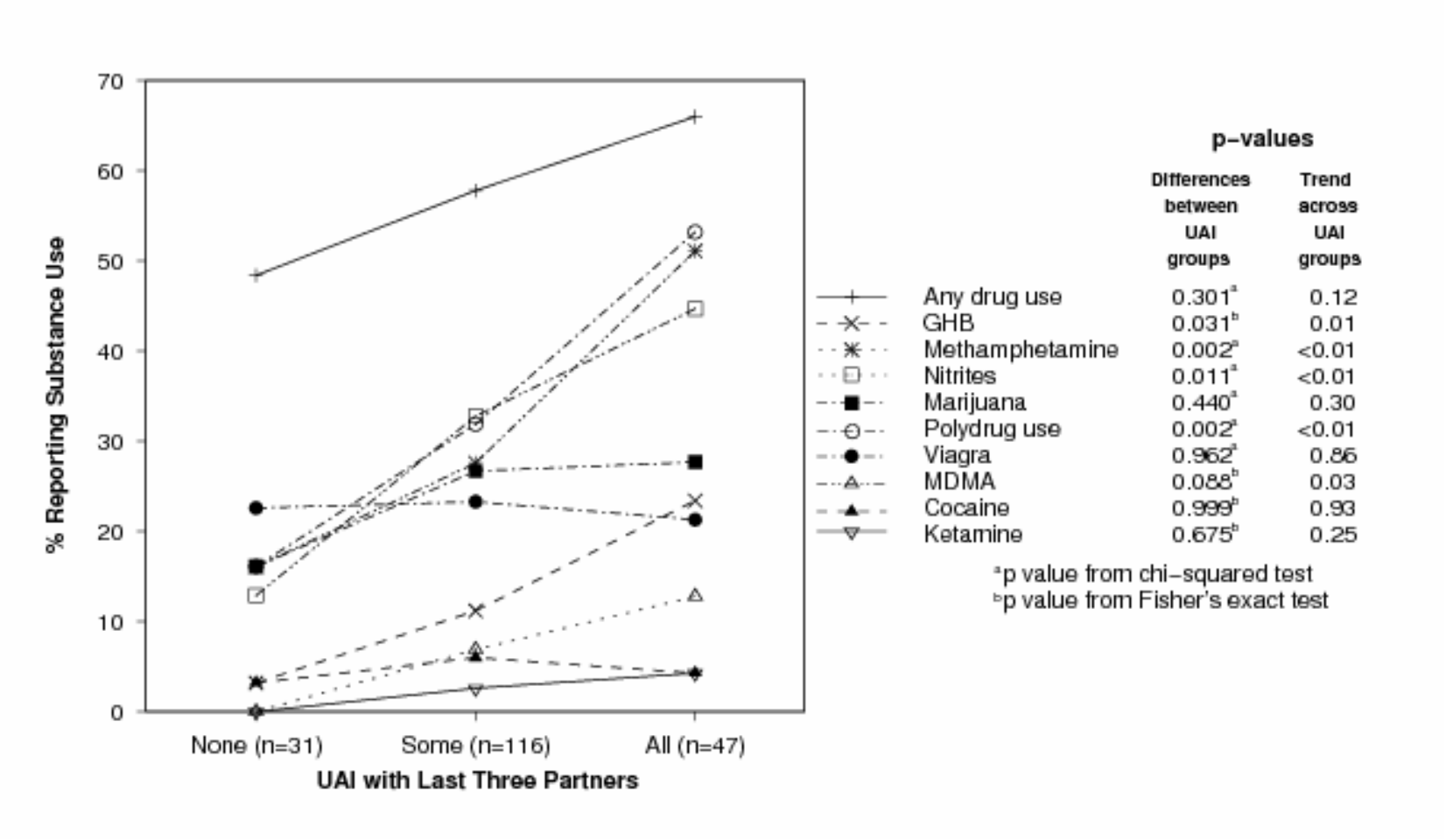


Figure 4-1: Frequency of reporting substance use with any of the last three partners by UAI category (none- no UAI with any of the last 3 v. some- UAI with some, but not all of the last three v. all- UAI with all of the last three) compared using chi-square analyses, Fisher's exact test, and Cuzick's test for trend (n=194).

Table 4-2: Univariate analysis of substance use by UAI across the last three partners using GEE for repeated measures among all participants and CLR for within subject comparisons among those who report variation in UAI by the last three partners

	Conditional Logistic Regression n=116			**GEE n=194**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Methamphetamine	**5.28**	**1.92, 14.6**	**0.001**	**3.13**	**1.96, 5.0**	**0.001**
Volatile Nitrites	**2.55**	**1.14, 5.69**	**0.023**	**2.27**	**1.42, 3.61**	**0.001**
GHB	3.39	0.87, 13.2	0.079	**4.22**	**1.86, 9.58**	**0.001**
MDMA	2.50	0.45, 14.0	0.297	2.74	1.0, 7.68	0.055
Ketamine	Too few observations			5.81	0.60, 56.6	0.130
Cocaine	3.07	0.56, 16.9	0.199	2.42	0.63, 9.23	0.197
Marijuana	**5.74**	**2.13, 15.5**	**0.001**	**3.09**	**1.73, 5.51**	**0.001**
Any Substance*	**3.83**	**1.89, 7.76**	**0.001**	**2.24**	**1.56, 3.23**	**0.001**
Polydrug Use**	**4.18**	**1.75, 9.99**	**0.001**	**3.39**	**2.08, 5.51**	**0.001**
EDM	2.65	0.97, 7.28	0.059	1.49	0.89, 2.51	0.131

OR= odds ratio CI= confidence interval

GEE= generalized estimating equations CLR= conditional logistic regression

UAI= unprotected anal intercourse EDM= erectile dysfunction medication

* Any substance refers to any illicit substance, but does not include EDM

** Polydrug use refers to the use of more than one type of substance, not including EDM

% using substance types differs between CLR and GEE due to different sample sizes

Table 4-3: Multivariate conditional logistic regression and generalized estimating equation (GEE) models comparing unprotected anal intercourse (UAI) and substance use among the last three partners

	Conditional Logistic Regression (n=116)			GEE (n=194)		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Methamphetamine	**4.86**	**1.36, 17.4**	**0.015**	**2.71**	**1.62, 4.55**	**0.001**
Volatile Nitrites	1.34	0.52, 3.42	0.546	1.64	0.98, 2.75	0.062
Marijuana	**4.01**	**1.35, 11.9**	**0.012**	**1.94**	**1.05, 3.61**	**0.036**
Main partner & EDM Use Interaction						
Other partner & no EDM	REF			REF		
Other partner, EDM used	1.52	0.46, 5.04	0.492	0.94	0.51, 1.74	0.833
Main partner, no EDM	1.88	0.90, 3.96	0.095	**2.20**	**1.31, 3.69**	**0.003**
Main partner, EDM used	**26.0**	**2.05, 330**	**0.012**	**17.1**	**1.78, 163**	**0.014**
Partner's Age (per year)	0.97	0.93, 1.01	0.123	1.00	0.98, 1.02	0.912
Days from Meeting to Sexual Intercourse	1.00	0.99, 1.01	0.540	1.00	0.99, 1.01	0.719
Partner HIV status:						
HIV positive	1.73	0.68, 4.44	0.253	**1.92**	**1.04, 3.56**	**0.038**
HIV negative	1.10	0.58, 2.07	0.774	1.08	0.72, 1.62	0.709
Unknown HIV serostatus	REF			REF		
Sex occurring before HIV diagnosis	1.43	0.68, 2.98	0.346	**1.62**	**1.10, 2.39**	**0.014**

OR= odds ratio CI=confidence interval
EDM=erectile dysfunction medication REF= reference category HIV= human immunodeficiency virus

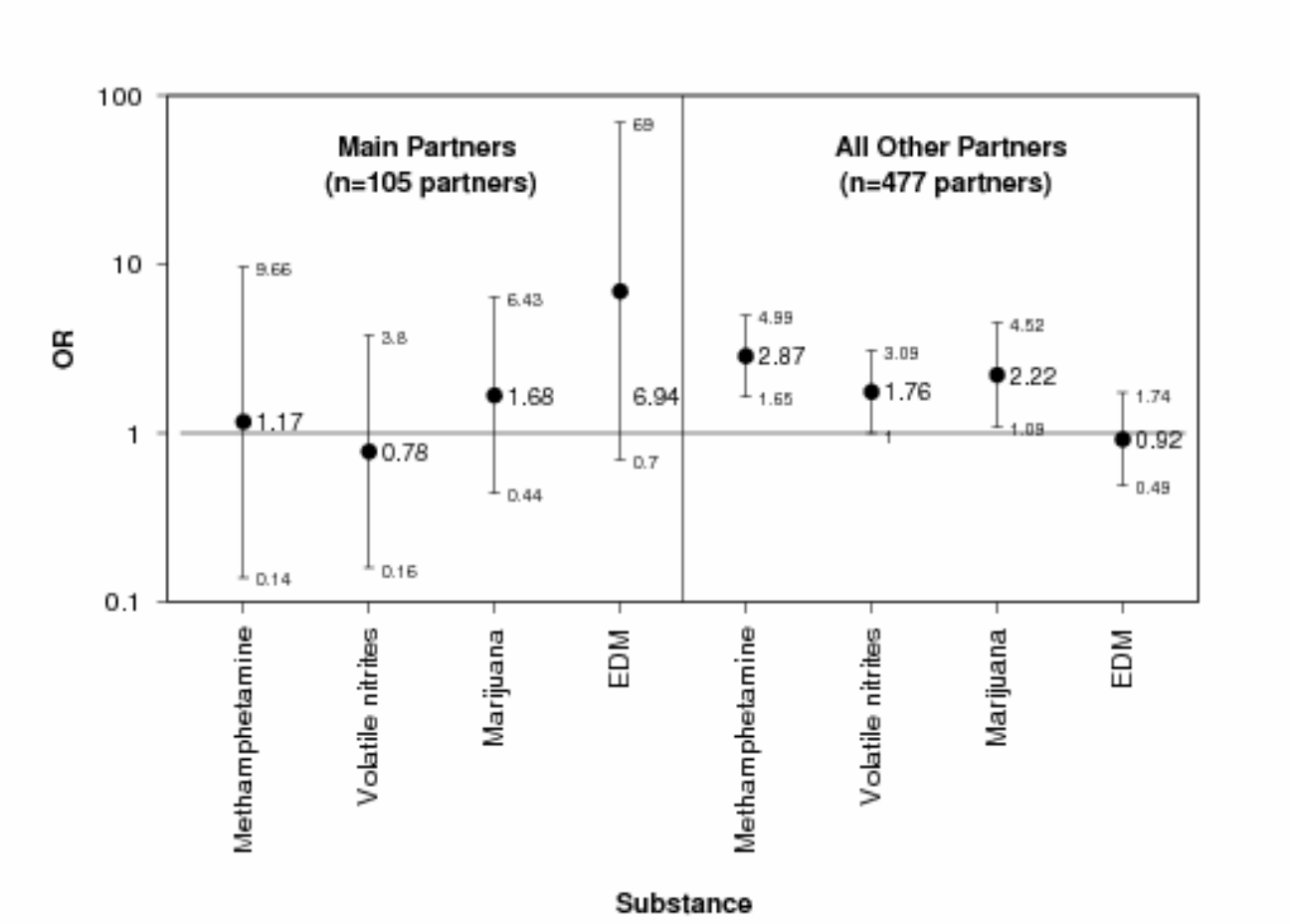


Figure 4-2: Separate multivariate generalized estimating equation (GEE) models comparing unprotected anal intercourse (UAI) and substance use among the last three partners, stratified by partner type (main partners v. all other partner types).

All models adjusted for variables in figure as well as partner's age, days between meeting partner and occurrence of first sexual intercourse, partner HIV status, and timing of sexual intercourse (i.e. before or after HIV diagnosis). EDM= erectile dysfunction medication.

H. References

(1) Burcham JL, Tindall B, Marmor M, Cooper DA, Berry G, Penny R. Incidence and risk factors for human immunodeficiency virus seroconversion in a cohort of Sydney homosexual men. *Med J Aust* 1989; 150:634-639.

(2) Page-Shafer K, Veugelers PJ, Moss AR, Strathdee S, Kaldor JM, van Griensven GJ. Sexual risk behavior and risk factors for HIV-1 seroconversion in homosexual men participating in the Tricontinental Seroconverter Study, 1982-1994. *Am J Epidemiol* 1997; 146:531-542.

(3) Chesney MA, Barrett DC, Stall R. Histories of substance use and risk behavior: Precursors to HIV seroconversion in homosexual men. *Am J Public Health* 1998; 88:113-116.

(4) Buchbinder S, Vittinghoff E, Heagerty P, Celum C, Seage G, Judson FN *et al.* Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J *Acquir Immune Defic Syndr* 2005; 39:82-89.

(5) Ostrow DG, DiFranceisco WJ, Chmiel JS, Wagstaff DA, Wesch J. A case-control study of human immunodeficiency virus type 1 seroconversion and risk-related behaviors in the Chicago MACS/CCS Cohort, 1984-1992. Multicenter AIDS Cohort Study. Coping and Change Study. *Am J Epidemiol* 1995; 142:875-883.

(6) Hirshfield S, Remien RH, Walavalkar I, Chiasson MA. Crystal methamphetamine use predicts incident STD infection among men who have sex with men recruited online: a nested case-control study. *J Med Internet Res* 2004; 6:e41.

(7) Cowan RL, Lyoo IK, Sung SM, Ahn KH, Kim MJ, Hwang J *et al.* Reduced cortical gray matter density in human MDMA (Ecstasy) users: a voxel-based morphometry study. *Drug Alcohol Depend* 2003; 72:225-235.

(8) Tabet SR, Krone MR, Paradise MA, Corey L, Stamm WE, Celum CL. Incidence of HIV and sexually transmitted diseases (STD) in a cohort of HIV-negative men who have sex with men (MSM). *AIDS* 1998; 12:2041-2048.

(9) Colfax GN, Mansergh G, Guzman R, Vittinghoff E, Marks G, Rader M *et al*. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr* 2001; 28:373-379.

(10) Rusch M, Lampinen TM, Schilder A, Hogg RS. Unprotected anal intercourse associated with recreational drug use among young men who have sex with men depends on partner type and intercourse role. *Sex Transm Dis* 2004; 31:492-498.

(11) Mulry G, Kalichman SC, Kelly JA. Substance use and unsafe sex among gay men - global versus situational use of substances. *J Sex Educ Ther* 1994; 20:175-184.

(12) Strathdee SA, Hogg RS, Martindale SL, Cornelisse PG, Craib KJ, Montaner JS *et al*. Determinants of sexual risk-taking among young HIV-negative gay and bisexual men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 19:61-66.

(13) Woody GE, Donnell D, Seage GR, Metzger D, Marmor M, Koblin BA *et al*. Non-injection substance use correlates with risky sex among men having sex with men: data from HIVNET. *Drug Alcohol Depend* 1999; 53:197-205.

(14) Clutterbuck DJ, Gorman D, McMillan A, Lewis R, Macintyre CC. Substance use and unsafe sex amongst homosexual men in Edinburgh. *AIDS Care* 2001; 13:527-535.

(15) Ekstrand ML, Stall RD, Paul JP, Osmond DH, Coates TJ. Gay men report high rates of unprotected anal sex with partners of unknown or discordant HIV status. *AIDS* 1999; 13:1525-1533.

(16) Morin SF, Steward WT, Charlebois ED, Remien RH, Pinkerton SD, Johnson MO *et al*. Prediciting HIV transmission risk among HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr* 2005; 40:226-235.

(17) Semple SJ, Patterson TL, Grant I. Psychosocial predictors of unprotected anal intercourse in a sample of HIV positive gay men who volunteer for a sexual risk reduction intervention. *AIDS Educ Prev* 2000; 12:416-430.

(18) Ross MW, Mattison AM, Franklin DR, Jr. Club drugs and sex on drugs are associated with different motivations for gay circuit party attendance in men. *Subst Use Misuse* 2003; 38:1173-1183.

(19) McCoul MD, Haslam N. Predicting high risk sexual behaviour in heterosexual and homosexual men: the roles of impulsivity and sensation seeking. *Pers Individ Dif* 2001; 31:1303-1310.

(20) Patterson TL, Semple SJ, Zians JK, Strathdee SA. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *J Urban Health* 2005; 82:I120-I126.

(21) Rhodes T, Stimson GV. What is the relationship between drug taking and sexual risk? *Sociol Health Illn* 1994; 16:209-228.

(22) Rhodes T. Culture, drugs and unsafe sex: confusion about casuation. *Addiction* 1996; 91:753-758.

(23) McKirnan DJ, Ostrow DG, Hope B. Sex, drugs and escape: a psychological model of HIV-risk sexual behaviours. *AIDS Care* 1996; 8:655-669.

(24) Ostrow D, McKirnan D. Prevention of substance-related high-risk sexual behavior among gay men: critical review of the literature and proposed harm reduction approach. *J Gay Lesbian Med Assoc* 1997; 1:97-110.

(25) McKirnan DJ, Vanable PA, Ostrow DG, Hope B. Expectancies of sexual "escape" and sexual risk among drug and alcohol-involved gay and bisexual men. *J Subst Abuse* 2001; 13:137-154.

(26) Leigh BC. Alcohol and condom use - A meta-analysis of event-level studies. *Sex Transm Dis* 2002; 29:476-482.

(27) Vanable PA, McKirnan DJ, Buchbinder SP, Bartholow BN, Douglas JM, Jr., Judson FN *et al*. Alcohol use and high-risk sexual behavior among men who have sex with men: the effects of consumption level and partner type. *Health Psychol* 2004; 23:525-532.

(28) Wingood GM, DiClemente RJ. The influence of psychosocial factors, alcohol, drug use on African-American women's high-risk sexual behavior. *Am J Prev Med* 1998; 15:54-59.

(29) Tawk HM, Simpson JM, Mindel A. Condom use in multi-partnered males: importance of HIV and hepatitis B status. *AIDS Care* 2004; 16:890-900.

(30) Stone E, Heagerty P, Vittinghoff E, Douglas JM, Jr., Koblin BA, Mayer KH *et al*. Correlates of condom failure in a sexually active cohort of men who have sex with men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; 20:495-501.

(31) Reback CJ, Larkins S, Shoptaw S. Changes in the meaning of sexual risk behaviors among gay and bisexual male methamphetamine abusers before and after drug treatment. *AIDS Behav* 2004; 8:87-98.

(32) Shoptaw S, Reback CJ, Frosch DL, Rawson RA. Stimulant abuse treatment as HIV prevention. *J Addict Dis* 1998; 17:19-32.

(33) Thiede H, Valleroy LA, MacKellar DA, Celentano DD, Ford WL, Hagan H *et al*. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health* 2003; 93:1915-1921.

(34) Beckett M, Burnam A, Collins RL, Kanouse DE, Beckman R. Substance use and high-risk sex among people with HIV: a comparison across exposure groups. *AIDS Behav* 2003; 7:209-219.

(35) Centers for Disease Control and Prevention. Increases in HIV diagnoses- 29 states, 1999-2002. *Morb Mortal Wkly Rep* 2003; 52:1145-1148.

(36) Quan VM, Steketee RW, Valleroy L, Weinstock H, Karon J, Janssen R. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr* 2002; 31:188-201.

(37) Leigh BC, Stall R. Substance use and risky sexual behavior for exposure to HIV: Issues in methodology, interpretation, and prevention. *Am Psychol* 1993; 48:1035-1045.

(38) Colfax G, Vittinghoff E, Husnik MJ, McKirnan D, Buchbinder S, Koblin B *et al*. Substance use and sexual risk: A participant- and episode-level analysis among a cohort of men who have sex with men. *Am J Epidemiol* 2004; 159:1002-1012.

(39) Gillmore MR, Morrison DM, Leigh BC, Hoppe MJ, Gaylord J, Rainy DT. Does "high=high risk"?: an event-based analysis of the relationship between substance use and unprotected anal sex among gay and bisexual men. *AIDS Behav* 2002; 6:361-370.

(40) Chu PL, McFarland W, Gibson S, Weide D, Henne J, Miller P et al. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr* 2003; 33:191-193.

(41) Crosby R, DiClemente RJ. Use of recreational Viagra among men having sex with men. *Sex Transm Dis* 2004; 80:466-468.

(42) Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS* 2002; 16:1425-1428.

(43) Sherr L, Bolding G, Maguire M. Viagra use and sexual risk behavior among gay men in London. *AIDS* 2000; 14:2051-2052.

(44) Paul JP, Pollack L, Osmond D, Catania JA. Viagra (sildenafil) use in a population-based sample of U.S. men who have sex with men. *Sex Transm Dis* 2005; 32:531-533.

(45) Aldridge J, Measham F. Sildenafil (Viagra) is used as a recreational drug in England. *Br Med J* 1999; 318:669.

(46) Crosby R, Diclemente RJ. Use of recreational Viagra among men having sex with men. *Sex Transm Infect* 2004; 80:466-468.

(47) Pilcher CD, Tien HC, Eron JJ, Vernazza PL, Leu SY, Stewart PW et al. Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *J Infect Dis* 2004; 189:1785-1792.

(48) Little SJ, Mclean AR, Spina CA, Richman DD, Havlir DV. Viral dynamics of acute HIV-1 infection. *J Exp Med* 1999; 190:841-850.

(49) Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L *et al*. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS* 2003; 17:1871-1879.

(50) Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li XB, Laeyendecker O *et al*. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005; 191:1403-1409.

(51) Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC *et al*. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med* 2002; 347:385-394.

(52) Breslow NE, Day NE. The Analysis of Case-Control Studies. In: *Statistical Methods in Cancer Research: Vol. 1.* Lyon, France: IARC Scientific Publications; 1980.

(53) Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986; 42:121-130.

(54) Colfax G, Coates TJ, Husnik MJ, Huang Y, Buchbinder S, Koblin B *et al*. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health* 2005; 82 (Suppl 1):i62-i70.

(55) Chmiel J, Detels R, Kaslow RA, Van Raden M, Kingsley LA, Brookmeyer R. Factors associated with prevalent HIV infection in the multicenter AIDS cohort. *Am J Epidemiol* 1997; 126:568-577.

(56) McKim WA. *Drugs and behavior*. 5th ed. Upper Saddle River: Prentice Hall; 2003.

(57) Green AI. "Chem friendly": the institutional basis of "club drug" use in a sample of urban gay men. *Deviant Behav* 2003; 24:427-447.

(58) Buffum J. Substance abuse and high-risk sexual behavior: drugs and sex--the dark side. *J Psychoactive Drugs* 1988; 20:165-168.

(59) Semple SJ, Patterson TL, Grant I. Motivations associated with methamphetamine use among HIV+ men who have sex with men. *J Subst Abuse Treat* 2002; 22:149-156.

(60) Gorman EM, Barr BD, Hansen A, Robertson B, Green C. Speed, sex, gay men, and HIV: ecological and community perspectives. *Med Anthropol Q* 1997; 11:505-515.

(61) Chesney MA, Barrett DC, Stall R. Histories of substance use and risk behavior: precursors to HIV seroconversion in homosexual men. *Am J Public Health* 2005; 88:113-116.

(62) French RS, Power R. Self-reported effects of alkyl nitrate use : a qualitative study amongst targeted groups. *Addict Res* 2001; 5:519-548.

(63) Patterson TL, Semple SJ, Zians JK, Strathdee SA. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *J Urban Health* 2005; 82:I120-I126.

(64) Parsons JT, Kutnick AH, Halkitis PN, Punzalan JC, Carbonari JP. Sexual risk behaviors and substance use among alcohol abusing HIV-positive men who have sex with men. *J Psychoactive Drugs* 2005; 37:27-36.

(65) Poppen PJ, Reisen CA, Zea MC, Bianchi FT, Echeverry JJ. Predictors of unprotected anal intercourse among HIV-positive Latino gay and bisexual men. *AIDS Behav* 2004; 8:379-389.

(66) Purcell DW, Parsons JT, Halkitis PN, Mizuno Y, Woods WJ. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse* 2001; 13:185-200.

(67) Hirshfield S, Remien RH, Humberstone M, Walavalkar I, Chiasson MA. Substance use and high-risk sex among men who have sex with men: a national online study in the USA. *AIDS Care* 2004; 16:1036-1047.

(68) Ruiz J, Facer M, Sun RK. Risk factors for human immunodeficiency virus infection and unprotected anal intercourse among young men who have sex with men. *Sex Transm Dis* 1998; 25:100-107.

(69) Sullivan PS, Nakashima AK, Purcell DW, Ward JW. Geographic differences in noninjection and injection substance use among HIV-seropositive men who have sex with men: Western United States versus other regions. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; 19:266-273.

V. MANUSCRIPT 3

Unprotected anal intercourse and substance use before and after HIV diagnosis among recently HIV infected men who have sex with men

A. Abstract

Background: Literature is conflicting regarding the extent to which men who have sex with men (MSM) modify their recreational substance use and sexual behavior after testing HIV-positive. We assessed associations between unprotected anal intercourse (UAI) and substance use before and after HIV diagnosis among recently HIV infected MSM.

Methods: 207 recently HIV-infected MSM were recruited in Southern California and completed computer assisted survey instruments (CASI) including questions regarding type and timing of sexual activity and substance use with their last three partners. Date of HIV diagnosis was extracted from medical records. Generalized estimating equations including interaction terms were used to assess associations between substance use and UAI before and after HIV diagnosis.

Results: Participants completed surveys on average 5 weeks after HIV diagnosis (13 weeks after estimated date of infection). The percent of partners with whom UAI occurred decreased after diagnosis (59.7 vs. 50.7%). Among partners with whom sexual activity occurred before diagnosis, UAI was associated with methamphetamine use alone (OR=4.80, 95% CI: 1.4, 16.1) and a combination of methamphetamine and other substances (OR=4.11, 95% CI: 1.9, 8.8). However after HIV diagnosis, UAI was associated with use of substances other than methamphetamine (OR=1.96, 95% CI: 1.3, 5.3) and a combination of methamphetamine and other substances (OR=5.08, 95% CI: 2.3, 11.2), but not methamphetamine alone.

Conclusions: Use of specific recreational substances may be differentially associated with UAI based on knowledge of HIV status. These findings have implications for prevention of onward HIV transmission.

B. Introduction

In recent years, the United States (U.S.) Centers for Disease Control and Prevention has called for human immunodeficiency virus type 1 (HIV) prevention efforts to shift from focusing only on HIV-negative individuals to include both HIV-negative and -positive individuals [1;2]. Such efforts are especially needed among men who have sex with men (MSM) who continue to bear a disproportionate burden of HIV infection in the U.S. and other developed countries [3-8].

Some MSM make a deliberate change in risk behavior after HIV diagnosis, possibly to prevent transmission to others. Among a sample of 104 New York City HIV-infected MSM with documented substance abuse disorders, 53 percent reported discontinuation of alcohol or substance use in response to HIV diagnosis [9]. In a longitudinal study of 78 HIV-infected individuals in Norway, of whom the majority were MSM, significant increases in condom use were reported after HIV diagnosis [10]. In a U.S. survey of 1,923 MSM who were infected with HIV for 12 months or more, 31 percent reported abstinence, only 40 percent reported insertive anal intercourse (IAI) with their last partner, and 75 percent of those reporting IAI used condoms with their last partner [11]. When compared to their HIV negative peers, some researchers have found that HIV-infected MSM report fewer partners [12], more condom use [13], and less frequent trading of sex for money or drugs [12].

Other studies report ongoing high-risk behaviors among HIV-infected MSM. In a study of HIV-infected MSM in Australia, those who were aware of that they had HIV were more likely to report UAI than those who were HIV-negative [14]. In a study in New York, HIV-infected MSM were more likely to be infected with syphilis than HIV-negative MSM [15]. In a study in San Francisco, over half (59%) of young MSM reported UAI despite knowing that they were HIV-positive [16].

Reductions in high risk sexual behavior following HIV diagnosis among MSM have been associated with specific attitudinal characteristics. Some HIV-infected MSM have reported that it was their responsibility to protect their sex partners from HIV [17;18]. It has been suggested that those who report that protecting their partners from HIV is not their responsibility are more likely to report insertive UAI than those who report that it is their responsibility [19]. Some HIV-infected MSM report sexual positioning, for example by participating in receptive rather than insertive UAI, in the hope of reducing the risk of HIV transmission to their partners [20;21]. Other studies have reported associations between increased risk of UAI and HIV treatment optimism or knowledge of reduced viral loads among HIV-positive MSM [22-25].

Some studies have suggested that use of illicit substances is associated with ongoing high-risk sexual behaviors among HIV-positive MSM. Use of alcohol [26] and nitrites [26;27] have been associated with UAI among HIV-positive MSM who were aware of their serostatus. Use of crack cocaine after HIV diagnosis has been associated with trading sex for money or illicit substances among MSM [28]. Illicit substance use may also modify the sense of shared responsibility for adopting safer sex behaviors. In a study of HIV-positive MSM conducted in Los Angeles, those who were methamphetamine-dependent were more likely to report that it was the HIV-negative person's responsibility to initiate a discussion about safer sex [29].

The period soon after HIV seroconversion is a critical juncture for prevention due to high HIV-1 viral loads that are associated with a higher probability of HIV transmission [30-34]. Reduction of risk behavior, coupled with early diagnosis of HIV infection, is important for preventing HIV among infected individuals. Understanding how risk behaviors are modified after diagnosis is important in designing appropriate behavioral interventions. However, most studies of behavior change have been

conducted in HIV-positive MSM who were not recently infected. The current study aims to elucidate the relationship between illicit substance use and UAI before and after HIV diagnosis among newly infected HIV-positive MSM.

C. Methods

Between May 2002 and October 2005, 265 recently HIV-infected persons were referred to the Acute Infection and Early Disease Research Program (AIEDRP) in San Diego and Los Angeles by physicians, HIV test-counselors, and community organizations. Of those referred, 97% (n=257) were eligible (i.e., had acute or early HIV infection) and consented to participate in AIEDRP. Eighty-six percent of these participants (n=222) were asked to complete a computer-assisted self interview (CASI) regarding HIV risk behaviors. Two-hundred eighteen (98%) volunteered to complete the CASI and provided informed consent. Of these, three were women, seven were men who reported sexual contact with only women in the previous 12 months, and 208 were men who reported sexual contact with other men in the previous 12 months. The current analyses include 207 MSM who responded to CASI and reported that at least one of their last three sexual partners was a man; one man reported all female partners among his last three partners.

All MSM had recent HIV infection as determined by one of the following: 1) presence of HIV RNA in plasma, but a negative enzyme immunoassay (EIA); 2) results on detuned and sensitive EIAs that were consistent with early HIV infection; or 3) HIV seroconversion within the previous 12 months (negative EIA followed by positive EIA). Estimated date of infection for all participants was based on last HIV negative test result and serology as previously described [35]. Date of HIV diagnosis was established

through reviewing medical records and assigned as the first positive HIV test that was reported to the participant.

Using CASI, participants were asked to provide detailed information about the last three people with whom they had had sexual contact. Questions were asked for each partner regarding duration of time between the interview and the first and last time they had sexual intercourse with each partner. Additionally, participants were asked about types of sexual activities that occurred (e.g., insertive or receptive oral and anal intercourse), substances used just prior to or during sexual activity (e.g., methamphetamine, marijuana, cocaine), partner demographic information, meeting location of partner, partner HIV status, and partner type (i.e., main, regular, friends, acquaintances, one-time, anonymous, and trade). Although participants were asked about specific substances, data for these analyses were collapsed into no substance use, methamphetamine only, substances other than methamphetamine, or a combination of methamphetamine and other substances. The protocol for this study was approved by the Institutional Review Boards of the University of California, San Diego; University of California, Los Angeles (UCLA); Harbor Hospital UCLA, and Cedars-Sinai Hospital.

Univariate and multivariate associations between UAI and substance among the 603 male partners reported by 207 MSM were conducted using generalized estimating equations (GEE) to correct for variance estimates of repeated measures [36]. Interactions between timing of sexual activity (i.e., before versus after HIV diagnosis) and substance use were included in GEE models to determine if there were significant temporal changes in the associations between UAI and substance use.

To further assess potential interactions and to describe changes in associations between UAI and the covariates before and after HIV diagnosis, we conducted a sub-

analysis in which participants' last three sexual partners were stratified into two different categories: those with whom all sexual contact occurred before the participant's medical record HIV diagnosis date and those with whom sexual contact occurred after the HIV diagnosis on participant's medical record. Separate GEE analyses were used to examine associations between UAI and substance use for each of these strata.

Contrasts were constructed to identify statistically significant differences between the effects of methamphetamine and other substances on UAI in all models. All GEE models were conducted using a binomial family, a logit link and an unstructured correlation matrix. Analyses were performed using STATA version 8.2 SE (STATA Corporation, College Station, TX).

D. Results

The 207 MSM included in this study completed their baseline interviews on average 13 (median 14) weeks after their estimated date of HIV infection, and on average 5 (median 3) weeks after receiving their HIV-positive diagnosis. Among the 207 MSM, 612 partners were reported, of whom nine were female; these partners were excluded from analysis because substance use and unprotected sexual activity may differ between same sex and opposite sex partnerships [13].

Of the 207 participants, the mean age was 35 years (range 18-65) and most were white (70.1%); 20.8% were Hispanic, 2.9% were African American/Black, 2.4% were Asian, and 3.9% reported other ethnicity. Almost half (46.9%) reported completing college or higher education and 30.4% were unemployed at the time of their interview (Table 1). The median reported number of male partners was: 20.0 in the previous 12 months (mean 38); 4 in the previous 3 months (mean 9.2); and 1 in the past month (mean 3.6). The average reported age of sexual debut was 16 years.

Of the last three partners, the mean reported age was 33 years, and most (62.2%) were white (Table 1). A range of different partner types were reported with the last three, including 18.4% who were main partners (e.g., boyfriend). The distribution of other partner types among the last three included: 25.5% unknown (e.g., anonymous), 16.3% onetime (i.e., a known onetime contact), 17.6% acquaintances (e.g., casual), 10.1% regular, but not main, 9.6% friends, and the remaining 1.1% trade (e.g., commercial sex work). Respondents reported meeting 12.1% of their last three partners in a bathhouse. Most (45.9%) of the last three partners were reported to have unknown HIV status, 42.2% were believed to be HIV-negative and 11.9% were believed to be HIV-positive. Sexual activity prior to diagnosis was reported with 317 (52.6%) of the partners and with 286 (47.4%) partners sexual activity occurred after diagnosis (Table 1).

Use of illicit substances just prior to or during sexual activity was reported with 45.9% of partners. Recreational substances were classified as follows: methamphetamine alone (5.5%), other substances alone (20.4%) and methamphetamine and other substances combined (18.1%) (Table 1). Among those reporting combined use of methamphetamine and other substances with the last three partners, nitrites (62.4%), gamma hydroxybutyrate (GHB) (44.0%), and marijuana (35.8%) were most commonly reported with methamphetamine. Among those reporting substance use other than methamphetamine with their last three partners, nitrites (44.7%) and marijuana (32.5%) were most commonly reported.

Use of substances other than methamphetamine just prior to sexual activity was reported with a greater proportion of sexual partners after diagnosis (29.0%) than before (12.6%, p=0.001) (Figure 1). In contrast, the proportion of sexual partners with whom methamphetamine use was reported, either alone (6.9% before vs. 3.9% after,

p=0.21) or in combination with other substances (19.2% vs.16.8%, respectively, p=0.34), did not change significantly following diagnosis.

In multivariate GEE models containing both independent variables and interaction terms (Table 2), methamphetamine use only (OR=4.39, p=0.01, CI: 1.36-14.2), methamphetamine and other substances (OR=4.01, p<0.01, CI: 1.9-8.45), and sexual contact occurring after HIV diagnosis as compared to exclusively before diagnosis (OR=0.65, p=0.05, CI: 0.42-1.01) were significantly associated with UAI as independent variables. In the same model (Table 2), interactions between timing of sexual activity and substance use revealed marginally significant (0.1 > p > 0.05) associations that were observed for methamphetamine only (p=0.08) and substances other than methamphetamine (p=0.01), but not methamphetamine and other substances combined (p=0.94).

Before diagnosis, those who used methamphetamine prior to or during sexual activity with a particular partner were more than four times as likely to report UAI with that partner (Figure 2) compared to MSM with no substance use. However, after HIV diagnosis those who reported methamphetamine use only with a particular partner were no more likely to report UAI with that partner than those who reported no substance use following HIV diagnosis. The difference in association between UAI and methamphetamine with partners in which all sexual contact occurred after diagnosis (OR=0.95) versus before diagnosis (OR=4.39) was marginally significant (p=0.08) (Figure 2). Similarly, there were marginally significant differences in the association between UAI and other substances when considering sexual contact before and after diagnosis through test by interaction (p=0.06) (Figure 2). However, the trend for other substances was the opposite of methamphetamine use (p=0.01). Those who reported other substance use with partners in which any sexual contact occurred before

diagnosis were no more likely than those who reported no substance use to report UAI with that partner (OR=0.79) (Figure 2). In comparison, those who reported substance use other than methamphetamine with partners in which all sexual activity occurred after diagnosis were 1.85 times more likely to report UAI with that partner compared to those who reported no substance use. In contrast, use of a combination of methamphetamine and other substances was significantly associated with UAI regardless of timing of sexual activity and did not change over time (p=0.94) (Figure 2).

To confirm differences in the associations between substance use and UAI relative to timing of HIV diagnosis suggested by these interactions, we stratified partners based on whether sexual contact occurred with the partner after diagnosis (n=286 partners) or before (n=317 partners), and analyzed the strata separately using two different GEE models (Table 3). The results of these models were highly consistent with the results from the whole sample, which modeled the effect of diagnosis using interaction terms. After controlling for partner's HIV status, partner type, and where the participant met his partner (bathhouses versus all other locations), those who reported methamphetamine use only and those who reported a combination of use of other substances and methamphetamine were more likely to report UAI than those who did not report substance use (OR=4.80, p=0.011, CI: 1.43-16.1 and OR=4.11, p=0.001, CI: 1.91-8.84 respectively). Substances other than methamphetamine were not associated with increased risk of UAI with partners who had sexual contact with the respondent before diagnosis. UAI with these partners was also more likely if the partner was a main partner (OR=2.09, p=0.04, CI: 1.02-4.27), but there was no association between UAI and partner HIV status or bathhouse meeting location. The effects of methamphetamine or a combination of methamphetamine and other substances on UAI were significantly different than other substances (p=0.01 and 0.001 respectively).

Among partners with whom all sexual contact occurred after diagnosis, UAI was associated with use of substances other than methamphetamine (OR=1.96, p=0.03, CI: 1.33-5.29), use of a combination of methamphetamine and other substances (OR=5.08, p=0.001, CI: 2.29-11.2), sexual contact with a main partner (OR=3.65, p=0.001, CI: 1.89-7.05), and the partner's perceived HIV status (OR=0.35, p=0.01, CI: 0.15-0.79 for negative vs. positive; OR=0.33, p=0.01, CI: 0.15-0.73 for unknown vs. positive). The effect of a combination of methamphetamine and other substances on UAI was significantly different than all other substances (p=0.03); however, the effect of methamphetamine only on UAI was not significantly different from other substance use (p=0.58) and marginally different from a combination of methamphetamine and other substances (p=0.08).

E. Discussion

In our study of recently HIV-infected MSM, reports of UAI with the last three sexual partners decreased from 59.6% before HIV diagnosis to 50.7% following HIV diagnosis. Of greater interest was our finding that use of specific illicit drugs had differential effects on UAI depending on whether or not sexual contact occurred with a partner before or after HIV diagnosis. Specifically, methamphetamine use was associated with higher odds of UAI with partners in which sexual contact occurred before HIV diagnosis, but was not associated with UAI after diagnosis after controlling for other substance use. In contrast, use of substances other than methamphetamine was not associated with UAI before HIV diagnosis, but was associated with a greater likelihood of UAI among partners in which sexual contact occurred after diagnosis. Use of methamphetamine combined with other substances increased the likelihood of UAI before and after diagnosis equally. These findings have implications with respect to

both the prevention of high risk sexual behavior and substance use among HIV-positive MSM and suggest that use of specific recreational substances may have differential effects on the risk of UAI based on an individual's knowledge of his HIV status.

We observed a modest reduction in UAI with sexual partners soon after HIV diagnosis, suggesting a deliberate reduction in transmission behaviors. A reduction in the number of sexual contacts (from an average of 7.9 to 5.2 three months later) has previously been observed in a subset of this cohort after HIV diagnosis [37]. In the present analyses, participants were significantly less likely to report UAI with HIV-negative or unknown status partners as compared to HIV-positive partners after HIV diagnosis, again suggesting a deliberate reduction in sexual activities that are associated with HIV transmission. However, prior to diagnosis, the partner's HIV status was not associated with UAI, suggesting that early diagnosis may help to prevent HIV transmission if such behavior changes occur. Since the data in this study were cross-sectional and participants reported behaviors over a short duration of time, it is unclear if sexual transmission risk reduction behavior will continue or if it will rebound with continued substance use.

The proportion of sexual partners with whom methamphetamine use was reported did not significantly change following HIV diagnosis, even though the association between methamphetamine and UAI changed markedly. These results suggest that MSM may have the potential to lower their HIV transmission risk behavior even if they continue to use methamphetamine during sexual activity. However, other investigators have suggested that partners' disclosure of their HIV status, type of venue in which sexual activity occurs, partner type, and perceived risk of sexual act all affect the decision of HIV-positive, methamphetamine-using MSM to disclose their HIV status, which is likely to result in condom use [29]. In our study, 22.7% of those who used

methamphetamine only with a partner before diagnosis reported that they met that partner in a bathhouse, but after diagnosis none of these partners were met in a bathhouse. Further studies are needed to directly evaluate changes in transmission risk behavior of methamphetamine-using MSM before and after diagnosis, including longitudinal studies that measure longer periods of time before and prolonged periods of time after HIV diagnosis.

On the other hand, use of substances other than methamphetamine immediately prior to or during sexual activity increased following HIV diagnosis. Use of substances other than methamphetamine was associated with higher rates of UAI among partners in which all sexual contact occurred after diagnosis, whereas methamphetamine use alone was not. However, a switch from methamphetamine to other substances was not observed, as use of methamphetamine alone or in combination with other substances prior to sexual activity did not change from before to after diagnosis. Instead, use of substances other than methamphetamine was more commonly reported with partners after diagnosis. This suggests that among recently HIV infected MSM, use of other substances may become more important in increasing UAI after HIV diagnosis. This may occur due to less public awareness of other substances' effects on UAI or because these other substances are perceived to have fewer personal health consequences than methamphetamine. However, we did not measure such beliefs in this study, nor do we know if post-test counseling covered the use of methamphetamine and risky sexual behavior, because not all participants were diagnosed in our clinic.

Although the temporal trends in associations between UAI and methamphetamine or other substances were not statistically significant ($p<0.05$), they were marginally significant ($0.1 > p > 0.05$), thus suggesting that a temporal trend is likely to exist. The power to detect a significant association is often an order of

magnitude less for interaction terms than for predictor variables within a statistical model [38-40]. However, there was a large difference in the magnitude of association of the point estimate between UAI and use of methamphetamine (4.5 times greater) and other substances (nearly 2.5 times less) before and after diagnosis (p=0.01), arguing that substance use patterns change following diagnosis. Although a small number of participants reported methamphetamine use alone with partners before (n=22) and after (n=11) diagnosis, the differences observed in the odds ratios should remain consistent even with a larger sample size.

Specific substances which comprise the “other” category were measured in the questionnaire and some substances were more commonly reported than others. The most commonly reported substances of use were nitrites, marijuana, and GHB; though GHB was much more common among users of both methamphetamine and another substance. There was considerable overlap in use of many different substances (i.e., polydrug use) with a single partner among our participants. Consequently, we were unable to explore all combinations of overlap or single use of these substances and methamphetamine as data would become too sparse, however we stress the relevance of such studies in larger samples.

Interestingly, those who reported use of methamphetamine and other substances with the same partner were more likely to report UAI with that partner than in partnerships in which no drugs were used, regardless of the participant’s HIV diagnosis. There may be two possible explanations for these observations. Firstly, the “combination” substance group could remain significantly associated with UAI regardless of timing with HIV diagnosis, because of the opposite effects of methamphetamine and other substances on UAI. Secondly, methamphetamine users who also use other substances may be more resistant to change or may be affected

less by HIV diagnosis. Previous studies have demonstrated that MSM who are polydrug users tend to report higher rates of UAI [41;42] as compared to single drug users; more sexual partners [43]; greater likelihood of STI [44]; and more UAI among HIV positive MSM with sero-discordant partners [[45]]. Polydrug use is also commonly reported in combination with methamphetamine use [42;45-47]. In this sample most (76.8%) methamphetamine users also reported use of other substances.

As with all observational studies there were some limitations. Due to time constraints we could not obtain additional information on the context of risk behaviors that may have helped to explain our results, such as whether or not subjects consciously altered their substance use and UAI behavior following HIV diagnosis. We were unable assess the affect of specific attitudes such as sense of responsibility, HIV treatment optimism, and beliefs about viral load and sexual positioning with regard to transmission to others on UAI in relation to substance use which have been shown to be important in other studies [17;20-25;48]. Additionally, general use of substances outside of sexual activity was only collected for half of the participants. For half of our participants we only captured UAI in general, but not insertive or receptive UAI, which may be important in determining the occurrence of sexual positioning. Our sample consisted of volunteers who were predominantly well-educated, white MSM, and may not be representative of all MSM who have recently become infected with HIV. Additionally, substance use among MSM may vary by geographic region [49;50], therefore these data may not be generalizable to all MSM.

Our study indicates that use of specific recreational substances may have differential effects on UAI before and after diagnosis among MSM, which has several implications for the study of substance use and HIV/STI. Our data suggest the need for designing studies that can specifically examine particular patterns of substance use with

regard to partnership and situational factors. Without examining the interaction between substance use and sexual timing in regard to UAI, we would have observed associations between substance use and UAI, but could have missed the change that occurred before and after diagnosis. Additionally, our data highlight the need for qualitative and quantitative studies that contribute to understanding modifiers and motivations for substance use and UAI, such as sense of responsibility with regard to prevention of HIV transmission, HIV treatment optimism, safer sex fatigue and social dynamics.

These data also have implications for HIV prevention. Our findings suggest that among MSM, interventions to reduce HIV transmission through substance use prevention should take into account different types of substance use. Counseling messages for MSM, regardless of HIV status, should clarify that while use of substances such as methamphetamine is particularly risky, any substance use that potentially modifies judgment about condom use should be avoided in the context of sexual activity. Risk reduction interventions at the time of HIV diagnosis that have an impact on users of substances other than methamphetamine and polydrug users are also needed.

F. Acknowledgements

The authors would like to acknowledge and thank Tari Gilbert, Jacqui Pitt, Paula Potter, Joanne Santangelo, and the University of California, San Diego Antiviral Research Center staff for their support in data collection; and W. Susan Cheng for her assistance in data collection and management. We would also like to thank Dr. Simon Frost for his suggestions and assistance in data analysis and writing this manuscript. Most of all we would like to thank our participants for volunteering for this study. Funding for this study was provided by: the National Institutes of Allergy and Infectious Diseases, grant # AI43638 (The Southern California Primary Infections Program); and the Universitywide AIDS Research Program, grant # ID01-SDSU-056; grant # IS02-SD-701; and grant # D03-SD-400.

G. Chapter Acknowledgements

This chapter was submitted in it's entirety as a manuscript for publication in Sexually Transmitted Diseases and is under review as of the completion of this dissertation. The author of this dissertation, Lydia N. Drumright, will appear as the primary author on this manuscript in publication. The following are the contributing authors and their affiliations in the order in which they appear on the submitted manuscript: Steffanie A. Strathdee, Ph.D., UCSD, Department of Family and Preventive Medicine, Head of the Division of Cross-Cultural Medicine and Harold Simon Chair; Susan J. Little, M.D., University of California, San Diego (UCSD), Department of Medicine, Antiviral Research Center; Maria Rosario G. Aaraneta, Ph.D., UCSD, Department of Family and Preventive Medicine; Donald J. Slymen, Ph.D., San Diego State University (SDSU), Graduate School of Public Health; Vanessa L. Malcarne, Ph.D., SDSU, Department of Psychology; Eric S. Daar, M.D., University of California, Los Angeles (UCLA), David Geffen School of Medicine and Harbor-UCLA Hospital, Biomedical Research Institute; and Pamina M. Gorbach, DrPH, UCLA, School of Public Health and David Geffen School of Medicine, Division of Infectious Diseases.

Table 5-1: Participant and partner demographics and sexual histories (n=207 individuals & 603 partners).

	Total Mean (median) % (n)
Individual characteristics	**n=207**
Age	35.0 (35)
White (vs. all other ethnicity)	70.1 (145)
Education: completed college or greater	46.9 (97)
Unemployed	30.4 (63)
Number of sex partners past 12 months	38.0 (20)
Number of sex partners past 3 months	9.2 (4)
Number of sex partners past month	3.6 (1)
Age at sexual debut	16.2 (16)
Partner/ partnership characteristics	**n=603**
Partner's age	33.2 (33)
Main partner (vs. all other types)	18.7 (113)
Partner's ethnicity is white	62.2 (375)
Timing of sexual contact	
Before diagnosis	52.6 (317)
After diagnosis	47.4 (286)
Met partner at bathhouse (v. all other locales)	12.1 (73)
Unprotected anal intercourse	55.4 (334)
Substance use during sexual activity	
No substances used	56.1 (338)
Methamphetamine only	5.5 (33)
Other substances except methamphetamine	20.4 (123)
Methamphetamine and other substances	18.1 (109)
Partner HIV status	
Positive	11.9 (72)
Negative	42.1 (254)
Unknown	45.9 (277)

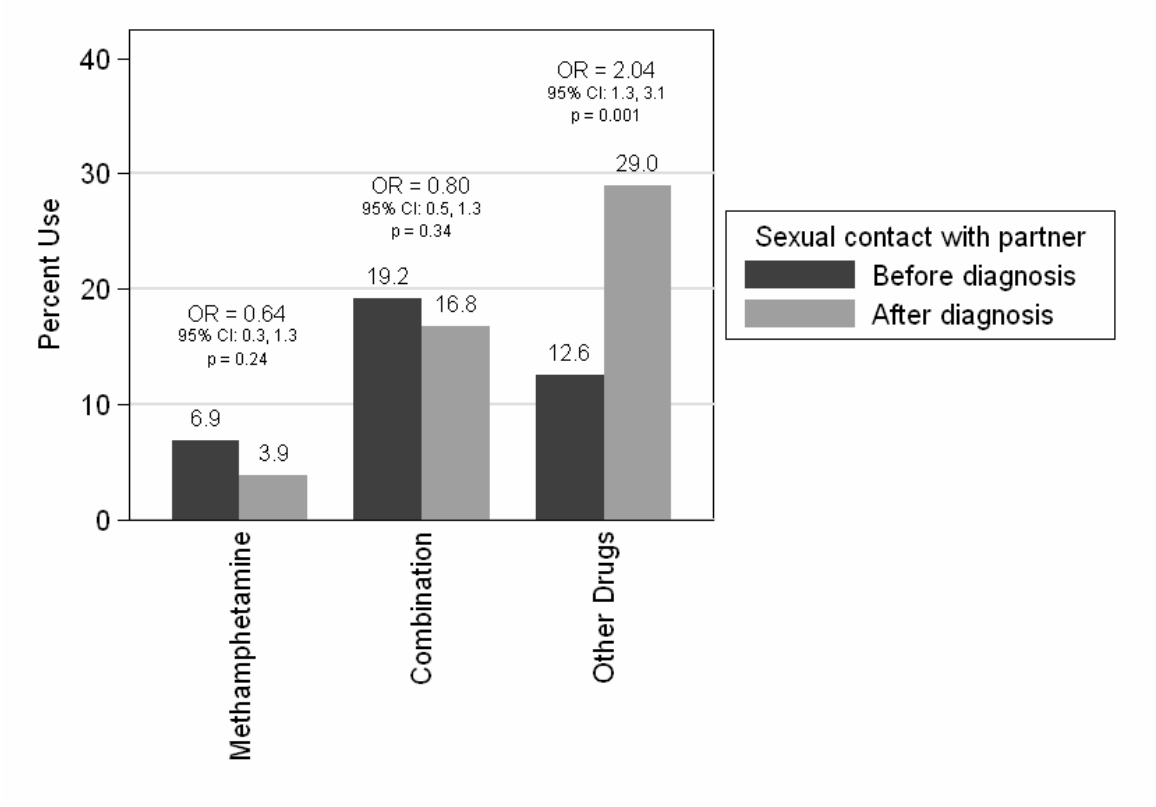


Figure 5-1: Differences in use of methamphetamine, other substances, or a combination of methamphetamine and other substances just prior to or during sexual contact with the last three sexual partners before and after HIV diagnosis (n=603 partners).

OR= the odds ratio of substance use after diagnosis as compared to before; 95% CI = the 95% confidence interval that corresponds to the odds ratio; Odds ratios, p-values, and confidence intervals adjusted for repeated measures using GEE

Table 5-2: Associations between UAI and substance use and differences before and after HIV diagnosis using GEE (n=603)

	OR	95% CI	p-value
Independent Variables			
Substance use			
No substances used	REF		
Methamphetamine only	**4.39**	**1.36, 14.2**	**0.01**
Substances other than methamphetamine	0.79	0.39, 1.60	0.55
Methamphetamine and other substances	**4.01**	**1.90, 8.45**	**<0.01**
Sexual contact occurring after diagnosis (compared to before diagnosis)	**0.65**	**0.42, 1.01**	**0.05**
Interactions			
Temporal differences in substance use and UAI			
Methamphetamine & sexual contact after diagnosis	**0.22**	**0.04, 1.20**	**0.08**
Other substances & sexual contact after diagnosis	**2.34**	**0.96, 5.70**	**0.06**
Combination & sexual contact after diagnosis	0.96	0.33, 2.75	0.94

*Odds ratios, confidence intervals, and p-values for all variables and interactions in this table are from a single multivariate model

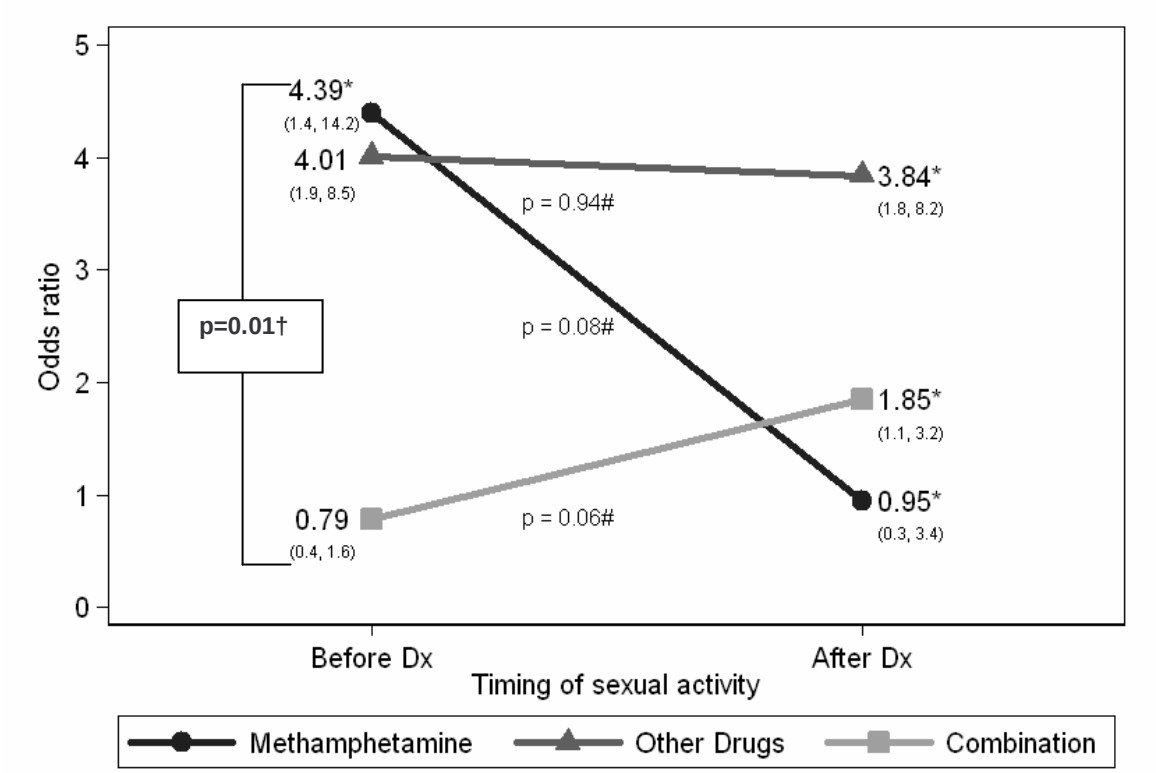


Figure 5-2: Interactions between timing of sexual contact (before or after diagnosis) and methamphetamine, other substance use excluding methamphetamine, or a combination of methamphetamine and other substances (n=603 partners)

* Odds ratio including interaction term, corresponding 95% confidence interval in parentheses below odds ratio

p-value to test the hypothesis of change in association between substance use and UAI by timing of sexual activity with regard to diagnosis

ŧ p-value calculated by interaction between substance use and timing of sexual activity with regard to diagnosis

† p-value from contrast between methamphetamine/timing interaction versus other substances/time interaction

Table 5-3: Different multivariate generalized estimating equations (GEE) analyses of UAI and substance use stratified by before and after HIV diagnosis samples

	Before HIV Diagnosis n=317			After HIV Diagnosis n=286		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Predictors of UAI						
Substance Use						
No substances used	REF			REF		
Methamphetamine	**4.80**	**1.43, 16.1**	**0.01**	1.32	1.06, 3.63	0.70
Substances other than methamphetamine	0.78	0.38, 1.62	0.51	**1.96**	**1.33, 5.29**	**0.03**
Combination of methamphetamine & other	**4.11**	**1.91, 8.84**	**0.001**	**5.08**	**2.29, 11.2**	**0.001**
Met partner in a bathhouse	1.73	0.78, 3.87	0.18	1.58	0.66, 3.79	0.31
Main partner v. all other types	**2.09**	**1.02, 4.27**	**0.04**	**3.65**	**1.89, 7.05**	**0.001**
Partner HIV status						
Positive	REF			REF		
Negative	1.02	0.42, 2.50	0.96	**0.35**	**0.15, 0.79**	**0.01**
Unknown	0.78	0.32, 1.93	0.58	**0.33**	**0.15, 0.73**	**0.01**
Contrasts						
Methamphetamine only v. Other substances	**6.25**	**1.59, 25.0**	**0.01**	0.67	0.16, 2.78	0.58
Methamphetamine only v. Combination	1.17	0.31, 4.42	0.82	0.26	0.06, 1.14	0.08
Other substances v. Combination	**0.19**	**0.07, 0.50**	**0.001**	**0.39**	**0.17, 0.90**	**0.03**

H. References

(1) Centers for Disease Control and Prevention. Advancing HIV prevention: new strategies for a changing epidemic- United States 2003. *Morbidity and Mortality Weekly Report*. 2003; 52:329-332.

(2) Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV. *Morbidity and Mortality Weekly Report*. 2003; 52:1-24.

(3) Centers for Disease Control and Prevention. Trends in HIV/AIDS diagnosis- 33 states, 2001-2004. *Morbidity and Mortality Weekly Report*. 2005; 54:1149-1153.

(4) Archibald CP, Sutherland J, Geduld J et al. Combining data sources to monitor the HIV epidemic in Canada. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S24-S32.

(5) Hamouda O. HIV/AIDS surveillance in Germany. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S49-S54.

(6) Kaldor J, McDonald A. HIV/AIDS surveillance systems in Australia. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S18-S23.

(7) Murphy G, Charlett A, Jordan LF et al. HIV incidence appears constant in men who have sex with men despite widespread use of effective antiretroviral therapy. *AIDS*. 2004; 18:265-272.

(8) Smith E. HIV/AIDS surveillance in Denmark: The challenges ahead. *Journal of Acquired Immune Deficiency Syndromes*. 2003; 32:S33-S38.

(9) Ferrando S, Goggin K, Sewell M et al. Substance use disorders in gay/bisexual men with HIV and AIDS. *American Journal on Addictions*. 1998; 7:51-60.

(10) Skrondal A, Eskid A, Thorvaldsen J. Changes in condom use after HIV diagnosis. *Scandinavian Journal of Public Health*. 2000; 28:71-76.

(11) Campsmith ML, Begley EB, Nakamura GV. High-risk sexual behavior by HIV-positive men who have sex with men - 16 sites, United States, 2000-2002 (Reprinted from MMWR, vol 53, pg 891-894, 2004). *JAMA-Journal of the American Medical Association*. 2004; 292:2333-2334.

(12) Fuller CM, Absalon J, Ompad DC et al. A comparison of HIV seropositive and seronegative young adult heroin- and cocaine-using men who have sex with men in New York city, 2000-2003. *Journal of Urban Health*. 2005; 82:I51-I61.

(13) Tawk HM, Simpson JM, Mindel A. Condom use in multi-partnered males: importance of HIV and hepatitis B status. *AIDS Care*. 2004; 16:890-900.

(14) VandeVen P, Campbell D, Kippax S et al. Factors associated with unprotected anal intercourse in gay men's casual partnerships in Sydney, Australia. *AIDS Care*. 1997; 9:637-649.

(15) Paz-Bailey G, Meyers A, Blank S et al. A case-control study of syphilis among men who have sex with men in New York City - Association with HIV infection. *Sexually Transmitted Diseases*. 2004; 31:581-587.

(16) Hays RB, Paul J, Ekstrand M et al. Actual versus perceived HIV status, sexual behaviors and predictors of unprotected sex among young gay and bisexual men who identify as HIV-negative, HIV-positive and untested. *AIDS*. 1997; 11:1495-1502.

(17) Wolitski RJ, Bailey CJ, O'Leary A et al. Self-perceived responsibility of HIV-seropositive men who have sex with men for preventing HIV transmission. *AIDS Behav*. 2003; 7:363-372.

(18) Parsons JT, Halkitis PN, Wolitski RJ et al. Correlates of sexual risk behaviors among HIV-positive men who have sex with men. *AIDS Educ Prev*. 2003; 15:383-400.

(19) Parsons JT, Halkitis PN, Wolitski RJ et al. Correlates of sexual risk behaviors among HIV-positive men who have sex with men. *AIDS Educ Prev*. 2003; 15:383-400.

(20) Van de Ven P, Kippax S, Crawford J et al. In a minority of gay men, sexual risk practice indicates strategic positioning for perceived risk reduction rather than unbridled sex. *AIDS Care*. 2002; 14:471-480.

(21) Valdiserri RO, Lyter D, Leviton LC et al. Variables influencing condom use in a cohort of gay and bisexual men. *American Journal of Public Health*. 1998; 78:801-805.

(22) Ostrow DE, Fox KJ, Chmiel JS et al. Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men. *AIDS*. 2002; 16:775-780.

(23) Vanable PA, Ostrow DG, McKirnan DJ et al. Impact of combination therapies on HIV risk perceptions and sexual risk among HIV-positive and HIV-negative gay and bisexual men. *Health Psychology*. 2000; 19:134-145.

(24) Miller M, Meyer L, Boufassa F. Sexual behavior changes and protease inhibitor therapy. *AIDS*. 2000; 14:F33-F39.

(25) Remien RH, Wagner G, Garballo-Dieguez A et al. Who may be engaging in high-risk sex due to medical treatment advances? *AIDS*. 1998; 12:1560-1561.

(26) Purcell DW, Parsons JT, Halkitis PN et al. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse*. 2001; 13:185-200.

(27) Kalichman SC, Kelly JA, Rompa D. Continued high-risk sex among HIV seropositive gay and bisexual men seeking HIV prevention services. *Health Psychology*. 1997; 16:369-373.

(28) Campsmith ML, Nakashima AK, Jones JL. Association between crack cocaine use and high-risk sexual behaviors after HIV diagnosis. *Journal of Acquired Immune Deficiency Syndromes*. 2000; 25:192-198.

(29) Larkins S, Reback CJ, Shoptaw S et al. Methamphetamine-dependent gay men's disclosure of their HIV status to sexual partners. *AIDS Care*. 2005; 17:521-532.

(30) Fiebig EW, Wright DJ, Rawal BD et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003; 17:1871-1879.

(31) Pilcher CD, Tien HC, Eron JJ et al. Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *Journal of Infectious Diseases*. 2004; 189:1785-1792.

(32) Little SJ, Mclean AR, Spina CA et al. Viral dynamics of acute HIV-1 infection. *Journal of Experimental Medicine*. 1999; 190:841-850.

(33) Quinn TC, Wawer M, Sewankambo NK et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *New England Journal of Medicine*. 2000; 342:921-929.

(34) Wawer MJ, Gray RH, Sewankambo NK et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *Journal of Infectious Diseases*. 2005; 191:1403-1409.

(35) Little SJ, Holte S, Routy JP et al. Antiretroviral-drug resistance among patients recently infected with HIV. *New England Journal of Medicine*. 2002; 347:385-394.

(36) Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biomterics*. 1986; 42:121-130.

(37) Gorbach PM, Drumright LN, Daar ES et al. Transmission behaviors of recently HIV-infected men who have sex with men. *Journal of Acquired Immune Deficiency Syndromes*. 2006; In press.

(38) Greenland S. Test for interaction in epidemiologic studies: a review and a study of power. Statistics in Medicine 2, 243-251. 1983. (Electronic Citation)

(39) Greenland S. Basic Problems in Interaction Assessment. *Environmental Health Perspectives*. 1993; 101:59-66.

(40) Breslow NE, Day NE. Statistical methods in cancer research II: the design and analysis of cohort studies. Lyon: International Agency on for Research on Cancer, 1987.

(41) Ostrow DG, Beltran ED, Joseph JG et al. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. *J Subst Abuse*. 1993; 5:311-325.

(42) Colfax G, Coates TJ, Husnik MJ et al. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health*. 2005; 82:i62-i70.

(43) Stall RD, Paul JP, Greenwood GL et al. Alcohol use, drug use and alcohol-realted problems among men who have sex with men: the Urban Men's Health Study. *Addiction*. 2001; 96:1589-1601.

(44) Greenwood GL, White EW, Page-Shafer K et al. Correlates of heavy substance use among young gay and bisexual men: The San Francisco Young Men's Health Study. *Drug and Alcohol Dependence*. 2001; 61:105-112.

(45) Patterson TL, Semple SJ, Zians JK et al. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:I120-I126.

(46) Degenhardt L, Topp L. 'Crystal meth' use among polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. *International Journal of Drug Policy*. 2003; 14:17-24.

(47) Halkitis PN, Green KA, Mourgues P. Longitudinal Investigation of Methamphetamine Use Among Gay and Bisexual Men in New York City: Findings from Project BUMPS. *J Urban Health*. 2005; 82:i18-i25.

(48) Parsons JT, Halkitis PN, Wolitski RJ et al. Correlates of sexual risk beaviors among HIV-positive men who have sex with men. *AIDS Education and Prevention*. 2003; 15:383-400.

(49) Sullivan PS, Nakashima AK, Purcell DW et al. Geographic differences in noninjection and injection substance use among HIV-seropositive men who have sex with men: Western United States versus other regions. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1998; 19:266-273.

(50) Thiede H, Valleroy LA, MacKellar DA et al. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health*. 2003; 93:1915-1921.

VI. DISCUSSION

The incidence of HIV among men who have sex with men (MSM) appears to be increasing in developed countries world-wide [1-6]. Previous studies suggest that the growing use of 'club drugs' may be one explanation for increased HIV incidence among MSM by increasing the likelihood of unprotected anal intercourse (UAI) [7-18]. However, others have argued that the association between UAI and substance use is confounded by a risk-taking personality trait [19;20] or a pre-planned decision for UAI [21-25]. Studies that examine event-level and within-subject use of specific recreational substances and the risk of HIV acquisition and transmission are needed in order to provide evidence for or against a causal association.

Three independent, yet related, studies have made up the basis of this dissertation, which adds to the body of literature on this topic. The first study reviews the current literature on "club drugs" and risk of HIV/STI acquisition and transmission, and makes recommendations for how future studies should be conducted. The next two studies examined associations between UAI and substance use among recently-HIV infected MSM. Manuscript 2 provides evidence that use of methamphetamine just prior to sexual activity increases the likelihood of UAI among MSM and suggests that methamphetamine, in particular, contributes to the increases observed in HIV incidence. Furthermore, manuscript 2 suggests that erectile dysfunction medication (EDM) use may be associated with increased risk of UAI among main partners, but not other partner types. Manuscript 3 suggests that different substances increase the risk of UAI before and after HIV diagnosis. Strengths, limitations, potential biases, and recommendations for future study needs and future directions of research are discussed.

A. Summary of the Studies

In the first manuscript, a review of club drugs as causal risk factors for HIV and STI among MSM, the following substances were examined for their potential to meet Hill's criteria [26] for causation: methamphetamine or amphetamine; methylenedioxymethamphetamine (MDMA); ketamine; gamma hydroxy-butyrate (GHB); lysergic acid diethylamide (LSD); flunitrazepam; erectile dysfunction medications (EDMs), specifically sildenafil citrate as specific studies have not been completed on other EDMs; and volatile nitrites. Few studies had been conducted that examined associations between use of most of these substances and risk for HIV or STI among MSM, or evidence for a causal association was incomplete. However, there was biological plausibility for such an association to exist for most of these substances. For all substances, studies that quantitatively address dose-response, analyze substances individually, examine partnership dynamics and sexual network structures, study effects of substance abuse treatment on behavior change, and use event-level and within-subjects methodologies and analyses were recommended.

Drawing from the recommendations in manuscript 1, manuscript 2 examined associations between use of methamphetamine, EDM, nitrites, or marijuana and UAI among recently HIV-infected MSM using pseudo dose-response trend, within-subjects, and complete sample analyses. In trend analysis, participants who reported use of methamphetamine, GHB, nitrites, or MDMA with at least one of their last three partners were also more likely to report UAI with all of their last three partners, than UAI with some or none of their last three partners, indicating a pseudo dose-response relationship. This relationship is considered a 'pseudo' dose-response because it was only inclusive of the last three partners, not all partners over a certain duration of time. A more appropriate study of dose-response would examine frequency and duration of

substance use and risk for HIV acquisition. However, the pseudo dose-response that was demonstrated in this study suggests that an actual dose-response relationship may exist between substance use and UAI. Among participants who reported UAI with some (but not all) partners, within-subjects analyses demonstrated that methamphetamine use was the strongest predictor of UAI while controlling for characteristics of the individual. Additionally, EDM use with a main partner was also a predictor of UAI. Among all participants, even those who did not report variation in UAI with their last three partners, methamphetamine use remained the strongest predictor of UAI. Additionally, marijuana use, EDM use with a main partner, reporting that the partner was a main partner or HIV positive, and reporting that sexual activity occurred before diagnosis were associated with UAI. These results suggest that use of methamphetamine, and EDM in some situations, are independent risk factors for UAI. Considering the high HIV infectivity of recently infected individuals, these results also suggest that methamphetamine use may increase the likelihood of HIV transmission to others by increasing the likelihood of UAI.

In order to examine the possibility that early HIV diagnosis may change patterns of behavior with regard to substance use and UAI, the third manuscript examined changes in the association between substance use and UAI before and after HIV diagnosis. In this study, the associations between methamphetamine use or use of substances other than methamphetamine and UAI differed before and after HIV diagnosis. Methamphetamine use alone was strongly associated with UAI among partners with whom sexual contact occurred before diagnosis, however this association was not observed among partners in which sexual activity occurred after diagnosis. The reverse associations were true for other types of substance use and UAI; use of substances other than methamphetamine was associated with UAI after, but not before

diagnosis. There were strong associations between UAI and use of methamphetamine and other substances, both before and after HIV diagnosis. These findings suggest that use of different substances may have differential effects on UAI before and after diagnosis, and that early diagnosis and interventions tailored for different types of substance use may help prevent HIV/STI transmission.

Taken together, these three manuscripts provide important insights about substance and risk for HIV and STI among MSM. Firstly, they indicate that substance use is a significant health problem among MSM who are at risk for HIV infection and MSM with recent HIV infection. Secondly, they indicate that the associations between substance use and UAI are complex and dynamic and may change based on partner type or personal knowledge of HIV status. Thirdly, they indicate that methamphetamine use may increase the risk of UAI among recently HIV infected MSM, thereby leading to continued HIV transmission to others. Hence interventions to reduce methamphetamine use (such as behavioral interventions or drug abuse treatment) could help to prevent HIV transmission. Fourthly, these data suggest that early diagnosis of HIV, in combination with appropriately designed interventions to ameliorate the misuse of methamphetamine alone and in combination with other substances, could help prevent HIV transmission among MSM. Lastly, more intensive studies of substance use and health risks among MSM are needed.

B. Sample Size Estimations and Power

For all proposed studies it is recommended to estimate the sample size necessary to detect a significant difference, if present, between groups or to obtain estimates with a desired precision. Estimating the sample size prior to conducting a study can help researchers to decide if a study is feasible and cost efficient, to develop

the best design to recruit the necessary number of participants, to estimate the duration and cost of a study, and to interpret negative results based on estimated power. However, sample size and power may be more difficult to estimate for studies that examine more complex associations and that include multiple measures on the same individual, especially when planning to examine many covariates or interactions in multivariate models. Additionally, using post-hoc power calculations in order to estimate the availability of power with the given sample and model, can be problematic in interpreting results.

A Prior Sample Size and Power Calculations

Due to a lack of available information on model parameters, including patterns of covariates, the correlation of the outcome within a subject across different partners, and the size of the effect of the confounders on the outcome, a priori sample size was not calculated for the GEE models specified in the studies, but instead for a logistic regression model. Table 6-1 provides the sample sizes necessary in each UAI group for a given UAI and substance use prevalence to achieve 80 percent power at an alpha-level of 0.05, testing a two sided hypothesis.

Reinterpreting these power calculations, given the prevalences observed for UAI and specific substances tested in manuscripts 2 and 3 (Table 6-2), the sample size for the effects observed in each manuscript can be located on Table 6-1. In manuscript 2 where the UAI prevalence is 55 percent, considering methamphetamine with a prevalence of approximately 24 percent (Table 2) and an odds ratio of around 3 in univariate and multivariate GEE models (Chapter 4, Tables 4-2 and 4-3), a sample size of approximately 58 to 75 in the group reporting UAI and 49 to 63 in the group reporting no UAI are necessary to detect a significant difference at an odds ratio of 3. For the

remaining variables, based on a priori sample size calculations, power was lacking (below 80%) for volatile nitrites, marijuana, and EDMs in manuscript 2, however univariate associations were observed for both nitrites and marijuana (Chapter 4, Table 4-2) in univariate analyses and for marijuana in multivariate analyses (Chapter 4, Table 4-3). Similarly, for manuscript 3 wherein the prevalence of UAI was 55 percent, according to Table 6-1, there was less than 80 percent power to detect the presence of a significant difference between methamphetamine only at an odds ratio of 4.0 and other substances only at an odds ratio of 2.0, however significant differences between UAI groups were detected either before or after HIV diagnosis. Table 6-1 is not a very accurate estimation of sample size as it is based on logistic regression and does not take into account repeated measures nor does it take into account analysis of interaction terms.

Post-Hoc Power and Sample Size Calculations

Post-hoc sample size calculations were also conducted for manuscripts 2 and 3. These were conducted in STATA using a bootstrap method [27] wherein the model used in the actual analyses was fitted using 1000 randomly generated data with similar proportions of predictors and outcomes and similar relationships between covariates. The bootstrap for the outcome was parametric and for the predictors and covariates it was non-parametric due to the structure of the original data. Power to detect each predictor was calculated as the proportion of the models in which the p-value associated with the predictor was 0.05 or less.

For manuscript 2, post-hoc power was calculated for univariate associations between UAI and use of methamphetamine, nitrites, or marijuana (Figure 6-1). For all three substances power to detect a significant difference if present was 80 percent

according to post-hoc power calculations (Figure 6-1). A significant difference between UAI group was observed for each of the subjects univariately in manuscript 2 (Chapter 4, Table 4-2). This may not be a valid assessment of power, as described in the next two paragraphs. However, it is important to note that at a sample size of about 130, 64 fewer individuals than the actual sample size, given the exact same conditions, would be necessary to achieve 80 percent power.

For manuscript 3, post-hoc power was calculated for associations between UAI and substance use while taking into account interactions between this association and sexual contact with each partner in regards to timing of HIV diagnosis in a multivariate model (Figure 6-2). This model was selected because the greatest concern in manuscript 3 was that there was insufficient power to detect the interactions that were marginally significant (Chapter 5). In addition, post-hoc power was calculated for the multivariate models that were stratified by timing of sexual contact, before (Figure 6-3) and after (Figure 6-4) HIV diagnosis. Although these post-hoc power calculations do not provide any new insight into whether or not there was sufficient power to detect these interactions, they do illustrate the limitations and values of calculating post-hoc power.

In Figure 6-2 power to detect a significant interaction if present is low for all three classes of substance use, with other substances just under 50 percent power at a sample size of 207, followed by methamphetamine alone at 35 percent and a combination of methamphetamine and other substances at around 5 percent or less. For both methamphetamine and other substances, power increases with sample size, but this is not the case for the combination of the two. In the original analysis (Chapter 5), both methamphetamine (p=0.08) and other substances (p=0.06) had marginally significant interactions, but the combination of the two did not (p0.94) (Chapter 5, Table 5-2). However if post-hoc power is calculated for only those partners in which sexual

contact was reported before diagnosis (Figure 6-3), power of greater than 80 percent is achieved with a sample size of 200 for methamphetamine and a combination of methamphetamine and other substances. Conversely, for other substances alone power is constant at about 7 percent for a sample size of 50 through 200. In the actual analysis (Chapter 5, Table 5-3), methamphetamine (OR=4.8, p=0.01) and a combination of methamphetamine and other substances (OR=4.1, p=0.001) were significantly associated with UAI, however other substances alone were not (OR=0.78, p=0.51). In contrast post-hoc power calculated for only those partners in which sexual activity occurred after HIV diagnosis (Figure 6-4), at a sample size of 200, there is greater than 80 percent power for a combination of methamphetamine and other substances, 65 percent power other substances alone, and around 7 percent power for methamphetamine alone, regardless of having a sample size of 50 or 200. Not surprisingly, the actual analyses were related to the post-hoc power calculations in the same way as the previous two examples (Chapter 5, Table 5-3). In the actual analyses of the data, Use of other substances (OR=1.96, p=0.03) or a combination of methamphetamine and other substances (OR=5.1, p=0.001) were associated with UAI, but use of methamphetamine alone (OR=1.3, p=0.70) was not (Table 5-3). Comparison of each for the post-hoc power calculations (Figures 6-2, 6-3, and 6-4) with the corresponding data analyses from the actual study (Tables 5-2 and 5-3) demonstrate a predictable relationship between post-hoc power and statistical significance.

These analyses point out the disadvantages of post-hoc power. Firstly, post-hoc power is based on parameter estimates using a particular model, not on the true parameter values in a given population. If the calculated parameter estimate of the model is incorrect, the power for detecting a true association given an actual population will be incorrect. A priori power differs from post-hoc power in that it is based on what is

expected in a true population. Secondly, post-hoc power for the sample size equal to that in the data is a one to one function of the p-value. As demonstrated in the examples above, power to detect a difference could not be achieved if the p-value in the corresponding model was greater than 0.05. Therefore, post-hoc power only provides information for sample sizes different from that of the sample in which the model was fit, and is only valid for sample sizes smaller than that of the sample. The best use of post-hoc power would be to estimate how much smaller of a sample size would be sufficient to detect an association given similar parameters.

C. Potential Biases that Effect Internal Validity

As with any study, there were potential biases and limitations in all three of the manuscripts that constitute this dissertation. Bias in epidemiology has been defined as an incorrect estimate of the association between the predictor and outcome due to an error in the design, conduct, or analysis of a study [28]. Biases are generally separated into different classes, including: selection bias (i.e., systematic error in the ascertainment of study subjects [29]); information bias (i.e., incorrect or imprecise data collection [30]); confounding; and dissemination bias. Additionally, biases may affect internal validity (i.e., the accurate association between outcome and predictor within the study population [31]) or external validity (i.e., the ability to generalize the results of a study to other populations [31]). Potential biases and limitations for this dissertation study are presented in Table 6-1. Potential biases that could affect internal validity in this study, the likelihood of each bias, the likely direction of the bias- although direction is often unpredictable-, and how biases were minimized are described below.

Dissemination Bias

Manuscript 1 was an in-depth review of the literature on club drug use as a risk factor for HIV acquisition among MSM. This study was a review of other studies and therefore has few biases in its own design, however there are some potential dissemination biases (i.e., bias associated with the publication and retrieval of information from other studies [30]). Dissemination biases can affect the internal validity of a meta-analysis or literature review.

The most probable bias is publication bias (i.e., studies that demonstrate an association between two factors are more likely to be published than those that demonstrate a lack of association [29;30;32;33]). When reviewing literature, publication bias is very difficult to avoid. Additionally, in studies that examined many risk factors for HIV or STI among MSM, non-significant associations between substance use and HIV, STI, or UAI may not be highlighted in the keywords, title, or abstract and therefore these studies may be difficult to find by using search engines and reviewing abstracts. Another potential bias introduced is language bias [30]. We only reviewed studies that were published in English, which could result in missing information from studies published in other languages [34]. However, most abstracts for articles that are published in other languages are also included in English. All abstracts written in English were reviewed. A final potential bias is citation bias (i.e., manuscripts that are more commonly cited are more easily found [30]). To minimize these biases, an exhaustive search of the literature was completed. All appropriate references from studies that were retrieved from the literature search were examined. Additionally, conference abstracts were searched electronically, and search engines were reviewed to make sure that they included all known journals that would publish studies on substance use and HIV risk among MSM.

Non-response Bias

Manuscripts 2 and 3 share similar potential biases and limitations because the data for these studies arose from the same source. One of the more obvious limitations in these studies is that nearly 40 percent of AIEDRP participants from Los Angeles were not asked to complete the CASI due to constraints of time or space. This has resulted in a smaller sample size and an under-representation of participants who were recruited in the Los Angeles area. Additionally, such a large percent of non-respondents may introduce non-response bias (i.e., those who respond to the CASI differ from those who do not respond [30;35]). Non-response bias can affect the internal validity of a study. However, there were no statistically significant differences in those who did and did not complete the CASI in Los Angeles, and there were no significant differences demographics or sexual histories between participants from Los Angeles and San Diego (see Chapter 3: Methods, Tables 3-7, 3-8, 3-9). Additionally, those who were AIEDRP participants in Los Angeles and did not complete CASI were selected by outside limitations, not based on participant characteristics, which reduces the likelihood of non-response bias.

Had Los Angeles patients differed from San Diego patients in terms of substance use, UAI, or factors that may be associated with these, such as age [36;37], ethnicity [38-42], this may have resulted in over or under sampling on specific outcome/exposure group [28-30;43] and exclusion of Los Angeles patients may have been appropriate. For example, if non-respondents were more likely to decline the CASI because they did not want to reveal that they had used illicit substances, the odds ratio of the association between substance use and UAI would most likely be greater than the true association if they were less likely to have UAI (under selection of the unexposed with the outcome; Figure 6-1a), and closer to the null than the true

association if they were more likely to have UAI (under selection of the exposed with the outcome; Figure 6-1b) [29]. However, if respondents were more likely to decline to complete the CASI because they did not want to report their substance use, but were not more or less likely to report UAI (Figure 6-1c), this could bias the odds ratio toward the null. Similar patterns in bias on the odds ratio could also be observed if non-response was based on not wanting to report UAI (Table 6-1 d-f). In this study, overall non-response occurred in only 15 percent of respondents. Even if selection bias did occur, the effect on the odds ratio would be minimal (i.e., if the true odds ratio were 2.0, the point estimate that was biased to the null would be 1.6, and away from the null would be approximately 2.1). In future analyses from these data, exclusion of Los Angeles patients will be considered to avoid any unforeseen bias from differences that could not be detected. Efforts to improve data collection from the Los Angeles site have begun, including a web-based CASI that can be completed by participants at home or at another interview location.

Reporting Bias

As with all studies of self-reported sexual and illicit substance using behavior there is the danger of reporting bias (e.g., participants are likely to provide answers that they believe the interviewer wants to hear, or that are more similar to the perceived social norm [30]). As with response bias, reporting bias primarily affects the internal validity of a study. The expected bias in this case would be to under-report substance use or UAI or both. However, if participants were concerned with “helping” find an association they may over-report substance use and/or UAI. In any of these scenarios misclassification would occur [29]. If people who were less likely to report UAI were also less likely to report substance use, this would create a serious problem with differential

misclassification and possibly create a spurious association between substance use and UAI that could bias the odds ratio further away from the null (Figure 6-2a). Additionally, if participants were concerned about reporting on UAI and substance use, they may be less likely to report both together. For example, some of those who used substances immediately prior to UAI may indicate that they did not use substances, while others may report that they did not have UAI (Figure 6-2b). This type of differential misclassification would most likely bias the odds ratio toward the null. Participants may also try to assist in finding an association between the exposure and the outcome by responding to a questionnaire in the way they believe the interviewer would like them to respond. If the participants were aware of the hypotheses this may result in biasing the odds ratio away from the null (Figure 6-2c). Additionally, non-differential misclassification could occur if participants in exposure category were misclassified independent of UAI [29] (or vice-versa), which could bias the odds ratio toward the null (Figure 6-3a).

It is very unlikely that the previously described differential or non-differential misclassifications have occurred in these data for a number of reasons. Firstly, most participants (84%) reported UAI with at least one of their last three partners for studies 2 and 3 (see Appendix C Tables C-5 and C-6). Secondly, 49 percent of people who did not report UAI reported substance use with at least one of their last three partners. Thirdly, these studies used the most currently available method to reduce reporting bias of sensitive information, CASI. Fourthly, all participants were assigned a study number so that no CASI data were linked to their names which should have allayed fears about disclosing sensitive information. Fifthly, participants were not told of the hypotheses that were being tested in this study. Participants were told that they were completing a questionnaire on HIV risk factors, therefore they would regard all questions as potential

exposures. Sixthly, the questions regarding substance use prior to sexual activity and types of sexual activity that occurred were separated by a number of other questions within the questionnaire, which may help to mask the hypotheses that were being tested. Seventhly, participants were given the option to decline to answer any questions that they did not feel comfortable responding to. No participants declined questions pertaining to sexual activities or substance use with the last three partners. Finally, all participants had the option to decline to answer questions that they were not comfortable answering, allowing those who did not wish to provide information the option of not providing it, instead of providing incorrect information.

Recall Bias

Recall bias shares some similarities with reporting bias in that it is due to participants reporting incorrect information and it can affect internal validity. Recall bias is most often attributed to case-control studies because it is the problem of cases having better recall of their past exposures than controls [29;30;35]. However, if the participant knows if s/he has the outcome, recall bias could occur in a cross-sectional study as well. If those who had UAI were more likely to recall that they had used substances prior to sexual activity and those who did not have UAI were less likely to recall substance use, it could result in a spurious association that was greater than the true odds ratio (Figure 6-2d). However, it is unlikely that recall bias occurred for a number of reasons. First, participants all had another disease, HIV, and did not know that UAI would be used as an outcome. Second, UAI is not a disease outcome, all of the participants acquired HIV through sexual activity and therefore the majority had UAI prior to HIV infection. Third, the duration of time between sexual contact with the last

three partners and interview was not so long that recall would be difficult (median of 7, 30, and 42 days for the last, second to last, third to last partner respectively).

Interviewer and Respondent Biases

Other information biases that may affect observational studies include interviewer and respondent biases. Interviewer bias occurs when the interviewer knows what the hypothesis is and unknowingly "leads" participants to a certain response [30]. Interviewer bias would most likely result in differential misclassification, causing a spurious association between the outcome and predictor that was biased away from the null. Interviewer bias is very unlikely in this study for two reasons. First, the interviewer did not reveal study hypotheses to the participants. Second, the interview was conducted using CASI and the interviewer was not present while the participants were answering the questions.

On the other hand, respondent bias is often the result of a predictor or outcome that is difficult for the respondent to define or interpret (e.g., a migraine headache) [29]. Respondent bias could result in both differential and non-differential misclassification. If the exposure was difficult to define, and participants were misclassified in equal proportions, independent of UAI status, then non-differential misclassification would occur (Figure 6-3a). Similarly, if some of the UAI cases were misclassified as no UAI, but an equal percent of exposed and unexposed were misclassified the result would be non-differential misclassification (Figure 6-3b). Non-differential misclassification, by definition usually biases the measure of association toward the null [29]. However, if uneven proportions are transferred across cells, it may result in differential misclassification (Figures 6-4a and 6-4b) and could bias the results in either direction, depending on which cell had greater misclassification of subjects. Similarly, if both the

exposure and the outcome are susceptible to respondent bias, differential misclassification would likely result and could result in biasing the measure of association in either direction (Figures 6-2e).

The most efficient means of preventing respondent bias is to establish a clear definition of the exposure and the outcome. In this study respondent bias was minimized in a number of ways. The questions pertaining to substance use requested participants to select all substances used just prior to or during sexual activity with a particular partner. The language and question was not difficult for participants to understand. Multiple street names for each substance were listed as well as the common name and a category labeled “other” was available. Participants had to either select a substance or select the ”no drugs used” category, therefore not having differential effort for response between substance and no substance users (see Appendix A for substance use questions). It would be unlikely for participants to misinterpret the substance use questions and therefore misclassification due to respondent bias would be unlikely. For anal intercourse a clear definition was provided to the participants before inquiring about sexual activity in order to prevent misinterpretation. Participants were asked to report if they had anal intercourse with or without using condoms, and participants could select both. As with substance use, participants had to select “decline to answer” or at least one other sexual behavior category to move to the next question, therefore removing any differential effort. Due to clear definitions it is also unlikely that misclassification by UAI occurred due to respondent bias. However, the specific practice of “dipping” (i.e., UAI for initial intercourse and condom use prior to ejaculation in one episode [44]) was not assessed. Therefore, it may be possible that a few participants had UAI for a small portion of a sexual episode with their partner.

Temporal Ambiguity

Another type of information bias, temporal ambiguity bias, occurs due to an inability to establish that the exposure preceded the outcome. Temporal ambiguity bias most often affects cross-sectional studies [30]. In cross-sectional studies it is important to design data collection measures that help clarify that the exposure occurred before the outcome. In this study, temporal ambiguity bias is unlikely because the specific questions about substance use referred to use prior to or during sexual intercourse (see Appendix A for questionnaire). Questions were written in this way to specify temporal order, therefore temporal ambiguity bias is unlikely in this study.

Confounding

Confounding can be viewed as a bias, as it results in an incorrect estimate of the association between the predictor and outcome due to an error in analysis. In all observational studies, confounding by one or more factors should be considered. In this study confounding was controlled for in a number of ways. The literature was reviewed in order to find factors that may be associated with both the outcome and the predictors of interest. Information about these factors was collected and confounding was tested using statistical analyses as described in Chapter 3: Methods. Use of multivariate models and conditional logistic regression also helped to minimize the potential for confounding. Multivariate generalized linear models provide the ability to control for many factors at once, even when strata become very sparse. Additionally, conditional logistic regression, which was used in manuscript 2, can control for individual level factors that may act as confounders but may not have been measured during data collection. It is therefore very unlikely that the analyses in this study were confounded

by additional factors. Overall, most biases that effect internal validity were unlikely due to selection of participants, study design, and data collection.

D. External Validity

The previous biases and limitations addressed issues associated with internal validity, or the validity of the association detected within the study population [31]. However, it is also important to understand the external validity of a study, or the ability to generalize information gained from the study to other populations [31]. In this section generalizability, volunteer bias, and healthcare access bias, for external validity, will be discussed.

Although collecting data on individuals who were recently infected with HIV has many advantages in addressing correlates of risk of HIV acquisition and transmission, there are also several disadvantages. Newly infected individuals are more difficult to identify, leading to smaller numbers of participants and slower data collection, which can be costly and could reduce generalizability of the sample to the MSM population. Additionally, those who are reached more easily by study outreach methods may not be fully representative of MSM who are becoming infected with HIV. The sample of all CASI participants that were collected by the time data analysis was conducted for the third manuscript, including heterosexual men and women, were compared to surveillance data on HIV cases from the United States, California, and San Diego County (Table 6-2). While the CASI sample differed from the National HIV cases with respect to gender, risk category, and ethnicity, they were somewhat similar to HIV cases in California and very similar to HIV cases in San Diego with regard to demographics and HIV risk characteristics. There are a number of reasons why a sample drawn from HIV cases in California may differ from the rest of the United States.

Most importantly, the most recent HIV/AIDS surveillance report for the United States does not include information on HIV cases from California because confidential HIV case reporting in California was established recently (July 2002) [45]. Additionally, different geographic regions of the United States have different population sizes with respect to demographics and risk behaviors (e.g., the populations of Southern, 53.6%, and Eastern, 18.0%, regions of the United States have greater African American representation than the West, 9.6% [46]).

In comparison to California and San Diego County, the sample of HIV cases that were included in AIEDRP most approximate San Diego with a few differences. AIEDRP cases are clearly over represented by MSM (87.7%) and men (98.6%) in general when compared to California (61.8% MSM and 85.3% men) and San Diego (71.8% MSM and 90% men) HIV cases (Table 6-2). This is expected as those who are referred to AIEDRP are more often recruited from gay neighborhoods. Additionally, this does not jeopardize generalizability as this was a study of MSM. Among MSM, however, MSM IDUs were represented in the AIEDRP CASI sample (6.8%) in the same proportion as in San Diego (6.8%) and a similar proportion as in California (5.9%). With respect to age, a slightly larger proportion of CASI AIEDRP participants were in 40-49 (24.5%) age categories than San Diego HIV cases (17.3), indicating that the CASI sample may be slightly older than San Diego HIV cases. However, the CASI HIV sample appears to be slightly younger than California HIV cases (i.e., a slightly larger proportion of CASI participants, 29.6%, were in the 20-29 age group when compared to California HIV cases, 26.1%). This is a good indication that the CASI AIEDRP participants are representative of the population that they were drawn from by age. Most participants came from San Diego, which has slightly younger HIV cases than California, however, some of the sample came from Los Angeles, representing another area of California

that may increase the age of participants. When Los Angeles and San Diego participants were compared by age (see Chapter 3, Methods, Tables 3-8 and 3-9), Los Angeles participants were on average older than San Diego participants, although the difference was not statistically significant.

With regard to ethnicity (Table 6-2), there were large proportional differences in HIV cases between the United States, California, and San Diego. Most notably, in both California and San Diego there were smaller proportions of Black or African American cases (19.4% and 13.2% respectively) and greater proportions of Caucasian or White (48.5% and 61.9% respectively) and Hispanic (25.8% and 21.8% respectively) cases than in the United States as a whole (Black/African American: 49%, Caucasian/White: 34.2%, Hispanic: 15%). The CASI AIEDRP sample approximated that of San Diego by ethnicity, except that there was an under-representation of Black/African American participants (5.5%) and a slight over representation of Caucasian/White (67.7), and Native American (1.4%) participants in the CASI sample when compared to San Diego (Table 6-2). Limited data on MSM HIV cases were available for ethnicity, but not other demographics, from the United States and San Diego, but not California (Table 6-3). Similar trends in CASI sample representation were observed among only MSM HIV cases as with all HIV cases. Ethnic proportions were different between the United States and San Diego, with greater proportions of African Americans and smaller proportions of every other ethnic group among United States HIV cases when compared to San Diego HIV cases. In comparing the AIEDRP CASI sample of MSM and cumulative San Diego MSM cases since 2002, there were similar proportions of Asian/Pacific Islanders (San Diego: 2.1% and CASI: 2.4%) and Hispanics (San Diego: 21.1% and CASI: 20.6%). However, African American (2.9% in CASI and 9.6% in San Diego) MSM were under represented in the CASI sample and Caucasian (70.2% in

CAS and 66.5% in San Diego), Native American (1.4% in CASI and 0.7% in San Diego), and other ethnicities (2.4% in CASI and none in San Diego) were over represented in the CASI sample. Under representation of African Americans in a sample of recently HIV infected MSM is not surprising. Data from the CDC indicate that African Americans and Hispanics are often diagnosed later in infection than people of Caucasian ethnicity [47]; therefore the CASI sample may be less representative by ethnicity of HIV cases in Southern California, but more representative of MSM who receive early HIV diagnoses. Education and recruitment efforts that target raising awareness for regular testing and self-identification of acute HIV infection symptoms among ethnic minorities, particularly African Americans, should be implemented.

In addition to insuring generalizability of a sample, there are other biases that may affect external validity, the most common of which is volunteer bias. Volunteer bias may occur because those who volunteer to participate in a study may be inherently different than those who do not volunteer [30]. In any observational study, such a bias is unavoidable because ethical research conduct dictates that all research subjects must volunteer. Since referral sources do not keep track for those that they refer to AIEDRP in San Diego and Los Angeles, there is no way of determining how many referees contacted the research sites. However, we do know that of the 265 people who screened for AIEDRP and were eligible to participate in San Diego and Los Angeles, 260 (98%) became study participants, and of those 85% completed the CASI (see Chapter 3, Methods, Table 3-6). Additionally, those who did not complete the CASI did not differ from those who did by demographics (see Chapter 3, Methods, Table 3-7). Additionally, those who completed the AIEDRP CASI were similar demographically to HIV cases in San Diego and California, indicating that volunteer bias is unlikely in this sample.

The final type of bias that may affect external validity is health care access bias. Healthcare access bias is defined as a bias that occurs because cases that access healthcare, and therefore are more likely to be referred or selected for study, are not representative of all cases of a disease or outcome [30]. Usually healthcare access bias is addressed as a selection bias and an internal validity issue in a case-control study, however, in this study it applies to external validity of the study. In this study there may be some healthcare access bias with regard to the under representation of African Americans in our sample. Even though African Americans may be more likely to be diagnosed with HIV at a later stage of infection [47], they still represent people with recent HIV infection, regardless of diagnosis. Although the sample population for this dissertation study may be fairly generalizable to MSM in Southern California with recent HIV infection, it is probably not as generalizable to African American MSM in Southern California with HIV infection.

Overall, the results of this study can be considered to have good external validity. Comparison of our sample to HIV cases in California and San Diego indicate that the sample population for this study was representative of MSM by most demographic characteristics. All ethnic groups except for African Americans, who may be difficult to find during early infection, were represented in similar proportions as the HIV cases identified in California and San Diego. The results of this study may not be generalizable to African American MSM with recent HIV infection and more studies are need for this population. Although external validity may be compromised for this population, it does not affect the internal validity of the study.

E. Issues in Measurement

In addition to the previously mentioned biases, there were a few questionnaire limitations that prevented measurement of all factors that may have been helpful in further understanding the associations observed in this study. When the questionnaire was first implemented there was a programming error in the question regarding sexual activity with each of the last three partners. Among the possible answers about sexual activity, the original questionnaire included “anal sex without a condom” and “anal sex using a condom”, but there was no way for the respondent to specify insertive or receptive anal intercourse. This discrepancy was noticed and changed after approximately half of the participants completed the baseline questionnaire. Data on sexual positioning during anal intercourse may have been useful in clarifying associations between substance use and UAI in both studies 2 and 3. Failure to collect data on sexual positioning is not believed to have affected the validity of the study since there is no reason to consider it as a confounder, but had these data been collected further description of UAI with respect to EDM use could have been elucidated.

F. Study Strengths

This dissertation contributes to the overall understanding of the associations between substance use and risk for HIV among MSM. The data for this dissertation have helped to generate hypotheses and direct future research. In addition, manuscripts 2 and 3 have a number of strengths including: 1) utilization of data from a unique sample of recently HIV-infected individuals studied shortly after diagnosis (and infection); 2) the availability of biologic data enabling the date of HIV infection to be estimated with good precision; 3) high participation rates among eligible subjects; 4) recruitment of participants through different sources; 5) avoiding some biases due to

cross-sectional study design; and 6) confidential data collection, using a computer assisted survey instrument (CASI). These aspects of the study are discussed more fully below.

Study Population

One of the primary strengths of manuscripts 2 and 3 was that the data were collected from MSM with recent HIV infection. The San Diego and Los Angeles AIEDRP cohorts contain a unique and rare group of people who were identified with HIV within weeks to months of infection. To date, few studies of HIV transmission risk factors have focused on the use of data from recently infected HIV positive MSM, most likely because they are difficult and expensive to identify. Collecting behavioral data on recently infected individuals can help to reduce biases associated with recall or behavior change. One problem with collecting behavior data through cross-sectional or case-control studies is lack of ability to recall information. If an individual has been recently infected with a disease, there is a higher probability that s/he will be able to recall behaviors just prior to infection.

Similarly, one of the primary biases that may be introduced from studying chronically infected patients is incidence-prevalence bias. With incidence-prevalence bias, prevalent cases may appear to have different exposures than incident cases either because of a long duration between exposure and disease assessment or because the exposure that was assessed is related to survival after disease occurrence [28]. Behaviors of HIV infected patients, especially sexual and risk taking behaviors, may change over time and may also change in response to diagnosis. Even if participants are newly diagnosed, but chronically infected with HIV, their risk behaviors for acquiring HIV may have been different at the time of infection. Additionally, data from recently

infected individuals allows for examination of sexual behaviors that either resulted in HIV acquisition or may contribute to onward transmission, as individuals who are in the early stages of infection may be more likely to transmit HIV to others (45-47).

Interviewing these patients shortly after infection and diagnosis has helped to reduce the possibility of incidence-prevalence bias. Additionally, lack of ability to recall information, not due to recall bias, but to natural limitations in memory, is minimized by selecting MSM with acute and early HIV infection.

Complete Data on Date of Diagnosis and Estimated Infection

In addition to collecting data on recently infected individuals, complete information regarding estimated date for infection and date of diagnosis was available for all participants. Knowledge of both HIV diagnosis date and estimated date of infection provide temporal structure to these cross-sectional data. If the date of diagnosis is known, reports of different behaviors with different partners can be examined by the participant's knowledge of his or her HIV status, such as in manuscript 3. This allows for inferences in changes across time even though data were collected cross-sectionally. Additionally, being able to estimate date of HIV infection allows one to investigate behaviors that occurred before, after, or around the time of infection, and to perform analyses that examine the highest risk time periods for HIV acquisition and transmission.

Identifying substance use patterns and behaviors that occurred just prior to and just after HIV acquisition are important in helping to establish or refute a causal association between substance use and HIV risk behavior. Substance use leading up to high-risk sexual behaviors prior to HIV infection may provide evidence for substance use as a causal factor in HIV acquisition. Establishing that high-risk sexual behavior

such as UAI occurs more often when illicit substances are used as compared to when they are not used just prior to sexual activity in the time period leading up to estimated date of infection, would provide further evidence of a strong causal association. Such analyses would provide evidence for temporality and strength of association in establishing a causal association [26]. For many substances there is a need for studies that examine temporal associations between substance use and HIV/STI acquisition risk among MSM (see Chapter 2, Table 2-5). On the other hand, establishing that high-risk sexual behavior is more often associated with substance use after the estimated date of infection provides more evidence for illicit substance use as a causal factor for HIV transmission to others.

Although more studies are needed to establish causal associations, the literature review (manuscript 1), suggests that some classes of substances are likely to be causally associated with HIV and STI acquisition among MSM. Results from manuscript 2 suggest that some substances, particularly methamphetamine, may be associated with onward transmission of HIV infection. On the other hand, manuscript 3 suggests that substances that affect transmission of HIV through UAI may change after HIV diagnosis.

Participation Rate

For manuscripts 2 and 3, there was good participation from eligible individuals. Between May 2002 and November 2005, 265 people (195 from San Diego and 70 from Los Angeles) were eligible for AIEDRP and 260 (98%) enrolled. Of these, 222 were asked to complete the CASI and 221 (99.5%) did. Eight participants were not asked to complete the CASI because they spoke Spanish only, three did not remain on AIEDRP long enough to complete the CASI, and there were not enough resources in Los

Angeles for 27 of the participants to complete CASI. Including all recently infected individuals who were identified by AIEDRP in San Diego and Los Angeles, even those who declined to participate in AIEDRP or were not offered CASI participation, 83 percent completed the CASI. Additionally, there were no significant demographic differences between those who did and did not complete the CASI (see Chapter 2: Methods, E Study Population).

As discussed previously in this chapter in more detail, these high participation rates are necessary to prevent non-response bias [30] and problems associated with external validity and generalizability [31]. If responders and non-responders are different, internal validity of a study could be compromised. Additionally, lack of participation and reduced likelihood to volunteer to participate in a study could result in a study sample that is not generalizable to the population from which it was recruited and therefore affect the external validity of a study. The high participation rates in this study allow for greater generalizability of study results to MSM populations in California and limit non-response bias.

Recruitment

In addition to good participation rates, AIEDRP participants were recruited from a variety of different sources. The San Diego AIEDRP site has strong ties to organizations within the gay community, physicians who diagnose and treat people with HIV, and public health resources that have the primary goal of HIV diagnosis and prevention. These ties allow for recruitment of participants from a wide range of sources that will identify a variety of infected people within the population. Recruitment of participants from multiple sites may help to prevent selection biases, such as popularity bias, and centripetal bias. In a cross-sectional study, such biases could affect external

validity. Popularity bias is of concern when one referral source, such as a testing site or hospital, that is very popular refers all the participants of a study [30]. People who choose a popular testing site or hospital may be different from those people who do not. If potential participants are referred by one physician who has a prestigious reputation, centripetal bias may occur [30], affecting external validity because those who chose a prestigious physician may be different than those who do not. For example, people with lower education may not have heard of the physician, or if they have lower income, they may not be able to afford the physician. Recruitment from different sources helps to ensure a representative sample of people who are diagnosed early in HIV infection. The more representative a sample is, the more generalizable that sample is, which will increase the external validity of a study [29;31].

Advantages to Cross-sectional Study Design

Although cross-sectional study designs suffer from disadvantages, most notably incidence-prevalence bias and temporal ambiguity [29], which were previously discussed in this chapter, they do have some advantages over other observational study designs. The two greatest advantages to cross-sectional data analysis are that data collection is relatively quick when compared to longitudinal studies and cross-sectional studies tend to be less expensive [28]. Since the data from this study come from the baseline CASI data collection of a longitudinal study, this study did not have the advantage of lower expense, however baseline data collection and analysis has been quicker than follow-up data collection.

It has been suggested that analyses of baseline data in a longitudinal study are extremely valuable because the results can be confirmed when prospective data are collected [29]. Analyses that confirm the associations between substance use and UAI

after HIV diagnosis from manuscript 3 will be conducted when the data become available. However, the longitudinal data may suffer from biases that were not incurred by a cross-sectional design. Problems inherent to longitudinal studies that were not experienced in this study include loss to follow-up or censoring and the Hawthorne effect. Although cross-sectional studies are susceptible to non-response and volunteer biases, by design loss to censoring of data cannot occur. Censoring of data can have the same effects as non-response bias. Additionally the Hawthorne effect (i.e., people who are aware that they are being observed tend to modify their behavior to more health protective choices or to increase the likelihood of a positive outcome [30]) is generally not a potential bias for cross-sectional and retrospective studies because the exposure and outcome have already occurred.

One of the criticisms of cross-sectional data analysis is that it represents a “snapshot” in time and therefore information is limited [29]. While this is true, HIV acquisition occurs at only one point in time and the same is true for HIV diagnosis. The complete data on estimated date of infection and date of diagnosis that was described previously in the chapter, have allowed for greater utilization of our cross-sectional data through examination of behavior near, before and after these dates. Additionally, collecting data retrospectively, not just at the moment in time that the questionnaire was administered, allowed for expansion of the traditional cross-sectional study and provided some temporality to the data. In a longitudinal study of HIV acquisition, exposures surrounding the moment of infection would still have to be collected retrospectively, as participants are measured for an outcome periodically.

Use of CASI

The choice of interview technique and coding of data for this study has contributed significantly to the quality of the data. Reports of personal information, such as sexual behavior and illicit substance use, are subject to inaccuracies due to participant reluctance to share personal information. A number of studies indicate that CASI increases reporting of sexual behavior [48;49] and substance use [50;51]. Use of CASI in comparison to face to face or self-administered paper and pencil interviews, has been associated with greater proportions of participants reporting socially sensitive or stigmatized behaviors [48;49;51-54] and decreased reporting of health protective behavior, such as condom use [52;55]. For example among 671 STD clinic patients in Baltimore, participants were more likely to report sexual contact with a same sex partner, receptive anal intercourse, orogenital intercourse, and a greater number of sexual partners in the past month with CASI as compared to face to face interviews [48]. A small number of studies have also demonstrated test-retest reliability when using CASI [56], validity of reporting with CASI [57;58], and acceptability of CASI as an interview technique [59].

Among the participants of this dissertation study, similar responses to the use of CASI may have occurred. Anecdotal reports from screening and nursing staff indicate that male participants were less likely to report sexual contact with women if they self-identified as gay and sexual contact with men if they self-identified as heterosexual in face to face interviews than on CASI. However, data entry of patients' medical charts has not been completed to determine if these differences were significant. However, if face to face interviews were conducted instead of CASI and a significant number of participants were less likely to report UAI and/or substance use, misclassification would occur. If participants were less likely to report any substance use or any UAI, this may

spuriously increase the odds ratio (Figure 6-2a), because data for cells A, B, and C would all be misclassified in to cell (in a simplified unadjusted model). However, the odds ratio would be affected differently depending on how participants were misclassified (see B. Biases). Additionally, some men who reported sexual contact with both men and women by CASI, but not in interviews with their nurse, would not have been included in these analyses.

Another strength that could have increased the validity of self-report among participants was questionnaire confidentiality. All participants were provided a unique study identification number, and CASI data were collected under this number. No names were associated with the data and participants completed the CASI in a private room with no-one else present, which has also been shown to increase reporting of sensitive information [60]. Study nurses were not given access to CASI data and participants were informed of this.

Use of CASI may have also reduced the potential of missing information bias. Although all participants were given the option to decline to answer any question in the interview, none of the participants included in these analyses decline to answer questions pertaining to sexual activity or substance use with their last three partners. Although participants may feel uncomfortable declining to answer questions in a face to face interview, there is no reason to believe that participants would select an incorrect response over declining to answer when alone with a computer. There is evidence that participants were comfortable declining to answer some questions on the CASI, as a small proportion of participants did decline to answer questions about non-consensual sex (n=2, 1%), a history of group sex (n=1, 0.5%), and ever buying (n=1, 0.5%) or selling (n=1, 0.5%) sex. Overall, considering the response rate, the lack of missing variables, the anecdotal differences between reports to study nurses and reports on

CASI, and consistency with previous CASI studies, data on self-reported sexual behavior in this study is likely to be accurate and is more valid than data collected using another type of interview design (i.e., face to face, paper and pencil).

G. Recommendations and Future Directions

The three studies that comprise this dissertation suggest the need for future studies of substance use and HIV/STI risk among MSM. Some of these recommendations will be used to direct future analyses of the CASI data that are still being collected on the San Diego AIEDRP cohort. Future recommendations for other studies or other cohorts were recommended in each manuscript and are summarized below. Additionally, future directions for the study of substance use and risk for HIV acquisition and transmission among the San Diego AIEDRP cohort are described below and include: implementation of case-control study design to examine associations between illicit substance use and EDM misuse and acquisition of HIV; longitudinal analyses that examine association between substance use and UAI months or years after HIV diagnosis and network modeling that examines substance use, HIV status, and attendance at social and sexual venues.

Recommendations for Future Studies

Each manuscript in this dissertation built upon one another and provided recommendations for future research needs. In manuscript 1, the following were suggested for future research to help elucidate the association between substance use and UAI; more studies are needed that: 1) examine different drugs individually, rather than grouping them as ‘club’ drugs; 2) are prospective and include adequate control of confounders; 3) address associations between substance use and unprotected sexual

activity using event-level and case-crossover methodologies; 4) examine dose-response relationships between drug use and HIV/STI; 5) describe patterns of substance use, such as polydrug use and EDM misuse; and 6) include analyses, where appropriate, that examine substance use in the context of partner type, partnership dynamics, meeting and sexual location, and knowledge of HIV status.

Utilizing recommendations from manuscript 1, manuscript 2 examined associations between use of individual substances and UAI using within-subjects analyses and took into account partnership type as a modifying factor. The results of manuscript 2 suggest the need to 1) study substance use in the context of partnership dynamics; 2) include sexual positioning (i.e., receptive or insertive) in studies of substance use and UAI; and 3) conduct more studies of EDM use as a risk factor for UAI and HIV/STI acquisition among MSM using case-control or longitudinal study designs.

Utilizing recommendations in manuscript 1, manuscript 3 expanded on the results of manuscript 2 by examining change in patterns of substance use and UAI before and after HIV diagnosis. Future research needs that were identified in this manuscript included studies 1) that examine partnership and situational factors associated with substance use and UAI; 2) that examine substances use behaviors before and after HIV diagnosis in larger samples; 3) that help to elucidate risks associated with patterns of substance use, such as polydrug use; and 4) that examine modifiers and motivations for substance use and UAI in the context of HIV treatment optimism and social factors.

The importance of each of these recommendations in understanding how substance could be a risk factor for HIV acquisition and transmission are described

below. Additionally, the value of qualitative and network modeling studies in substance use and HIV/STI research are also discussed.

Examination of Individual Substances Using Multivariate Analyses

In manuscript 1 a number of articles were excluded because club drugs were combined or analyses were not used to examine multivariate associations. Combining substances may prevent identifying differential associations between specific substances and UAI by a third factor, as was observed in manuscript 3. Had all substances been combined in analyses for manuscript 3, the change in association between UAI and other substances or methamphetamine after HIV diagnosis would have been missed. Combining substances also prevents understanding of which of the substances are associated with UAI, which may affect internal validity. Similarly, failing to control for confounding in statistical analyses can also result in lack of internal validity, as previously described in this chapter.

Event-Level and Within-Subjects Analyses

Manuscript 1 highlighted Leigh and Stall's methodological review of studies that examined substance use and high-risk sexual behavior [61]. In their manuscript, Leigh and Stall argue that most studies examine global and situational associations, however event-level analyses may provide a better understanding of the causal association between risky sexual activity and substance use because they provide temporality and direct association by examining substance exposure prior to each sexual event. Within-subjects analyses are also encouraged as they can control for confounding that may not have been measured by data collection methods, through use of the subject as his/her own control. Few studies of UAI and substance use among MSM have been published

that examine within-subjects or event level analyses. Such studies were recommended to help minimize temporal bias and confounding, and to help support or refute a causal association between substance use and UAI.

In manuscript 2, within-subjects analyses among MSM who reported variation in UAI (with some, but not all partners) revealed similar associations to those seen those seen in the overall sample (Chapter 4). This suggests that individual traits that remain stable over the time period between partners, such as personality traits, are not confounding the association between substance use and UAI. Such assumptions can only be made from studies that include within-subjects analyses. It is also suggested that comparisons between global, situational, event-level, and within-subjects analyses can provide additional understanding of associations. For example in Manuscript 2 (Chapter 4), the similar associations observed in the within-subjects and overall sample analyses helped to validate one another.

Dose-Response

Similarly, few studies were identified that examined a dose-response relationship between substance use and UAI. Just as it is important to establish evidence of a temporal association or consistency of association between studies, establishing a dose-response relationship can help provide evidence for a causal association [26]. It is therefore recommended that future studies examine duration of substance use and proportion of UAI episodes that were associated with substance use prior to HIV or STI acquisition.

In manuscript 2, a ‘pseudo’ dose-response relationship was observed between proportion of last three partners that were UAI partners (none, some, or all) and proportion of participants reporting substance use with any of the last three partners in

each category of UAI. A significant trend of increasing proportion of substances users was observed from UAI category of ‘none’ to UAI category of ‘all’, suggesting that the probability of using substances prior to sexual activity increase with the probability of having UAI. Although this is a ‘pseudo’ dose-response, because it only takes into account the last three partners, it does suggest that dose-response associations may exist for some recreational substances. Future studies that demonstrate dose-response would be beneficial in establishing a causal association between substance use and UAI.

Temporality

In addition to examining effects of specific substances on UAI, temporality, and dose-response, manuscript 2 also called for studies that examine patterns of substance use, such as polydrug (i.e., using multiple classes of substances) and misuse of medically controlled substances, such as EDMs. Previous studies have noted that many MSM report polydrug use [62-64], and this pattern was also observed in our cohort in manuscript 3. In previous studies, polydrug users were who were MSM reported higher rates of UAI [65;66] as compared to non-users or single substance users; more sexual partners [67]; a greater likelihood of STI [63]; HIV-positive serostatus [63;67]; and more UAI among HIV positive MSM with sero-discordant partners [68]. Additionally, in manuscript 3, polydrug use of methamphetamine and other recreational substances was associated with increased risk of UAI both before and after HIV diagnosis (Chapter 5). In combination, these studies suggest the need to elucidate a better understanding of the reasons for increased risk of polydrug users over single substance users. Additionally, potential misuse of EDMs among MSM has raised concern that EDM abuse could increase the risk for HIV transmission [13;15;69;70]. In manuscript 2, EDM

use was associated with increased risk of UAI, but only when used with a main partner (Chapter 4). Further understanding of patterns of EDM use and dynamics of use within given situations would help to elucidate the importance of EDM misuse as a risk for HIV acquisition and transmission.

Substances that were Under-studied

More studies in general are needed for MDM, GHB, ketamine, LSD, EDM use, and Flunitrazepam, as few studies, if any, examined these substances as risks for UAI, HIV or STI among MSM. It is recommended that longitudinal studies are designed around methamphetamine questions and that other substances be included. Although there are a number of good quality studies that suggest a direct causal relationship between methamphetamine and HIV risk that warrant cost of a longitudinal design, there is little evidence for a causal relationship between MDMA, GHB, ketamine, EDM, LSD, or flunitrazepam and UAI. Use of less expensive pilot studies, such as cross-sectional or case-control, is recommended if only asking about one of the less studied substances to prevent wasting valuable health resources and promising results from hypothesis generating studies, such as cross-sectional studies, should lead to more expensive studies, such as case-control and finally longitudinal. For example, a number of cross-sectional studies suggest an association between EDM use and UAI [13;15;69-71], however these studies are not sufficient to determine if EDM use is a risk factor for HIV/STI acquisition among MSM. A case-control study that includes recently infected cases and high-risk controls may be useful in helping to determine if a causal association is likely. Furthermore, there is a need to examine amount and duration of use of EDM, as well as context of use with regard to other substances and partnership dynamics.

Partnership Dynamics

It is recommended that associations between substance use and HIV/STI risk should be examined in the context of partner type, location of sexual encounter and dynamics of the partnership in which sexual contact occurs. Sexual encounters are part of a complex dynamic between individuals and are likely to contain more factors than just substance use; for example, reasons for sexual attraction, partner choice, level of emotional connection and trust between partners, and perceived HIV serostatus of self and partner. Such dynamics may dictate choice of sexual activity and use of substances, and should therefore be taken into account in order to prevent confounding and to establish a better understanding of how substance use may modify sexual activity choice.

In manuscripts 2 (Chapter 4) and 3 (Chapter 5), UAI was associated with sexual contact with a main partner independent from substance use. Additionally in manuscript 2, methamphetamine was associated with increased risk of UAI in general, but not with the main partner. In comparison, EDM use was associated with UAI when sexual activity occurred with a main partner, but not with other partner types or in the overall sample analyses. This indicates modification of substance effect on UAI based on partner type. Inclusion of data on partnership dynamics may assist in identifying factors that modify the association between substance use and UAI, which can clarify causal associations. Additionally, understanding effect modification by partner type may help in developing interventions that deal with HIV prevention differently based on the type of partners an individual reports.

Sexual Positioning

In both manuscripts 2 and 3, examination of associations between substance use and type of UAI (receptive versus insertive) was not possible due to limitations in the questionnaire that were previously discussed in this chapter. However, inclusion of sexual positioning and beliefs about sexual positioning and HIV risk is recommended in future studies of substance use and UAI. Working with the theoretical framework from manuscript 1 (Chapter 2), for some substances, plausibility of a causal association may be more likely to be associated with either insertive or receptive UAI, but not both. For example, EDMs are designed to increase a man's ability to obtain and sustain an erection. It is therefore more plausible that EDM use would increase the risk of HIV acquisition for the insertive partner than the receptive partner. Associations between insertive UAI and EDM use as a risk factor for HIV acquisition and transmission may have more biological credibility than receptive UAI and EDM use.

Additionally, beliefs about sexual positioning and risk for HIV acquisition or transmission may play a role in choice of sexual activity and change in sexual behavior after HIV diagnosis. For example, among MSM who believe that insertive UAI is associated with minimal risk for HIV acquisition, may switch from practicing insertive UAI to only practicing receptive UAI after HIV diagnosis. Although UAI may still be practiced, the belief may be that his partners are not at risk of acquiring HIV. Understanding such beliefs in choice of sexual activity may be important in targeting effective interventions or using interventions to modify such beliefs.

Substance Use Before and After HIV Diagnosis

Manuscript 3 demonstrated the need for more studies that examine type of substance used and risk for UAI before and after HIV diagnosis, as it appears that

associations between type of substance used and UAI could change based on knowledge of HIV status. In particular, longitudinal studies that examine longer durations of time before and after HIV diagnosis are needed to establish that there is a constant trend in both the association between methamphetamine and UAI before HIV diagnosis and that other substances continue to be associated with UAI after diagnosis. Additionally, examination of longitudinal data pertaining to UAI and substance use after HIV diagnosis would help to determine if associations persist. Understanding such associations are important for designing HIV interventions. For example, if the results in manuscript 3 are also observed in longitudinal studies, then an effective intervention may target methamphetamine prevention and cessation among MSM with perceived HIV-negative or unknown HIV status, and target prevention and cessation of all illicit substances among MSM who are HIV-positive.

Additionally, larger studies are recommended that examine substance use and UAI before and after HIV diagnosis. Large sample sizes are important for such studies to allow for enough power to detect interactions. In manuscript 3, marginally significant interaction ($0.1 > p > 0.05$) were observed for the interactions that examined changes in associations between methamphetamine and UAI or other substances and UAI, however the odds ratios were very different (Chapter 5). It has been suggested that this may be a result of low power to detect interactions, as the power may be an order of magnitude less for interaction terms than for predictor variables [72-74]. Additionally, studies with larger sample sizes may have the ability to examine all types of substance use, not only methamphetamine as compared to other substances, which may help elucidate which substances were associated with greatest risk for UAI in the other category.

Qualitative and Network Modeling Studies

In addition to traditional observational studies, use of qualitative data and modeling the structure of sexual and substance use networks may be helpful in understanding how substance use can increase the risk of HIV transmission and acquisition among MSM and what interventions may be most effective. Qualitative studies can assist researchers in focusing quantitative analyses and provide evidence for hypotheses. Such studies should focus on biological and cognitive changes that substance users report experiencing while under the influence and how these changes may contribute to increased risky behavior. Additionally, it would be helpful to explore settings and partner dynamics in situations where substance use and sexual activity coincide. Exploring triggers for substance use and risky behavior may also help to focus intervention studies. Additionally, more studies that examine factors that modify and motivate HIV-negative and HIV-positive MSM to use substances and practice UAI may help to support or refute causal associations between substance use and UAI and to develop more effective prevention interventions that focus on substance use prevention and cessation among MSM.

Modeling sexual, social, and substance use networks can provide a better understanding of how use of a particular substance brings people together to increase HIV transmission risk. Modeling studies may be helpful in determining the specific groups of individuals or regions to target for the most efficient and effective delivery of interventions.

Future Directions for the San Diego AIEDRP CASI Study

Drawing from the recommendations provided in this dissertation, future analyses of AIEDRP data have been planned. These analyses include case-control studies using

additional data that were collected on HIV negative controls, network modeling, and examination of longitudinal data.

Data collection on HIV negative controls that were recruited from failed AIEDRP screens; San Diego County STD clinics; the Gay, Lesbian, and Bisexual Center; and the Gay Men's Health Clinic is complete and a number of case-control studies have been planned. Planned future studies include case-control studies that further examine risk factors for HIV acquisition including EDM use, polydrug use, and use of other substances that are commonly reported by this cohort (e.g., methamphetamine, GHB, marijuana, and volatile nitrates). Of particular interest, is a case-control study that will examine duration and frequency of EDM use as a risk factor for HIV acquisition. Reasons for EDM use, EDM use behaviors, and how EDMs are obtained will also be examined.

Additionally, attempts will be made to model the network structures of infected and non-infected individuals and substance using and non-using individuals. The results of this study may help to determine the amount of overlap in locations of sexual recruitment of HIV-negative and HIV-positive MSM who use substances, thus allowing for indirect estimation of HIV risk among HIV-negative substance users. Additionally, such information may be useful in determining the high-risk groups of HIV-positive and negative MSM to target for substance use prevention studies.

Attempts will be made to examine associations between substance use and UAI using data from follow-up interviews on AIEDRP CASI participants. These analyses will help to determine if the lack of associations observed between UAI and methamphetamine use and the positive association observed between other substances and UAI in manuscript 3 stay constant over a longer duration of time. Such

information is useful in determining what types of substance use to target for UAI prevention after HIV diagnosis among MSM.

H. Conclusions

Well into the third decade of the recognized pandemic, HIV transmission continues unabated worldwide. Currently, identification of infection, social and behavioral modification, and, in some instances, anti-retroviral therapy (ART) are the only options for prevention. Observational studies inherently have more methodological challenges than experimental studies, however the nature of epidemiological research dictates that most ethical research be conducted in the form of observational studies. Therefore, high quality observational studies that are designed to minimize threats to internal and external validity and provide support for or refute potential causal associations between potential risk factors and HIV acquisition and transmission should be conducted. Identifying risk factors associated with acquisition and transmission of HIV is a vital prerequisite for developing appropriate interventions.

This dissertation has focused on substance use as a risk factor for HIV acquisition and transmission among MSM. A review of the literature was conducted and recommendations for future studies that would assist in establishing or refuting causal associations between substance use and UAI were provided. Additionally analyses, which have been included in two manuscripts, examining UAI in recently HIV-infected MSM demonstrated that the use of specific substances in specific contexts is associated with UAI. Within each manuscript recommendation for future studies that may assist in further understanding the associations between UAI and substance use are addressed. These recommendations are further summarized and their importance

in understanding causal associations or creating interventions are explained in the discussion.

The overall findings of this dissertation study suggest that methamphetamine, and possibly other substances increase the risk of UAI among MSM. Associations between substance use and UAI risk are modified by the type of partner with which sexual activity occurs and knowledge of one's own HIV status. Further studies are needed to determine if causal associations exist between specific substances and UAI, however interventions that target substance use may have the potential to limit the ongoing HIV epidemic among MSM.

Table 6-1: A Priori Sample Size and Power Calculations for Logistic Regression (including prevalence of STI, prevalence of reporting sildenafil use, a power of 80%, an α-level of 0.05 and testing a two side hypothesis).

UAI Prevalence	Substance Use Prevalence	Odds Ratio 2.0		3.0		4.0		5.0	
		UAI	No UAI	UAI	No UAI	UAI	No UAI	UAI	No UAI
30		207	476	73	167	42	96	30	68
40	10	235	335	82	122	47	71	33	49
50		277	277	95	95	55	55	38	38
60		331	323	114	80	65	46	46	32
30		152	349	55	126	33	75	24	54
40	15	173	206	62	93	37	55	27	40
50		204	204	73	73	43	43	31	31
60		245	172	87	61	52	36	37	26
30		126	288	47	107	29	65	21	48
40	20	144	215	53	80	32	48	24	35
50		170	170	63	63	38	38	28	28
60		162	113	75	53	46	32	33	24
30		111	255	43	97	26	60	20	45
40	25	127	191	49	73	30	45	22	33
50		151	151	58	58	36	36	26	26
60		144	101	69	49	43	30	32	22
30		103	238	40	92	25	58	19	43
40	30	118	177	46	69	29	43	22	32
50		141	141	55	55	35	35	26	26
60		170	119	66	47	42	29	31	22
30		98	224	39	89	25	57	19	43
40	35	113	169	45	67	29	43	22	33
50		135	135	54	54	34	34	26	26
60		163	114	65	46	42	29	32	22
30		96	219	39	89	25	57	19	44
40	40	111	166	45	67	29	44	22	33
50		132	132	54	54	35	35	27	27
60		161	113	66	46	43	30	33	23
30		96	219	40	90	26	59	20	46
40	45	111	166	46	69	30	45	23	35
50		133	133	55	55	36	36	28	28
60		162	113	67	47	44	31	34	24
30		97	223	41	94	27	62	21	48
40	50	113	170	48	71	32	47	25	37
50		136	136	58	58	38	38	30	30
60		166	116	70	49	47	33	37	26

* Sample sizes generated using the Daysmith [75] program from StatLib (http://lib.stat.cmu.edu).

Table 6-2: Prevalence of substance use or UAI among the last three partners for manuscripts 2 and 3

	% prevalence (n)
Manuscript 2	**n = 572**
Unprotected Anal Intercourse	54.9 (314)
Methamphetamine	23.6 (135)
Volatile Nitrites	19.4 (111)
Gamma Hydroxy-butyrate	8.2 (47)
Marijuana	13.1 (75)
Erectile Dysfunction Medication	14.2 (81)
Manuscript 3	**n = 603**
Unprotected Anal Intercourse	55.4 (334)
Methamphetamine only	5.5 (33)
Substances Other than Methamphetamine	20.4 (123)
Methamphetamine and Other Substances	18.1 (109)

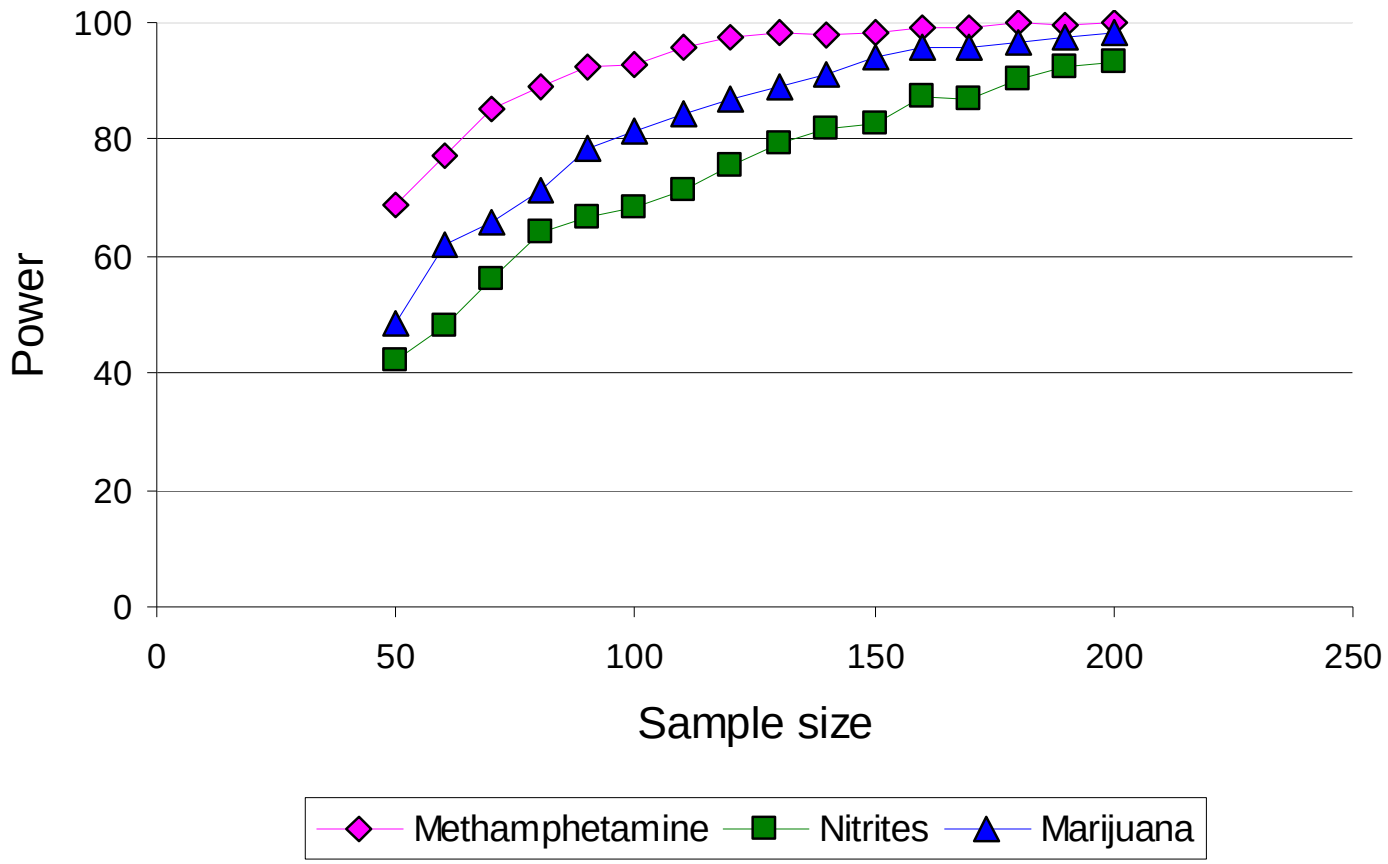


Figure 6-1: Post-Hoc Power for Univariate Associations between UAI and Substance Use in Manuscript 2

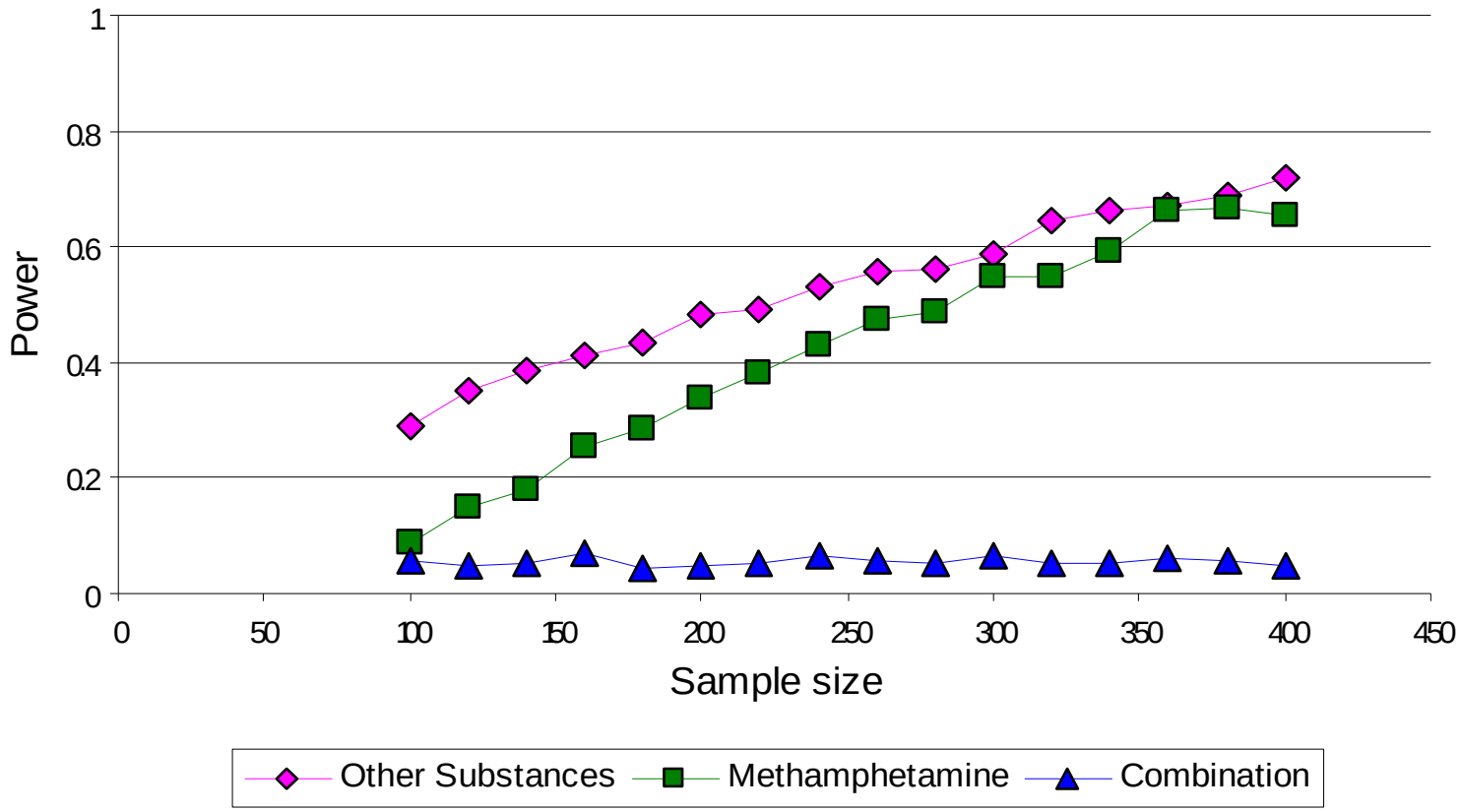


Figure 6-2: Post-Hoc Power for Interactions between Substance Use and Timing of Sexual Activity in Manuscript 3

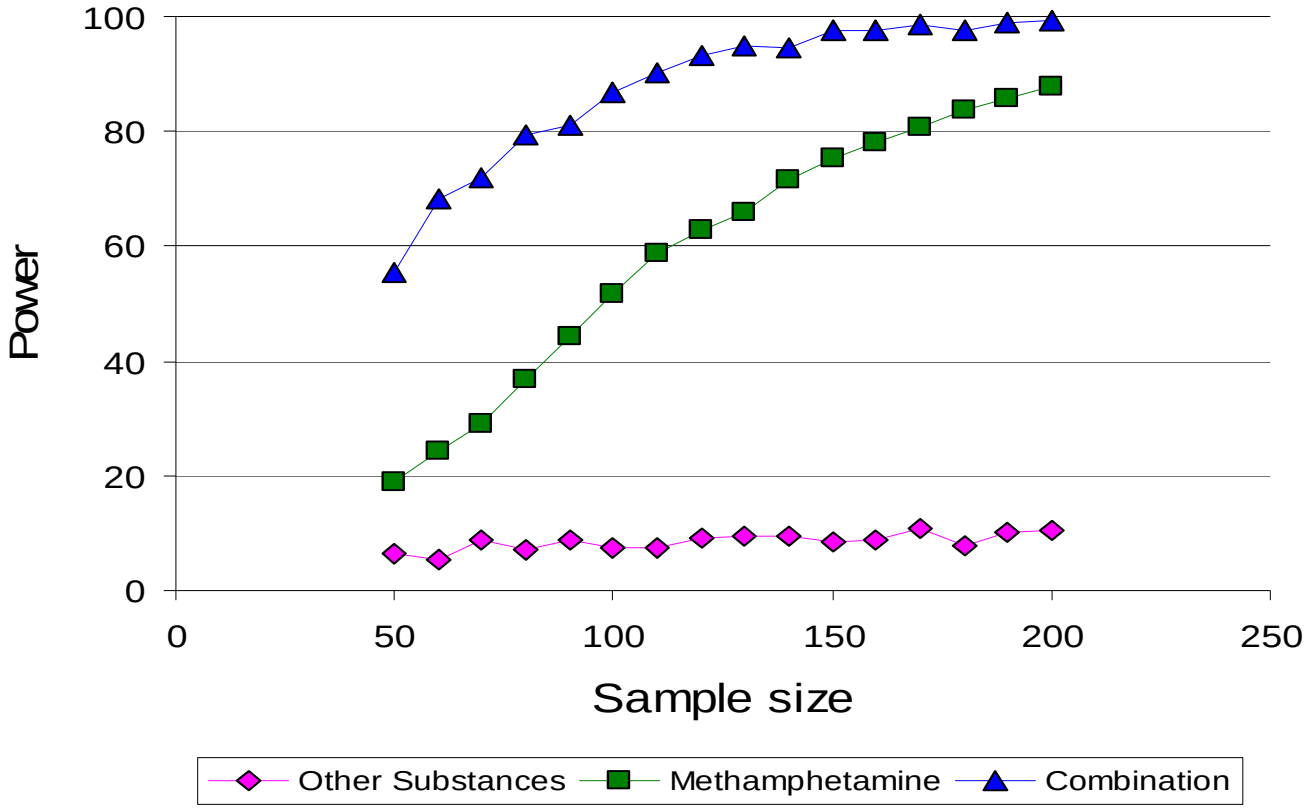


Figure 6-3: Post-Hoc Power for Substance Use and UAI before Diagnosis in Manuscript 3

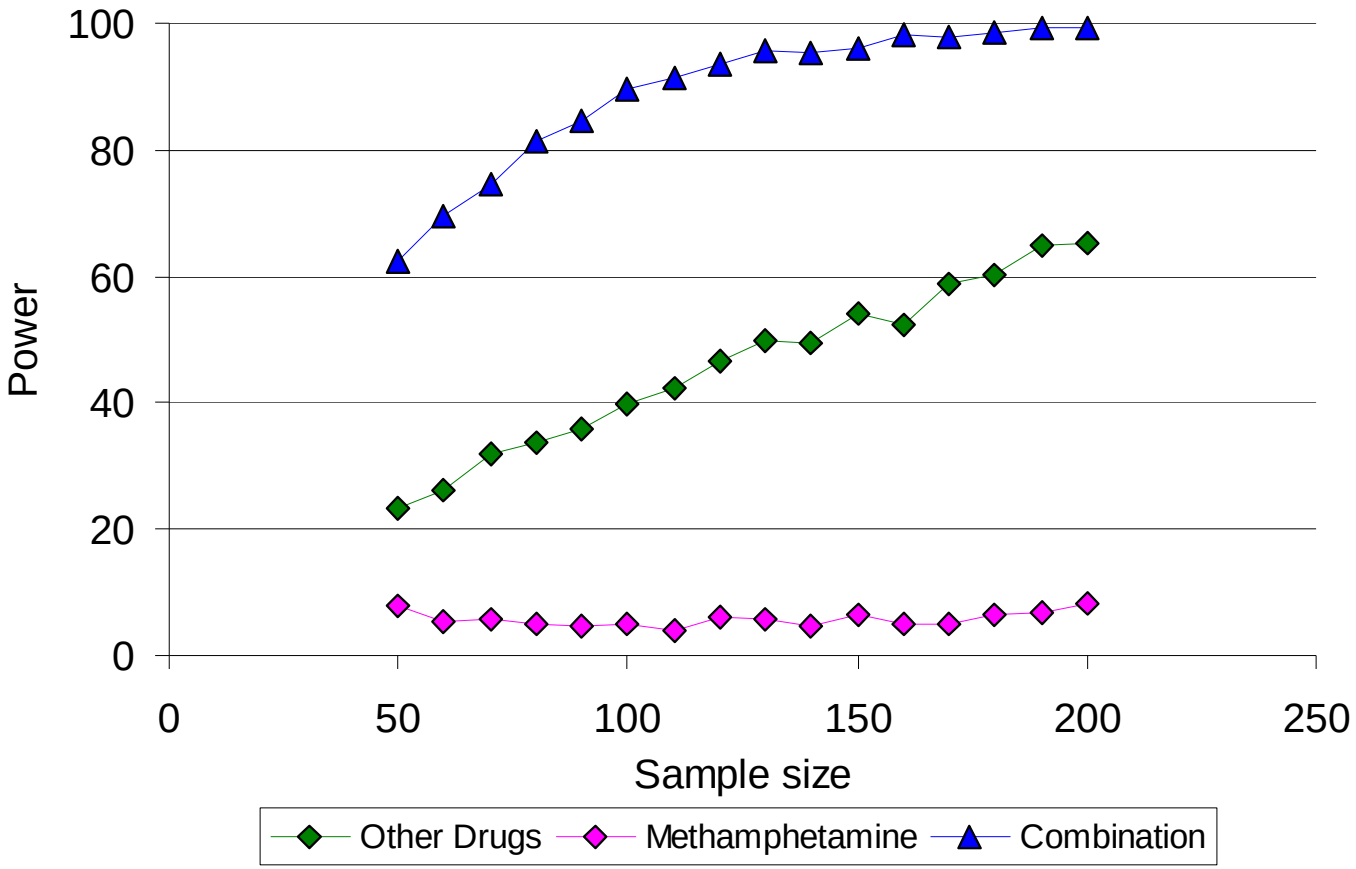


Figure 6-4: Post-Hoc Power for Substance Use and UAI after Diagnosis in Manuscript 3

Table 6-3: Potential Biases in Cross-sectional Observational Studies and Likelihood of Occurrence in the Dissertation Study

Bias Class Bias Name	**Description**	**Threat to Validity**	**Likelihood**	**Reasoning for Presence or Absence and Methods for Avoiding the Bias**
Dissemination				
Publication	Studies that demonstrate associations are more likely to be published than those that do not	Internal	Unknown	A thorough search of the literature was completed, however may be difficult to avoid.
Citation	Articles that are more frequently cited are more easily found and therefore more likely to be included	Internal	Unlikely	A thorough search of the literature was completed.
Language	Studies published in other languages are not included	Internal	Somewhat Unlikely	Most abstracts published in English, all abstracts reviewed.
Selection				
Incidence-Prevalence (Neyman)	Selection of prevalent (as opposed to incident) cases in a cross-sectional or case control study	Internal	Very Unlikely	Only incident cases were used for this study
Loss to Follow-up	Loss to follow-up is uneven in exposure or outcome categories	Internal	Very Unlikely	Cross-sectional study design
Missing Information	Participants with complete data differ from those with incomplete data	Internal	Very Unlikely	There were complete data for all variables that were assessed.
Non-response	Those who do not respond differ from those who do	Internal	Unlikely	Respondents and non-respondents were similar with respect to demographics.
Healthcare Access	Patients admitted to a particular institution are not representative of those with the disease/outcome	External	Possible	Different referral sources were used, however representation of all incident HIV cases unlikely.
Volunteer	Those who volunteer are inherently different than those who do not	External	May be present	Unavoidable, in all studies participants are volunteers. Participants were mostly recruited through referral by physicians and HIV test counselors, therefore may be more likely to participate than self-referral.
Generalizability	The sample is not generalizable to all individuals at risk for the outcome	External	Unlikely	CASI sample approximates California and San Diego HIV cases

(Table 6-3 continued on next page)

Table 6-3: Potential Biases in Cross-sectional Observational Studies and Likelihood of Occurrence (continued)

Bias Class Bias Name	**Description**	**Threat to Validity**	**Likelihood**	**Reasoning for Presence or Absence and Methods for Avoiding the Bias**
Information Recall	Ability to recall past exposure is dependent on outcome status (e.g., those with the outcome are more likely to recall exposure).	Internal	Somewhat Unlikely	Outcome was not a particular disease as with a case-control study, all participants had HIV and did not know that UAI would be an outcome.
Interviewer	Outcome or diagnosis is not independent of knowledge of exposure. Participant is "lead" by interviewer emphasizing what s/he would like to hear.	Internal	Very Unlikely	CASI interview used
Respondent	Soft outcomes, left to respondent interpretation (e.g., migraine headaches)	Internal	Somewhat Unlikely	Anal intercourse was defined and use of a condom is often not mistaken among adults.
Temporal Ambiguity	Proper temporal sequence cannot be firmly established (risk factor-> disease)	Internal	Somewhat Unlikely	Participants were asked if they used substances prior to sexual activity.
Reporting	Participants provide the answers that they believe researchers would like to hear	Internal	Unlikely	The participants were not told of which associations were being examined. Distance placed between sexual activity and substance use questions on CASI.
Hawthorne Effect	Participants under study modify their behavior to reduce the likelihood of a negative outcome	Internal	Very Unlikely	Usually a problem of a longitudinal or repeated measures study
Confounding	A result of a factor that is not controlled for in analyses or sampling and is associated with the outcome and main predictor, but is not part of the causal pathway, which causes a spurious association between the variables of interest	Internal	Unlikely	Confounding was controlled for in statistical analyses.

Exposure:

A: Under selection of substance users reporting no UAI

	UAI	No UAI
Drug	A	B - 40%
No Drug	C	D

OR=(A)(D)/(0.6 B)(C)

B: Under selection of substance users reporting UAI

	UAI	No UAI
Drug	A - 40%	B
No Drug	C	D

OR=(0.6 A)(D)/(B)(C)

C: Similar selection of substance users reporting UAI and no UAI

	UAI	No UAI
Drug	A - 20%	B - 20%
No Drug	C	D

OR=(0.8 A)(D)/(0.8 B)(C)

Outcome:

D: Under selection of those who report UAI and substance use

	UAI	No UAI
Drug	A – 40%	B
No Drug	C	D

OR=(0.6 A)(D)/(B)(C)

E: Under selection of those who report UAI and no substance use

	UAI	No UAI
Drug	A	B
No Drug	C - 40%	D

OR=(A)(D)/(B)(0.6 C)

F: Similar selection of those who report UAI and substance / no substance use

	UAI	No UAI
Drug	A - 20%	B
No Drug	C - 20%	D

OR=(0.8 A)(D)/(B)(0.8 C)

Figure 6-5: Potential effects of selection bias on the association between substance use and UAI

True OR=(A)(D)/(B)(C)

A: Participants are less likely to report UAI and or substance use

	UAI	No UAI
Drug	A – 40%	B – 20%
No Drug	C – 20%	D + (.4A + .2B +.2C)

OR=(.6A)(D+.4A+.2B+.2C)/(0.8 B)(0.8 C)

D: Participant is more likely to recall the exposure if he had the outcome

	UAI	No UAI
Drug	A +.2B	B - 20%
No Drug	C -20%	D +.2C

OR=(A+.2B)(D+.2C)/(0.8 B)(0.8 C)

B: Participants are more likely to report UAI if they used substances or substance use if they had UAI

	UAI	No UAI
Drug	A + (.3C +3.B)	B - 30%
No Drug	C - 30%	D

OR=(A+.3B+.3C)(D)/(0.7 B)(0.7 C)

E: Indiscriminant misclassification

	UAI	No UAI
Drug	A - 20% (+.3C)	B - 40% (+.5D)
No Drug	C - 30% (+.2A)	D - 50% (+.4B)

OR=(0.8A +.3C)(0.5D+.4B)/(0.6B+.5D)(0.7C+.2A)

C: Participants are less likely to report substance use if they had UAI or UAI if they used substances

	UAI	No UAI
Drug	A - 50%	B +.25A
No Drug	C +.25A	D

OR=(0.5A)(D)/(B+.25A)(C+.25A)

Figure 6-6: Potential effects of differential misclassification due to information bias on the association between substance use and UAI

[**True OR=(A)(D)/(B)(C)]**

A: 20% of those with exposure are misclassified as not having exposure regardless of UAI

	UAI	No UAI
Drug	A – 20%	B – 20%
No Drug	C + .2A	D + .2B

Correctly Classified

	UAI	No UAI
Drug	40	30
No Drug	40	100

OR=(40)(100)/ (30)(40)= 3.33

Misclassified

	UAI	No UAI
Drug	40-8	30-6
No Drug	40+8	100+6

OR=(32) (106)/(24)(48)=2.94

B: 40% of those with UAI are misclassified as not having UAI regardless of exposure

	UAI	No UAI
Drug	A - 40%	B + .4A
No Drug	C -40%	D + .4C

Correctly Classified

	UAI	No UAI
Drug	80	50
No Drug	80	200

OR=(80)(200)/ (50)(80)= 4.0

Misclassified

	UAI	No UAI
Drug	80-32	50 +32
No Drug	80-32	200 +32

OR=(48)(232)/ (82)(48)= 2.83

Figure 6-7: Potential effects of non-differential misclassification due to information bias on the association between substance use and UAI

[**OR=(A)(D)/(B)(C)]**

A: 20% and 40% of those with exposure are misclassified

	UAI	No UAI
Drug	A – 40%	B – 20%
No Drug	C + .4A	D + .2B

B: 20% and 40% of those with the outcome are misclassified

	UAI	No UAI
Drug	A – 20%	B + .2A
No Drug	C – 40%	D + .4C

Correctly Classified

	UAI	No UAI
Drug	40	30
No Drug	40	100

OR=(40)(100)/ (30)(40)= 3.33

Correctly Classified

	UAI	No UAI
Drug	80	50
No Drug	80	200

OR=(80)(200)/ (50)(80)= 4.0

Misclassified

	UAI	No UAI
Drug	40-16	30-6
No Drug	40 + 16	100 + 6

OR=(24)(106)/ (24)(56)= 1.89

Misclassified

	UAI	No UAI
Drug	80-8	50 + 8
No Drug	80 - 32	200 + 32

OR=(72)(232)/ (58)(48)= 6.0

Figure 6-8: Potential effects of uneven proportions of misclassification (resulting in differential misclassification) by outcome or exposure due to information bias on the association between substance use and UAI. 6-3A will result in an odds ratio closer to the null because the larger proportion of subjects are misclassified from the exposed with outcome cell (A). In 6-3B the reverse is true, fewer subjects are misclassified from cell A.

Table 6-4: Comparisons of demographics and risk categories of HIV cases in the United States, California, San Diego, and AIEDRP participants who completed CASI

Characteristic	United States† % (n) n=224 597	California ŧ % (n) n=40 096	San Diego‡ % (n) n=4616	AIEDRP % (n) n=220
Gender				
Male	69.5 (156 095)	85.3 (34 181)	90.0 (4152)	98.6 (217)
Female	30.5 (68 502)	13.8 (5539)	10.0 (464)	1.4 (3)
Transgender	Not reported	0.9 (374)	0	0
Unknown	Not reported	< 0.1 (2)	0	0
Risk Category				
MSM	33.8 (76 003)	61.8 (24 780)	71.8 (3315)	87.7 (193)
Heterosexual	19.7 (44 208)	9.0 (3606)	10.3 (477)	5.0 (11)
IDU	14.1 (31 709)	8.3 (3341)	6.0 (277)	0
MSM/ IDU	3.7 (8298)	5.9 (2375)	6.8 (312)	6.8 (15)
Other/ Unknown	28.7 (64 379)	15.0 (5994)	5.1 (235)	0.5 (1)
Age∂				
> 20	2.9 (13 371)	2.2 (875)	2.1 (98)	2.3 (5)
20-29	17.0 (76 969)	26.1 (10 478)	32.2 (1486)	29.6 (64)
30-39	39.6 (179 828)	40.5 (16 247)	43.1 (1989)	36.6 (79)
40-49	29.1 (132 386)	22.8 (9146)	17.3 (797)	24.5 (53)
50 +	11.4 (51 602)	8.4 (3350)	5.4 (248)	6.9 (15)
Ethnicity				
Asian/ Pacific Islander	0.6 (1306)	2.8 (1129)	2.3 (105)	2.3 (5)
Black/ African American	49.0 (109 991)	19.4 (7767)	13.2 (607)	5.5 (12)
Caucasian	34.2 (76 703)	48.5 (19 450)	61.9 (2857)	67.7 (149)
Hispanic	15.0 (33 640)	25.8 (10 351)	21.8 (1007)	20.9 (46)
Native American	0.5 (1068)	0.6 (238)	0.8 (40)	1.4 (3)
Other	0.8 (1889)	2.9 (1129)	0	2.3 (5)

† Data for the United States based on cumulative HIV cases reported to the Centers for disease control and prevention through 12/31/04 [45].

ŧ Data for the State of California based on cumulative HIV cases through 01/31/06 [76]

‡ Data for San Diego County based on cumulative HIV cases through 12/31/04 [77]

∂ Age statistics for the United States are based on people living with HIV/AIDS through 12/31/04 (n=454 156), as age for those with HIV was not available, and may not be representative of the age at HIV diagnosis, or comparable to age at HIV diagnosis reported for California, San Diego, and AIEDRP.

Table 6-5: Comparisons of ethnicity among MSM and MSM/IDU with HIV in the United States, San Diego County, and AIEDRP CASI Respondents

Ethnicity	**United States†** **% (n)** **n=84 301**	**San Diego‡** **% (n)** **n=3627**	**AIEDRP** **% (n)** **n=208**
Asian/ Pacific Islander	0.7 (575)	2.1 (75)	2.4 (5)
Black/ African American	30.1 (25 356)	9.6 (349)	2.9 (6)
Caucasian	54.7 (46 085)	66.5 (2410)	70.2 (146)
Hispanic	13.5 (11 347)	21.1 (766)	20.6 (43)
Native American	0.6 (517)	0.7 (27)	1.4 (3)
Other	0.5 (421)	0	2.4 (5)

† Data for the United States based on cumulative HIV cases reported to the Centers for disease control and prevention through 12/31/04 [45].

‡ Data for San Diego County based on cumulative HIV cases through 12/31/04 [77]

F. References

(1) Hogg RS, Weber AE, Chan K *et al*. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS*. 2001; 15:1321-1322.

(2) del Romero J, Castilla J, Garcia S. *et al*. Time trend in incidence of HIV seroconversion among homosexual men repeatedly tested in Madrid, 1988-2000. *AIDS*. 2001; 15:1319-1321.

(3) Kellogg TA, McFarland W, Perlman JL *et al*. HIV incidence among repeat HIV testers at a county hospital, San Francisco, California, USA. *Journal of Acquired Immune Deficiency Syndromes*. 2001; 28:59-64.

(4) Calzavara L, Burchell AN, Major C *et al*. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS*. 2002; 16:1655-1661.

(5) Dukers NHTM, Spaargaren J, Geskus RB *et al*. HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. *AIDS*. 2002; 16:F19-F24.

(6) Centers for Disease Control and Prevention. Increases in HIV diagnoses- 29 states, 1999-2002. *Morbidity and Mortality Weekly Report*. 2003; 52:1145-1148.

(7) Ostrow DG, Beltran ED, Joseph JG *et al*. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. *J Subst Abuse*. 1993; 5:311-325.

(8) Strathdee SA, Hogg RS, Martindale SL *et al*. Determinants of sexual risk-taking among young HIV-negative gay and bisexual men. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*. 1998; 19:61-66.

(9) Molitor F, Truax SR, Ruiz JD *et al*. Association of methamphetamine use during sex with risky sexual behaviors and HIV infection among non-injection drug users. *Western Journal of Medicine*. 1998; 168:93-97.

(10) Woody GE, Donnell D, Seage GR *et al*. Non-injection substance use correlates with risky sex among men having sex with men: data from HIVNET. *Drug Alcohol Depend*. 1999; 53:197-205.

(11) Mulry G, Kalichman SC, Kelly JA. Substance Use and Unsafe Sex Among Gay Men - Global Versus Situational Use of Substances. *Journal of Sex Education & Therapy*. 1994; 20:175-184.

(12) Clutterbuck DJ, Gorman D, McMillan A *et al*. Substance use and unsafe sex amongst homosexual men in Edinburgh. *AIDS Care*. 2001; 13:527-535.

(13) Colfax GN, Mansergh G, Guzman R *et al*. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr*. 2001; 28:373-379.

(14) Klitzman RL, Greenberg JD, Pollack LM *et al*. MDMA ('ecstasy') use, and its association with high risk behaviors, mental health, and other factors among gay/bisexual men in New York City. *Drug and Alcohol Dependence*. 2002; 66:115-125.

(15) Chu PL, McFarland W, Gibson S *et al*. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr*. 2003; 33:191-193.

(16) Hirshfield S, Remien RH, Walavalkar I *et al*. Crystal methamphetamine use predicts incident STD infection among men who have sex with men recruited online: A nested case-control study. *Journal of Medical Internet Research*. 2004; 6:42-49.

(17) Rusch M, Lampinen TM, Schilder A *et al*. Unprotected anal intercourse associated with recreational drug use among young men who have sex with men depends on partner type and intercourse role. *Sex Transm Dis*. 2004; 31:492-498.

(18) Colfax G, Vittinghoff E, Husnik MJ *et al*. Substance use and sexual risk: A participant- and episode-level analysis among a cohort of men who have sex with men. *American Journal of Epidemiology*. 2004; 159:1002-1012.

(19) Kokkevi A, Stefanis N, Anastasopoulou E *et al*. Personality disorders in drug abusers: Prevalence and their association with AXIS I disorders as predictors of treatment retention. *Addictive Behaviors*. 1998; 23:841-853.

(20) Semple SJ, Patterson TL, Grant I. Psychosocial predictors of unprotected anal intercourse in a sample of HIV positive gay men who volunteer for a sexual risk reduction intervention. *AIDS Education and Prevention*. 2000; 12:416-430.

(21) Rhodes T, Stimson GV. What is the relationship between drug taking and sexual risk? social realtions and social research. *Sociology of Health and Illness*. 1994; 16:209-228.

(22) Rhodes T. Culture, drugs and unsafe sex: confusion about casuation. *Addiction*. 1996; 91:753-758.

(23) Ostrow D, McKirnan D. Prevention of substance-related high-risk sexual behavior among gay men: critical review of the literature and proposed harm reduction approach. *Journal of the Gay and Lesbian Medical Association*. 1997; 1:97-110.

(24) McKirnan DJ, Ostrow DG, Hope B. Sex, drugs and escape: a psychological model of HIV-risk sexual behaviours. *AIDS Care*. 1996; 8:655-669.

(25) McKirnan DJ, Vanable PA, Ostrow DG *et al*. Expectancies of sexual "escape" and sexual risk among drug and alcohol-involved gay and bisexual men. *Journal of Substance Abuse*. 2001; 13:137-154.

(26) Hill AB. The environment and disease: associations or causation? *Proceedings of the Royal Society of Medicine*. 1965; 58:295-300.

(27) Liu G, Liang KY. Sample size calculations for studies with correlated observations. *Biometrics*. 1997; 53:937-947.

(28) Gordis L. Epidemiology. 1st ed. Philadelphia: W.B.Saunders Company, 1996.

(29) Szklo M, Nieto FJ. Epidemiology: beyond the basics. Gaithersberg: 2000.

(30) Delgado-Rodriguez M, Llorca J. Bias. *Journal of Epidemiology and Community Health*. 2004; 58:635-641.

(31) Rothman KJ, Greenland S. Precision and Validity in Epidemiologic Studies. In: Rothman KJ, Greenland S, editors. Modern Epidemiology. Philidelphia: Lippincott, William, and Wilkins, 1998: 115-134.

(32) Jones DR. Metaanalysis of Observational Epidemiologic Studies. *Journal of the Royal Society of Medicine*. 1992; 85:165-168.

(33) Blettner M, Sauerbrei W, Schlehofer B *et al*. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *International Journal of Epidemiology*. 1999; 28:1-9.

(34) Gregoire G, Derderian F, Lelorier J. Selecting the Language of the Publications Included in A Metaanalysis - Is There A Tower-Of-Babel Bias. *Journal of Clinical Epidemiology*. 1995; 48:159-163.

(35) Schlesselman JJ, Stolley PD. Sources of Bias. In: Schlesselman JJ, editor. Case-Control Studies: Design, Conduct, Analysis. New York: Oxford University Press, 1982: 124-143.

(36) Colfax G, Coates TJ, Husnik MJ *et al*. Longitudinal patterns of methamphetamine, popper (Amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of San Francisco men who have sex with men. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:I62-I70.

(37) Crepaz N, Marks G, Mansergh G *et al*. Age-related risk for HIV infection in men who have sex with men: Examination of behavioral, relationship, and serostatus variables. *AIDS Education and Prevention*. 2000; 12:405-415.

(38) Harawa NT, Greenland S, Bingham TA *et al*. Associations of race/ethnicity with HIV prevalence and HIV-related behaviors among young men who have sex with men in 7 urban centers in the United States. *Journal of Acquired Immune Deficiency Syndromes*. 2004; 35:526-536.

(39) Valleroy LA, MacKellar DA, Karon JM *et al*. HIV prevalence and associated risks in young men who have sex with men. *Jama-Journal of the American Medical Association*. 2000; 284:198-204.

(40) Celentano DD, Sifakis F, Hylton J *et al*. Race/ethnic differences in HIV prevalence and risks among adolescent and young adult men who have sex with men. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:610-621.

(41) Hickson F, Reid D, Weatherburn P *et al*. HIV, sexual risk, and ethnicity among men in England who have sex with men. *Sexually Transmitted Infections*. 2004; 80:443-450.

(42) Thiede H, Valleroy LA, MacKellar DA *et al*. Regional patterns and correlates of substance use among young men who have sex with men in 7 US urban areas. *Am J Public Health*. 2003; 93:1915-1921.

(43) Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 1998.

(44) Hoff CC, Faigeles B, Wolitski RJ *et al*. Sexual risk of HIV transmission is missed by traditional methods of data collection. *AIDS*. 2004; 18:340-342.

(45) Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2004. Volumne 16. 2005. Atlanta, United States Department of Health and Human Services. (Report)

(46) United States Census Bureau. Census Brief: Black Population 2000. http://www.census.gov/prod/2001pubs/c2kbr01-5.pdf. 2001. United States Department of Commerce. (Electronic Citation)

(47) Centers for Disease Control and Prevention. Late versus early testing of HIV-16 sites, United States 2000-2003. *Morbidity and Mortaility Weekely Report*. 2003; 52:581-586.

(48) Ghanem KG, Hutton HE, Zenilman JM *et al*. Audio computer assisted self interview and face to face interview modes in assessing response bias among STD clinic patients. *Sexually Transmitted Infections*. 2005; 81:421-425.

(49) Kurth AE, Martin DP, Golden MR *et al*. A comparison between audio computer-assisted self-interviews and clinician interviews for obtaining the sexual history. *Sexually Transmitted Diseases*. 2004; 31:719-726.

(50) Tourangeau R, Smith TW. Asking sensitive questions - The impact of data collection mode, question format, and question context. *Public Opinion Quarterly*. 1996; 60:275-304.

(51) Perlis TE, Des Jarlais DC, Friedman SR *et al*. Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. *Addiction*. 2004; 99:885-896.

(52) Rogers SM, Willis G, Al Tayyib A *et al*. Audio computer assisted interviewing to measure HIV risk behaviours in a clinic population. *Sexually Transmitted Infections*. 2005; 81:501-507.

(53) Mears M, Coonrod DV, Bay RC *et al*. Routine history as compared to audio computer-assisted self-interview for prenatal care history taking. *Journal of Reproductive Medicine*. 2005; 50:701-706.

(54) Hewett PC, Mensch BS, Erulkar AS. Consistency in the reporting of sexual behaviour by adolescent girls in Kenya: a comparison of interviewing methods. *Sexually Transmitted Infections*. 2004; 80:43-48.

(55) Macalino GE, Celentano DD, Latkin C *et al*. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. *AIDS Education and Prevention*. 2002; 14:367-378.

(56) Krawczyk CS, Gardner LI, Wang JC *et al*. Test-retest reliability of a complex human immunodeficiency virus research questionnaire administered by an audio computer-assisted self-interviewing system. *Medical Care*. 2003; 41:853-858.

(57) Paschall MJ, Ornstein ML, Flewelling RL. African American male adolescents' involvement in the criminal justice system: The criterion validity of self-report measures in a prospective study. *Journal of Research in Crime and Delinquency*. 2001; 38:174-187.

(58) Murphy DA, Durako S, Muenz LR *et al*. Marijuana use among HIV-positive and high-risk adolescents: A comparison of self-report through audio computer-assisted self-administered interviewing and urinalysis. *American Journal of Epidemiology*. 2000; 152:805-813.

(59) Jones R. Survey data collection using audio computer assisted self-interview. *Western Journal of Nursing Research*. 2003; 25:349-358.

(60) Rasinski KA, Willis GB, Baldwin AK *et al*. Methods of data collection, perceptions of risks and losses, and motivation to give truthful answers to sensitive survey questions. *Applied Cognitive Psychology*. 1999; 13:465-484.

(61) Leigh BC, Stall R. Substance use and risky sexual behavior for exposure to HIV: Issues in methodology, interpretation, and prevention. *American Psychologist*. 1993; 48:1035-1045.

(62) Lee SJ, Galanter M, Dermatis H *et al*. Circuit parties and patterns of drug use in a subset of gay men. *J Addict Dis*. 2003; 22:47-60.

(63) Greenwood GL, White EW, Page-Shafer K *et al*. Correlates of heavy substance use among young gay and bisexual men: The San Francisco Young Men's Health Study. *Drug and Alcohol Dependence*. 2001; 61:105-112.

(64) Halkitis PN, Green KA, Mourgues P. Longitudinal Investigation of Methamphetamine Use Among Gay and Bisexual Men in New York City: Findings from Project BUMPS. *J Urban Health*. 2005; 82:i18-i25.

(65) Ostrow DG, Beltran ED, Joseph JG *et al*. Recreational drugs and sexual behavior in the Chicago MACS/CCS cohort of homosexually active men. Chicago Multicenter AIDS Cohort Study (MACS)/Coping and Change Study. *J Subst Abuse*. 1993; 5:311-325.

(66) Colfax G, Coates TJ, Husnik MJ *et al*. Longitudinal patterns of methamphetamine, popper (amyl nitrite), and cocaine use and high-risk sexual behavior among a cohort of san francisco men who have sex with men. *J Urban Health*. 2005; 82:i62-i70.

(67) Stall RD, Paul JP, Greenwood GL *et al*. Alcohol use, drug use and alcohol-realted problems among men who have sex with men: the Urban Men's Health Study. *Addiction*. 2001; 96:1589-1601.

(68) Patterson TL, Semple SJ, Zians JK *et al*. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82:I120-I126.

(69) Kim AA, Kent CK, Klausner JD. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000-2001. *AIDS*. 2002; 16:1425-1428.

(70) Hirshfield S, Remien RH, Humberstone M *et al*. Substance use and high-risk sex among men who have sex with men: a national online study in the USA. *AIDS Care*. 2004; 16:1036-1047.

(71) Sherr L, Bolding G, Maguire M. Viagra use and sexual risk behavior among gay men in London. *AIDS*. 2000; 14:2051-2052.

(72) Greenland S. Test for interaction in epidemiologic studies: a review and a study of power. Statistics in Medicine 2, 243-251. 1983. (Electronic Citation)

(73) Greenland S. Basic Problems in Interaction Assessment. *Environmental Health Perspectives*. 1993; 101:59-66.

(74) Breslow NE, Day NE. Statistical methods in cancer research II: the design and analysis of cohort studies. Lyon: International Agency on for Research on Cancer, 1987.

(75) Edwardes MD. Sample size requirements for case-control study designs. BMC Medical Research Methodology 11[1]. 2001. (Electronic Citation)

(76) California Office of AIDS. California HIV Surveillance Report: Cumulative Cases as of January 31, 2006. http://www.dhs.ca.gov/ps/ooa/Statistics/pdf/Stats2006/Jan06HIVmerged.pdf. 2006. (Electronic Citation) Accessed 10 February 2006.

(77) County of San Diego HIV/ AIDS Epidemiology. HIV/AIDS Epidemiology Report, 2005. 2005. San Diego, County of San Diego Health and Human Services Agency. (Report)

APPENDIX A:

QUESTIONS FROM DATA COLLECTION INSTRUMENT

Demographics

1. What is your date of birth?

2. Are you male or female?

1 male
2 female

3. Please type the number of the highest year or grade of school that you have completed and received credit for:

1 No formal school
2 1st through 8th grade
3 grade 9
4 grade 10
5 grade 11
6 grade 12
7 some college
8 completed college
9 some post-graduate training
10 masters degree
11 Dr.PH, DVM, J.D., M.D, Ph.D. or other graduate degree beyond Masters

4. What is your ethnicity or racial background? (Please select all that you feel describe you)

1 Asian
2 African American or Black
3 Caucasian (white - non Hispanic)
4 Hispanic or Latino
5 Pacific Islander
6 Native American/American Indian/Alaskan Native
7 Other (Please specify)_____

5. Are you currently working full-time, part-time or not at all?

1 full-time

2 part-time

3 not working now

Sexual History

Introduction: In the next series of questions we will ask about your sexual history.

For the purpose of this questionnaire when we ask about SEXUAL ACTIVITY we are talking about any of the following activities:

oral sex

vaginal sex

anal sex

rimming

fisting

group sex

6. In the LAST 12 MONTHS, have you had sexual activity with men, women, or both men and women?

1 men only

2 women only

3 both men & women

4 had NO sexual activity AT ALL in the LAST 12 MONTHS

7. Counting all of your male sexual contacts, even those that you had sexual activity with only once, how many men have you had sexual activity with in your LIFE?

If you had sexual activity with 999 or more men, type 999.

If you cannot remember how many men, please guess.

8. During the LAST 12 MONTHS, how many men, if any, did you have sexual activity with?

PLEASE COUNT EVERY MAN, EVEN THOSE THAT YOU HAD SEXUAL ACTIVITY WITH ONLY ONCE.

If you had sexual activity with 999 or more men type 999.

9. During the LAST 3 MONTHS, how many men, if any, did you have sexual activity with?

PLEASE COUNT EVERY MAN, EVEN THOSE THAT YOU HAD SEXUAL ACTIVITY WITH ONLY ONCE..

If you had sexual activity with 999 or more men, type 999.

10. During the LAST MONTH, how many men, if any, did you have sexual activity with?

PLEASE COUNT EVERY MAN, EVEN THOSE THAT YOU HAD SEXUAL ACTIVITY WITH ONLY ONCE.

11. Have you ever had sexual activity with more than one person at one time (group sex)?

1 Yes

2 No

(If answer is “No” skip to question 13)

12. In the LAST 12 MONTHS how many times have you had group sex?

(If you cannot remember, please estimate.)

If 99 times or greater, type 99.

13. Have you ever given someone money or goods for sexual activity (In other words, have you ever bought or paid for sex)?

1 Yes

2 No

14. Have you ever had sexual activity for money or goods
(In other words, have you ever sold sex yourself)?

1 Yes
2 No

15. Are you a professional sex worker or escort?

1 professional sex worker
2 escort
3 no

16. Have you ever injected drugs?

1 Yes
2 No
(If answer is “No” skip to question 18)

17. In the LAST 12 MONTHS, have you injected drugs?

1 Yes
2 No

Introduction: Many people have had an experience where they were forced to have sex in their lifetime. We would like to know more about people's experience with forced sex so we can help other people in the future. Therefore we would like to ask you some questions about whether you have experienced such a situation and if so, what occurred.

If you feel that it would be too hard to answer these questions right now, please feel free to type 0 now and move on to the next set of questions. If you would be willing to answer these questions, please press the 1 key. Remember that you can decline to answer individual questions by typing -1.

18. Have you ever felt that you have been molested, raped or forced to have sex?

1 Yes

2 No

19. In the next series of questions we will ask about your sexual history... Thinking about the very first time in your life that you had sexual intercourse, how old were you?

(Please tell us how old you were the very first time, even if you were forced, raped or molested.)

By SEXUAL INTERCOURSE we mean:

ANAL SEX BETWEEN TWO MEN: (one man putting his penis in another man's anus, rectum, butt or asshole)

OR VAGINAL SEX BETWEEN A MAN AND WOMAN: (a man putting his penis into a woman's vagina).

Last Three Partners Series (the following questions were repeated for all three partner)

Introduction: In the next series of questions we will ask about the last 3 people that you had sexual activity with.

(These people could be men, women or both men and women.)

20. Please type the first name or nickname of one of the last person that you had sexual activity with below.

(This does not have to be a real name, but this name will be used to refer to this person for the next series of questions. To help prevent confusion, please use the same name to represent the same person throughout this interview).

21. Please type the first name or nickname of the second to last person that you had sexual activity with below.

(This does not have to be a real name, but this name will be used to refer to this person for the next series of questions. To help prevent confusion, please use the same name for the same person throughout this interview).

22. Please type the first name or nickname of the third to last person that you had sexual activity with below.

(This does not have to be a real name, but this name will be used to refer to this person for the next series of questions. To help prevent confusion, please use the same name for the same person throughout this interview).

23. Is (partner name) a male or a female?

1 = male

2 = female

24. How old is (partner name)?

IF YOU DON'T KNOW TYPE 99.

25. Please guess the age of (partner name).

1 younger than 18
2 18 - 24
3 25 - 30
4 31 - 35
5 36 - 40
6 41 - 50
7 51 - 60
8 61 - 70
9 older than 70

26. What is (partner name's) ethnicity or racial background? (Please select as many as apply)

IF YOU DON'T KNOW, PLEASE GUESS.

1 Asian
2 African American or Black
3 Caucasian (white - non Hispanic)
4 Hispanic or Latino
5 Pacific Islander
6 Native American/American Indian/Alaskan Native
7 Other

Partner types were previously described to the participant as follows:

UNKNOWN PERSON- someone that you had never met before you had sexual contact and never plan to see again

ONETIME PARTNER- someone you know or could find again, but you had sexual contact with only one time

ACQUAINTANCE- someone you have had sexual contact with more than once, but not on a regular basis, and who you don't socialize with

FRIEND- someone you have had sexual contact with more than once, but not on a regular basis, and you normally socialize with

REGULAR PARTNER- someone who you have sex with on a regular basis

MAIN PARTNER- someone who is your primary sexual partner

TRADE PARTNER- someone who you gave sex to for money or other goods or someone who gave you sex for money or other goods (including any work in adult film or where you were paid to have sex with another person as a job, career or entertainment for someone else)

27. Using the types of sexual contacts that we asked you about previously, how would you describe (partner name)?

1 Unknown partner

2 Onetime partner

3 Acquaintance

4 Friend

5 Repeat partner

6 Main partner

7 Trade partner

8 Decline

28. How long ago did you met (partner name)?

1 Days

2 Weeks

3 Months

4 Years

29. Where did you first meet (partner name)?

1 Park
2 Bathhouse
3 Circuit party
4 Through friends
5 Bar or club
6 Work or school
7 On a business trip or vacation
8 Through the Internet
9 Other. (Please specify) _____

30. How long after you met (partner name) did you have sexual activity?

1 Minutes
2 Hours
3 Days
4 Weeks
5 Months
6 Years

31. How long ago did you last have sexual activity with (partner name)?

IF YOU ARE NOT SURE, PLEASE ESTIMATE.

1 Hours
2 Days
3 Weeks
4 Months
5 Years

32. What types of sexual activity have you had with (partner name)?

1 received oral sex using a condom
2 received oral sex without a condom
3 gave oral sex using a condom
4 gave oral sex without a condom
5 insertive (you were the top) anal sex using a condom
6 insertive (you were the top) anal sex without a condom
7 receptive (you were the bottom) anal sex using a condom
8 receptive (you were the bottom) anal sex without a condom
9 group sex
10 other. (please specify) _____
11 decline to answer

Original Question (32)

What types of sexual activity have you had with (partner name)?

1 received oral sex using a condom
2 received oral sex without a condom
3 gave oral sex using a condom
4 gave oral sex without a condom
5 vaginal sex using a condom
6 vaginal sex without a condom
7 anal sex using a condom
8 anal sex without a condom
9 group sex
10 other. (please specify)_____
11 decline to answer

33. What type of drug(s), if any, have you used when having sexual activity with (partner name) ? (Please select all that apply)

1 Crystal (glass, meth, amphetamine, methamphetamine, tina, speed)
2 Ecstasy (E,X, XTC, MDMA, Adam)
3 Poppers (Amyl nitrite, Butyl nitrite)
4 Special K (Ketamine, K)
5 GHB (liquid Ecstasy, G, Georgia home boy)
6 Cocaine (blow, coke, toot, candy, C, charlie, snow, crack)
7 Heroin (smack, harry, rock, skag)
8 Marijuana (Mary Jane, pot, grass, ganja, dope, joints, cannabis, M)
9 Acid (LSD)
10 Mushrooms (magic mushrooms, shrooms)
11 Oxycontin (roxy)
12 Vicodine
13 Valium
14 Other drugs (please specify)_____
15 No drugs used

34. Have you used Viagra, Levitra or Cialis when having sex with (partner name)?

1 Used Viagra, Levitra or Cialis only
2 Used Viagra, Levitra or Cialis with ritonavir
3 Did not use Viagra, Levitra or Cialis

Original Question

Questions 33 and 34 were originally combined with “Viagra, Levitra, or Cialis as part of the substance list seen in question #33

35. Have you and (partner name) talked about his HIV status?

1 Yes
2 No

36. Did (partner name) say he was HIV positive or HIV negative?

1 Positive

2 Negative

3 He did not know his status

4 He would not tell me his status

5 I can't remember

6 Other

APPENDIX B:

SAN DIEGO AIEDRP FORMS AND RULES

A. AIEDRP Eligibility Form

AEH 001 ELG0100
Page 1 of 1

ELIGIBILITY CHECKLIST

AEH PID: 0 1 ☐☐☐☐ Pt. Initials: ☐☐☐
AEH Study: 0 0 1 Date: ☐☐ (mm) ☐☐ (dd) ☐☐☐☐ (yyyy)
Form/Study Week: ☐☐☐ *Seq. No. ☐ ** Step No. ☐

* Enter a "1" if this is the first of this form for this date. Designate subsequent forms on the same date with a 2, 3, etc.
**Enter the subject's current study step number. Enter '1' if the study does not have multiple steps.

INSTRUCTIONS:
- Complete this form at enrollment only.
- **The use of "-1" is not an acceptable answer to any question.**

I. INCLUSION CRITERIA: Responses must be checked YES for patient to be enrolled in the study.	
1. ☐ Yes ☐ No	Patient is ≥13 years of age.
2. ☐ Yes ☐ No	Patient agrees to participate in the study by giving informed consent.
3. Acute HIV-1 Infection ☐ Yes ☐ No	Patient meets the diagnostic criteria for Acute HIV-1 Infection – defined as a positive plasma HIV-1 RNA (≥ 2,000 copies/mL) **or** detectable serum p24 antigen within 14 days of study entry, **and** one of the following: a. Negative HIV-1 EIA, or b. Positive HIV-1 EIA, but negative or indeterminate Western Blot[5], or c. Positive HIV-1 EIA and Western Blot but with documented negative HIV-1 EIA, HIV-1 Western Blot, plasma HIV-1 RNA, or Western Blot lacking a p31 band in the preceding 30 days.
OR	
Recent HIV-1 Infection ☐ Yes ☐ No	Patient needs the diagnostic criteria for Recent HIV-1 Infection – defined as a positive HIV-1 EIA and a positive Western Blot within 14 days of study entry, **and** one of the following: a. Negative HIV-1 EIA or plasma HIV-1 RNA documented in preceding 1 year, or b. Detuned HIV-1 EIA standardized OD measurement (defined as sample OD-negative control OD/positive control OD of ≤1.0 in the presence of a CD4 cell count >200mm^3, or CD4 percent >14.
[5]The Western Blot criteria are those defined by the CDC/ASTPHLD (*MMWR* July 21, 1989/38 (S-7);1-7), i.e. a positive test result is the presence of any two of the following bands: p24, gp41, and/or gp120/160; an indeterminate test result is the presence of any other band or bands that fail to meet the positive criteria and a negative test result is the absence of all bands.	
II. EXCLUSION CRITERIA: Responses must be checked ***NO*** for patient to be enrolled in the study.	
1. ☐ Yes ☐ No	More than 7 days prior antiretroviral therapy.

Key Operator Code: ☐☐☐
Date Form Keyed (DO NOT KEY): _____ / _____ / _____

AEH REVISION: 11/10/2003

B. Estimated Date of Infection Rules

ESTIMATED DATE OF INFECTION RULES

Estimated Date of Infection - Performed only on subjects who satisfy eligibility requirements and applied to laboratory data from the first screening visit:

These rules are listed in order of application (i.e. apply rule #1 first, then #2, etc)

1. If HIV EIA negative and HIV RNA >5000 copies/ml, use date 21 days prior to RNA date. Also, #2 on HIV0100 form cannot have a HIV EIA positive date and the RNA result must be within the first 7 days of HIV EIA negative date. The HIV EIA negative date must be on day 0 or up to 7 days prior.

2. If HIV EIA positive and WB indeterminate, use the date 28 days prior to indeterminate WB. The HIV EIA positive and WB indeterminate date must be on or after day 0.

3. If HIV EIA positive and WB positive, but less than or equal to 5 bands indicated as positive on WB, then use the date 45 days prior to WB date (date on WBX0100 form). The HIV EIA positive date must be on or up to 365 days prior to baseline and WB must be on or after baseline.

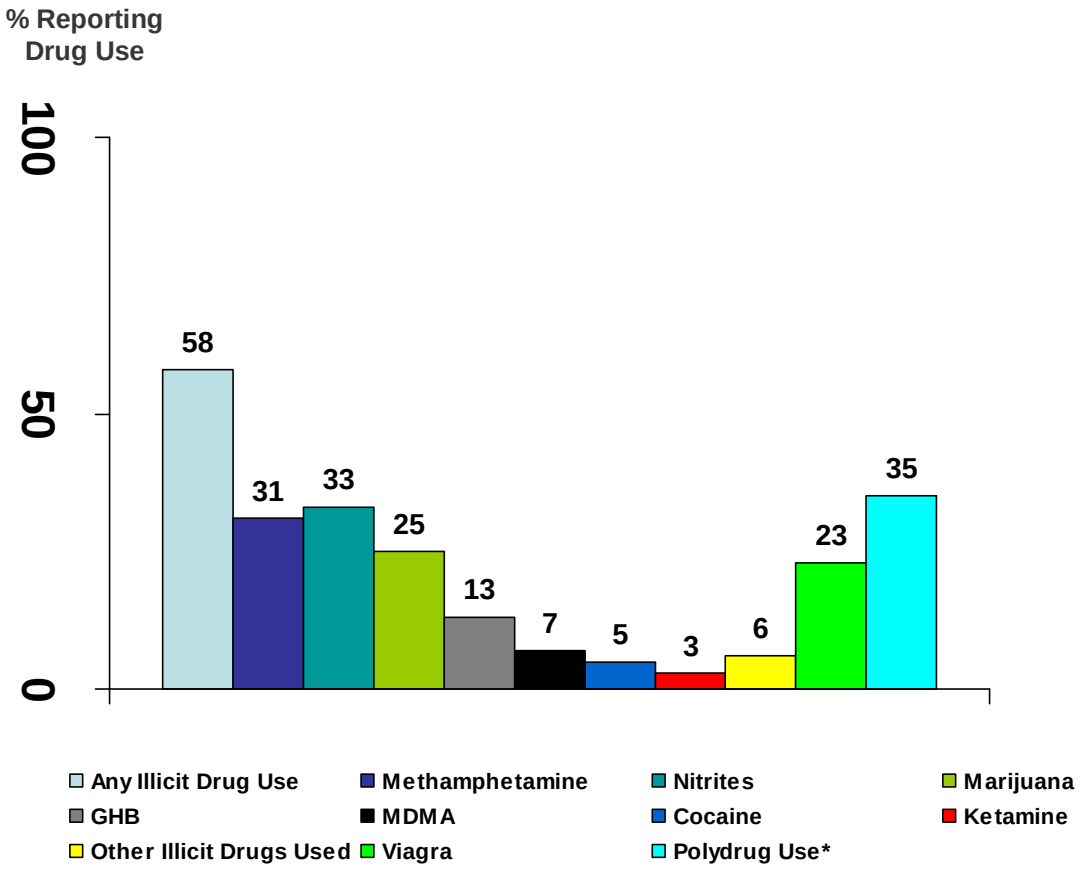
4. If HIV EIA positive and WB positive (i.e. 5 or more bands positive) and a detuned EIA (DT-EIA) is available within 14 days of the screening HIV EIA with DT-EIA test value less than or equal to 1.0 for the Vironostika OR less than or equal to 1.5 for the Abbott assay AND the CD4 cell percentage is greater than 14% or CD4 absolute count is greater than or equal to 200, then use the date 85 days prior to the date of the DT-EIA test. Both the positive EIA date and WB date can be prior to baseline

5. If none of the above criteria met (ie. HIV EIA positive, WB positive with more than 5 bands, and DT-EIA greater than 1.0 for Vironostika or 1.5 for Abbott asssay [or no DT-EIA ever done]), then use the midpoint between the date of the first DOCUMENTED positive EIA and the last historically documented negative EIA (prior to study entry). Also, HIV EIA negative, HIV EIA positive and WB must be on or up to 365 days prior to day 0.

Study entry date is the date of first screening for all subjects who satisfy inclusion/exclusion criteria.

APPENDIX C:

ADDITIONAL TABLES AND FIGURES



* polydrug use is defined as the use of more than one type of drug

Figure C-1: Percent of MSM reporting drug use with any of their last three sexual partners in manuscript 2 (n=194)

Table C-1: Multivariate generalized linear latent and mixed models (GLLAMM) comparing unprotected anal intercourse (UAI) and drug use among the last three partners stratified by partner type, manuscript 2 (n=194)

	Other (n=104)			Main (n=88)			All		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Methamphetamine	6.77	2.34, 19.6	0.001	0.85	0.05, 15.8	0.914	3.90	1.92, 7.91	0.001
Volatile Nitrates	1.99	0.90, 4.42	0.089	0.39	0.02, 9.78	0.564	1.76	0.94, 3.39	0.079
Marijuana	3.02	1.06, 8.63	0.039	4.05	0.25, 66.2	0.326	2.16	1.02, 4.58	0.045
Viagra	0.91	0.41, 2.04	0.825	14.5	0.81, 262.0	0.070	0.88	0.43, 1.82	0.734
Partner's Age (per year)	0.99	0.96, 1.02	0.441	1.09	0.94, 1.27	0.261	1.00	0.97, 1.03	0.928
Main Partner		N/A			N/A		2.63	1.39, 4.95	0.003
Days from Meeting to Sexual Intercourse (per day)	1.88	0.74, 4.73	0.182	15.5	0.62, 389.8	0.095	1.00	0.99, 1.01	0.850
Partner HIV+ vs. unknown	1.08	0.60, 1.95	0.788	4.52	0.22, 94.2	0.330	2.22	1.03, 4.77	0.042
Partner HIV- vs. unknown	2.26	1.26, 4.05	0.006	0.44	0.37, 13.9	0.375	1.08	0.66, 1.75	0.763
Sex occurring before HIV diagnosis	6.77	2.34, 19.6	0.001	0.85	0.05, 15.8	0.914	1.78	1.12, 2.82	0.015

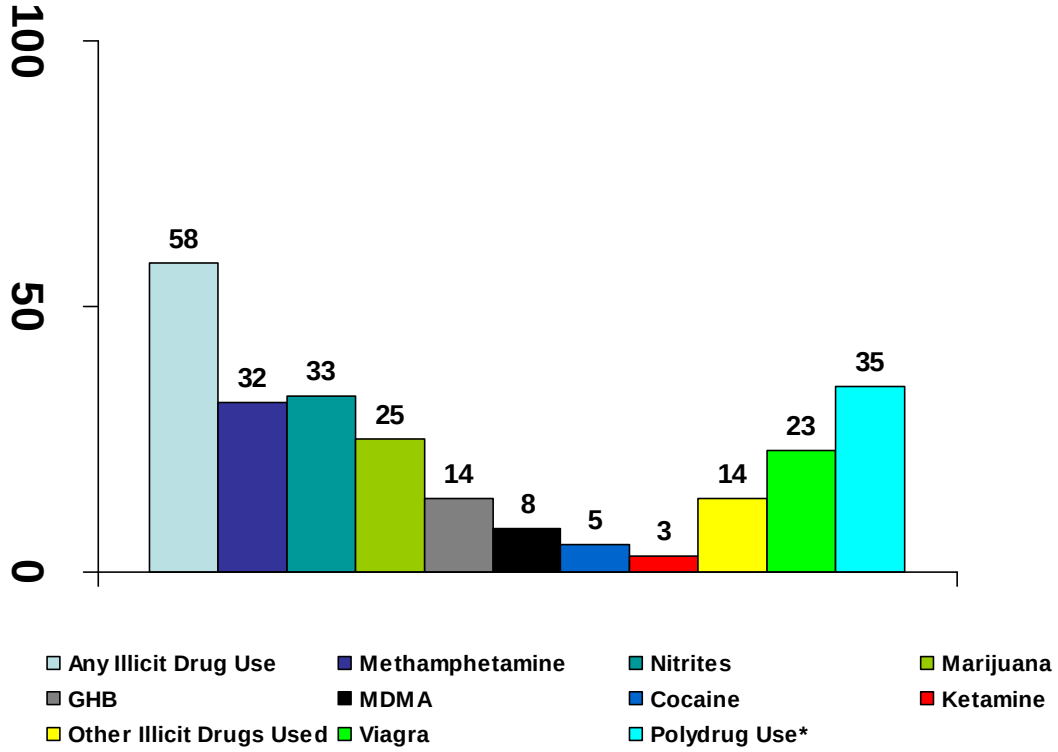


Figure C-2: Percent of MSM reporting drug use with any of their last three sexual partners in manuscript 3 (n=207)

Table C-2: Multivariate generalized linear latent and mixed models (GLLAMM) comparing unprotected anal intercourse (UAI) and drug use among the last three partners stratified by timing of sexual activity, manuscript 3 (n=207)

	Before Diagnosis (n=)			After Diagnosis (n=)			All		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Substance Used									
None	REF			REF			REF		
Methamphetamine	9.01	1.66, 48.9	0.01	1.40	0.25, 7.88	0.71	3.87	1.31, 11.4	0.01
Other Substances	0.85	0.32, 2.25	0.74	2.27	1.04, 5.00	0.04	1.47	0.83, 2.59	0.19
Methamphetamine & Other	6.68	2.23, 20.1	0.001	6.84	2.22, 21.1	0.001	6.34	3.03, 13.3	0.001
Met Partner in Bathhouse	2.04	0.71, 5.86	0.186	1.72	0.56, 5.27	0.35	1.89	0.94, 3.83	0.08
Main Partner	2.25	0.83, 6.13	0.112	4.57	2.06, 10.1	0.001	3.45	1.90, 6.26	0.001
Partner's HIV status									
Positive	REF			REF			REF		
Negative	1.03	0.33, 3.22	0.96	0.29	0.10, 0.81	0.02	0.56	0.27, 1.16	0.12
Unknown	0.71	0.22, 2.26	0.56	0.26	0.09, 0.75	0.01	0.44	0.21, 0.90	0.02
Sex occurring after HIV diagnosis		N/A			N/A		0.55	0.35, 0.86	0.01

Table C-3: Participant and partner demographics and sexual history by occurrence of UAI in manuscript 2 (n=194 individuals & 572 partnerships)

Measure	UAI Measure			
Individual characteristics	**No UAIǂ % (n) mean (median) n=31**	**UAI† % (n) mean (median) n=163**	**p-value**	**Total n=194**
Age	33.8 (34)	35.3 (37)	0.43	35.0 (35)
White (vs. all other ethnicity)	61.3 (19)	71.2 (116)	0.27	69.6 (135)
Education: completed college or greater	38.7 (12)	49.7 (81)	0.26	47.9 (93)
Unemployed	38.7 (12)	27.6 (45)	0.21	29.4 (57)
Number of sex partners past 12 months	52.0 (14)	35.6 (22)	0.23	38.2 (20.5)
Number of sex partners past 3 months	8.4 (3)	9.5 (5)	0.66	9.2 (4)
Number of sex partners past month	3.4 (2)	3.8 (1)	0.22	3.7 (1)
Partner/ partnership characteristics	**No UAI % (n) mean (median) n=258**	**UAI % (n) mean (median) n=314**	**p-value***	**Total n=572**
Partner's age	33.1 (33)	33.8 (33)	0.63	33.5 (33)
Main partner (vs. all other types)	12.4 (32)	23.3 (73)	0.001	18.4 (105)
Partner's ethnicity is white	62.8 (162)	62.1 (195)	0.43	62.4 (357)
Met partner at bathhouse (v. all other locales)	9.3 (24)	15.3 (48)	0.03	12.6 (72)
Contact with partner occurred after diagnosis	51.6 (133)	42.7 (134)	0.04	46.7 (267)
Methamphetamine used during intercourse	13.6 (35)	31.9 (100)	0.001	23.6 (135)
Nitrites used during sexual activity	12.8 (33)	24.8 (78)	0.001	19.4 (111)
Marijuana used during sexual activity	7.4 (19)	17.8 (56)	0.001	13.1 (75)
GHB used during sexual activity	3.1 (8)	12.4 (39)	0.001	8.2 (47)
Partner HIV status				
Positive	7.8 (20)	14.3 (45)	REF	11.4 (65)
Negative	39.2 (101)	42.4 (133)	0.10	40.9 (234)
Unknown	53.1 (137)	43.3 (136)	0.01	47.7 (273)

* p-value adjusted for repeated measures using GEE

ǂ for individual level, no UAI is with any of the last three partners; for partner level, no UAI is with that partner

† for individual level, UAI is with at least one of the last three partners: for partner level, UAI is with that partner

Table C-4: Participant and partner demographics and sexual history by occurrence of UAI in manuscript 3 (n=207 individuals & 603 partnerships)

Measure	UAI Measure			
Individual characteristics	**No UAIǂ % (n) mean (med) n=33**	**UAI† % (n) mean (med) n=174**	**p-value**	**Total n=207**
Age	34.6 (34)	35.0 (35)	0.792	35.0 (35)
White (vs. all other ethnicity)	60.6 (20)	71.8 (125)	0.196	70.1 (145)
Education: completed college or greater	39.4 (13)	48.3 (84)	0.349	46.9 (97)
Unemployed	39.4 (13)	28.7 (50)	0.222	30.4 (63)
Number of sex partners past 12 months	51.1 (15)	35.6 (21)	0.232	38.0 (20)
Number of sex partners past 3 months	8.2 (4)	9.4 (5)	0.571	9.2 (4)
Number of sex partners past month	3.3 (2)	3.7 (1)	0.730	3.6 (1)
Partner/ partnership characteristics	**No UAI % (n) mean (med) n=269**	**UAI % (n) mean (med) n=334**	**p-value***	**Total n=603**
Partner's age	32.7 (33)	33.5 (33)	0.49	33.1 (33)
Main partner (vs. all other types)	12.1 (34)	23.7 (79)	0.001	18.4 (113)
Partner's ethnicity is white	62.1 (167)	62.3 (208)	0.53	62.2 (375)
Met partner at bathhouse (v. all other locales)	8.9 (24)	14.7 (49)	0.04	12.1 (73)
Contact with partner occurred after diagnosis	52.4 (141)	43.4 (145)	0.04	47.4 (286)
Methamphetamine used during intercourse	12.5 (35)	32.0 (107)	0.001	23.1 (142)
Nitrites used during sexual activity	12.8 (36)	26.1 (87)	0.001	20.0 (123)
Marijuana used during sexual activity	7.5 (21)	17.4 (58)	0.001	12.9 (79)
GHB used during sexual activity	3.2 (9)	13.5 (45)	0.001	8.8 (54)
Partner HIV status				
Positive	8.6 (23)	14.7 (49)	REF	11.9 (72)
Negative	40.1 (108)	43.7 (146)	0.15	42.2 (254)
Unknown	51.3 (138)	41.6 (139)	0.01	45.9 (277)

* p-value adjusted for repeated measures using GEE

ǂ for individual level, no UAI is with any of the last three partners; for partner level, no UAI is with that partner

† for individual level, UAI is with at least one of the last three partners: for partner level, UAI is with that partner

Table C-5: Participant and partner demographics and sexual history by substance use in manuscript 2 (n=194 individuals & 572 partnerships)

Measure	Substance Use Measure			
Individual characteristics	**No substance use‡ % (n) mean (median) n=81**	**Substance use† % (n) mean (median) n=113**	**p-value**	**Total n=194**
Age	33.9 (33)	35.9 (37)	0.14	35.0(35)
White (vs. all other ethnicity)	65.4 (53)	72.6 (82)	0.29	69.6 (135)
Education: completed college or greater	45.7 (37)	49.6 (56)	0.59	47.9 (93)
Unemployed	23.5 (19)	33.6 (38)	0.13	29.4 (57)
Number of sex partners past 12 months	35.0 (15)	40.5 (25)	0.59	38.2 (20.5)
Number of sex partners past 3 months	6.6 (3)	11.2 (7)	0.01	9.2 (4)
Number of sex partners past month	2.5 (1)	4.6 (2)	0.02	3.7 (1)
Partner/ partnership characteristics	**No Substance use % (n) mean (median) n=320**	**Substance use % (n) mean (median) n=252**	**p-value***	**Total n=572**
Partner's age	32.9 (33)	34.1 (33)	0.12	33.5 (33)
Main partner (vs. all other types)	20.3 (67)	15.1 (38)	0.86	18.0 (105)
Partner's ethnicity is white	60.6 (200)	62.3 (157)	0.70	61.3 (357)
Met partner at bathhouse (v. all other locales)	7.3 (24)	19.1 (48)	0.02	12.4 (72)
Contact with partner occurred after diagnosis	44.7 (143)	49.2 (124)	0.84	46.7 (267)
UAI with partner	47.2 (151)	64.9 (163)	0.001	54.9 (314)
Partner HIV status				
Positive	12.5 (40)	9.9 (25)	REF	11.4 (65)
Negative	44.4 (142)	36.5 (92)	0.44	40.9 (234)
Unknown	43.1 (138)	53.6 (135)	0.50	47.7 (273)

* p-value adjusted for repeated measures using GEE

‡ for individual level, no substance use with any of the last three partners; for partner level, no substance use is with that partner

† for individual level, substance use with at least one of the last three partners: for partner level, substance use is with that partner

Table C-6: Participant and partner demographics and sexual history by substance use in manuscript 3 (n=207 individuals & 603 partnerships)

Measure	Substance Use Measure			
Individual characteristics	**No substance use‡ % (n) mean (median) n=87**	**Substance use† % (n) mean (median) n=120**	**p-value**	**Total n=207**
Age	34.0 (34)	35.6 (37)	0.20	35.0 (35)
White (vs. all other ethnicity)	65.5 (57)	73.3 (88)	0.23	70.1 (145)
Education: completed college or greater	46.0 (40)	47.5 (57)	0.83	46.9 (97)
Unemployed	25.3 (22)	34.2 (41)	0.71	30.4 (63)
Number of sex partners past 12 months	34.3 (15)	40.7 (25)	0.51	38.0 (20)
Number of sex partners past 3 months	6.6 (3)	11.2 (6.5)	0.01	9.2 (4)
Number of sex partners past month	2.5 (1)	4.5 (2)	0.03	3.6 (1)
Partner/ partnership characteristics	**No Substance use % (n) mean (median) n=338**	**Substance use % (n) mean (median) n=265**	**p-value***	**Total n=603**
Partner's age	32.8 (33)	33.8 (33)	0.21	33.1 (33)
Main partner (vs. all other types)	21.0 (71)	15.9 (42)	0.96	18.4 (113)
Partner's ethnicity is white	61.8 (209)	62.6 (166)	0.86	62.2 (375)
Met partner at bathhouse (v. all other locales)	7.1 (24)	18.5 (49)	0.02	12.1 (73)
Contact with partner occurred after diagnosis	42.6 (144)	53.6 (142)	0.34	47.4 (286)
UAI with partner	48.2 (163)	64.5 (171)	0.001	55.4 (334)
Partner HIV status				
Positive	12.7 (43)	10.9 (29)	REF	11.9 (72)
Negative	45.6 (154)	37.7 (100)	0.40	42.2 (254)
Unknown	41.7 (141)	51.3 (136)	0.68	45.9 (277)

* p-value adjusted for repeated measures using GEE

ŧ for individual level, no substance use with any of the last three partners; for partner level, no substance use is with that partner

† for individual level, substance use with at least one of the last three partners: for partner level, substance use is with that partner