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Cohort Study of Persons with Human t-cell lymphotropic virus

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Cohort Study of Persons with Human T-cell Lymphotropic Virus

by

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DISSERTATION

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Deborah A. DeVita RN MS PhDc

This dissertation includes a chapter (Chapter 3) that was accepted for publication in *BioMed Central Medical Research Methodology, 2009, 9:19.* Chapters 1 and 4 will be submitted for publication. The work that Deborah A. DeVita completed on Chapter 3, and all of the other dissertation chapters, was sufficient to meet all UCSF, Graduate Division, and School of Nursing dissertation requirements relating to the use of published data and relating to the requirements associated with the graduate student having been responsible for writing and revising the dissertation material.

Mary C. White RN MPH PhD
Dissertation Committee Chair

DISSERTATION ABSTRACT

Cohort Study of Persons with Human T-cell Lymphotropic Virus

Deborah A. DeVita

Background: The HTLV Outcomes Study (HOST) is a longitudinal prospective study of 155 HTLV-I, 387 HTLV-II and 799 HTLV seronegative persons enrolled in 1990-92 following attempted blood donation at five blood centers in the United States. The study has completed eight subject visits over 18 years and has data from health questionnaires, neurologic and lymph node examinations, and phlebotomy.

Objectives: To familiarize healthcare workers with the literature pertaining to the biological properties and the epidemiology of the HTLV viruses and present clinical and statistical information about persons in a study of HTLV.

Methods: An existing data set from HOST is used for this study. The original aims of HOST were to better define the disease outcomes and the risk factors associated with HTLV-I and -II infection, and to assess the prevalence and incidence of adult T-cell leukemia (ATL) and HTLV-associated myelopathy (HAM). The current study has three chapters. The first chapter reviews the HTLV literature to present the public health relevance and counseling recommendations for HTLV to healthcare providers. The second chapter calculates odds ratios with generalized estimated equations to analyze fixed and time-varying predictors of HOST participation. The third chapter provides some insights about the concerns and fears of persons living with HTLV.

Results: With millions of people estimated to be infected by HTLV worldwide and a lack of effective therapy, health care provider knowledge of the natural history of the virus is vital to secondary and tertiary prevention efforts.

The main findings of chapter three were that persons with higher incomes and more education were more likely to participate in study visits and men and persons of Black and other race/ethnicity were less likely to participate. In the third chapter, a majority of subjects reported specific concerns such as fear of future progression to HTLV-related disease and fear of transmitting HTLV to others.

Discussion: The clinical importance of HTLV-I and HTLV-II has been overlooked by nurses and other health care workers because it is fairly obscure, and due to confusion between HTLV and human immunodeficiency virus (HIV). While studies have shown that blood donors as a group have higher socioeconomic status, the persistent and independent influence of race/ethnicity, education and income demonstrates the continued and urgent need to develop and test strategies to encourage participation by under-represented groups. HTLV health care providers need to inquire about the fears and concerns of their patients.

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CHAPTER 1

Dissertation Introduction:

A Cohort Study of Persons with Human t-cell Lymphotropic Virus

Deborah A. DeVita RN, MS, PhDc

Dissertation Introduction :

A Cohort Study of Persons with Human t-cell Lymphotropic Virus

Human t-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are little known viruses outside of the fields of retrovirology, hematology, neurology and transfusion medicine. An ancient infection of humans, they were discovered after a long search that began in the 1950s with intensive efforts to find human counterparts to cancer-causing retroviruses of animals, helped along by the 1970s breakthrough of reverse transcriptase, and finally isolated in 1980 from the cell lines and blood of patients with adult t-cell leukemia (ATL) (Poiesz, Ruscetti, Gazdar et al., 1980; Poiesz, Ruscetti, Mier, Woods, & Gallo, 1980). The clinical importance of HTLV-I and HTLV-II has been overlooked by nurses and other health care workers because it is fairly obscure, and due to confusion between HTLV and human immunodeficiency virus (HIV).

The risk of developing either of the two diseases associated with HLTV is low (1-4%), but each has devastating outcomes. With millions of people estimated to be infected by HTLV worldwide and a lack of effective therapy, health care provider knowledge of the natural history of the virus is vital to secondary and tertiary prevention efforts.

The three major routes of HTLV transmission are mother to child, sexual contact and infected blood. The 1988 introduction of systematic blood screening in the United States greatly reduced the incidence of infection by transfusion (Schreiber, Busch, Kleinman, & Korelitz, 1996). In developing countries, however, blood transfusions remain a major risk factor of HTLV infection. Efforts to stop breastfeeding by HTLV

seropositive mothers significantly decreases transmission to children in endemic areas (Hino et al., 1997). Intravenous drug abuse and sexual activity, although amenable to prevention efforts, continue to be efficient transmitters of HTLV infection (Feigal et al., 1991; Roucoux et al., 2005)

World wide, it is estimated that roughly 5 to 10 million people are infected with HTLV-I, and several million are infected with HTLV-II (Oh & Jacobson, 2008). Blood banks, often the first line of discovery of blood borne diseases, continue to identify donors who are unknowingly infected with HTLV. Donors found to be HTLV positive receive counseling and are deferred from future donations. Researchers have used blood bank data to generate cohorts for study to follow this infection and subsequent disease. There are approximately 350 scientists from around the world who are actively studying HTLV, publishing their findings and meeting at conferences to share and disseminate information. There are two cohort studies that are actively adding to the literature about living with HTLV, although there is a lack of information on many aspects of the lives of persons living with the disease.

The cohort study that this dissertation work is based on is the HTLV Outcomes Study, known as HOST, a study of blood donors. Long-term studies of blood donors were established in the early 1990s in response to a call from the United States National Institutes of Health National Heart, Lung and Blood Institute (NHLBI) to develop a multicenter epidemiologic study of the human retroviruses HIV-1, HIV-2, HTLV-I, and HTLV-II in volunteer blood donors in the United States. The umbrella term for the five community blood banks participating in the study is REDS (Retrovirus Epidemiology Donor Study). Over the years, the REDS database has provided a framework that allows

for rapid response to research questions of critical importance to the safety of the blood supply (Zuck et al, 1995). For example, the well-developed database has provided prevalence and incidence estimates of infectious disease markers that have been key to descriptions of transfusion related risks.

The HTLV Outcomes Study (HOST) which started under REDS but is now independently funded by NHLBI, is a prospective cohort of HTLV-I and-II seropositive blood donors, with a control group of seronegative donors, designed to investigate HTLV transmission risk factors and disease outcomes. It is the only cohort study of HTLV in the United States. HOST researchers took inspiration from the Miyazaki Cohort Study (MCS), which was established in 1984 to evaluate HTLV-I infection in an endemic population in two villages in southwestern Japan on the island of Kyushu. MCS is an international collaboration between the Miyazaki Medical School and the Harvard School of Public Health, which is funded by the NCI. The HOST and MCS are long term prospective cohorts that have provided the foundation of knowledge of the natural history of HTLV.

The results of this dissertation were obtained using baseline and follow-up data from HOST. Chapter 2, a literature review of HTLV, provides the background of the importance of studying this retrovirus and differentiates it from its infamous cousin, human immunodeficiency virus (HIV). Chapter 3 is a study examining subject visit participation in HOST over the long period of follow-up of the cohort. Chapter 4 presents data on recent questions asked of HOST participants and sheds some light on the fears and concerns of persons infected with HTLV. Chapter 5 concludes the dissertation, which discusses the cohort research and implications for future study.

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CHAPTER 2

A Review of the HTLV Literature for the Health Care Provider

Deborah A. DeVita RN, MS

ABSTRACT

A Review of the Human t-cell Lymphotropic Virus (HTLV) Literature for the Nursing Health Care Provider

Background: The clinical importance of Human t-cell Lymphotropic viruses type I and type II (HTLV-I and HTLV-II) has been overlooked by nurses and other health care workers due to confusion between HTLV and human immunodeficiency virus (HIV). The risk of developing either of the two diseases associated with HLTV is low (1-4%), but each has devastating outcomes. With millions of people estimated to be infected by HTLV worldwide, and a lack of effective therapy, health care provider knowledge of the natural history of the virus is vital to prevention efforts.

Objectives: This review presents the HTLV literature pertaining to the biological properties and the epidemiology of the HTLV viruses in human populations. The goals are to present the public health relevance of studying this virus by comparing it with and contrasting it to HIV, to present the Centers for Disease Control and Prevention (CDC) recommendations for counseling HTLV-I and HTLV-II infected persons, and to describe the role of nurses in the prevention, detection and management of this virus and its sequelae.

Method: This review of the literature includes studies published in English from the discovery of the virus in the early 1980s to the present. Classic and frequently cited references are also used, including virology textbooks.

Summary: The overwhelming impact of HIV to nursing and health care providers is clear; the biologic and medical significance of HTLV, another retrovirus, is less well

known but has importance. It is a challenge to counsel or expect long term follow up in patients with a viral infection known for its long latency period and lacking definitive biomarkers. The confusion about the similarities and differences between HIV and HTLV persists in the public consciousness, and it is up to nurses and other health care providers to be informed about HTLV and be equipped to advise patients by knowing the natural history, clinical presentation and counseling guidelines.

A Review of the HTLV Literature for the Health Care Provider

The clinical importance of Human T-Lymphotropic Virus type I and type II (HTLV-I and HTLV-II) has been overlooked by physicians and health care workers. These were the first two human retroviruses discovered, type I in 1980 (Poiesz et al., 1980) and type II in 1982 (Kalyanaraman et al., 1982). In contrast to human immunodeficiency virus (HIV), the second of the two known types (HTLV and HIV) retroviruses that affects humans, HTLV-I and II are characterized by their low pathogenicity and high genomic stability (Gessain, Gallo, & Franchini, 1992). All three retroviruses are believed to have jumped the species barrier from primates, in the form of Simian T-cell Lymphotropic Virus, to humans at some point in the distant past. Once these viruses entered the human population they were transported around the world through human migration. The confusion between HIV and HTLV begin in 1983 when the cause of AIDS was ascribed to a virus first called HTLV-III. It was renamed HIV in 1986 by an international committee and recognized as a distinct entity unrelated to HTLV-I or HTLV-II. Since then, the overwhelming impact of HIV has taken attention away from the biologic and clinical significance of HTLV.

The purpose of this paper is to present the HTLV literature pertaining to the biological properties and the epidemiology of the HTLV viruses in human populations. The goals are to present the public health relevance of studying this virus by comparing it with and contrasting it to HIV, to provide evidence in support of keeping the blood supply free of HTLV and all blood-borne pathogens, and finally to present

recommendations developed by the Centers for Disease Control and Prevention (CDC) for counseling HTLV-I and HTLV-II infected persons.

Biological Properties of the HTLVs

This review begins with what is known about retroviruses in general as described primarily in recent virology textbooks and HTLV in particular from the current literature. Viruses are classified by their type of genetic material, either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). A retrovirus differs from other viruses in the way it replicates. Normally the flow of genetic material follows this sequence: DNA encodes for an RNA product which in turn can encode for a protein product. But a retrovirus, composed of a single piece of RNA encapsulated by a protein, attaches to and penetrates the cell it enters, then copies itself into a piece of DNA by going backward, or "retrograde", RNA making a piece of DNA instead of the other (and more usual) way around, thus the name "retrovirus". From there, the virus becomes part of the host chromosome and is called a provirus (a DNA copy of the retrovirus genome) and can then go through the usual DNA to RNA to protein cycle to make viral proteins and new viral particles.

Viral classification. The classification of retroviruses is based on comparisons of the size of the genome and morphologic characteristics. HTLV was formerly grouped in the genus lentivirus, (*lenti* is Latin for "slow") a group of slow viruses of the Retroviridae family, which includes HIV. They are characterized by a long incubation period and non-oncogenic properties. Relative to other retrovirus genus, lentiviruses can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. Lentivirus is still the genus name

for HIV, and although HTLV is also known for long incubation that would qualify it as a *lenti*, HTLV has the ability to induce cancer in the host organism. The more recent studies put HTLV in the subfamily Retroviridae within the genus *Deltaretrovirus* and note that it carries oncogenes in its genome (van Regenmortel, Fauquet, Bishop, & al, 2000). An oncogene normally encode proteins involved in cell growth or regulation but may foster malignant processes if mutated or activated by contact with retroviruses (Gladwin & Trattler, 2004). Since the 1970s, dozens of oncogenes have been identified in cancer. Harold Varmus and Michael Bishop won the Nobel Prize for physiology or medicine in 1989 for their contributions to the discovery of oncogenes.

Genome basics. The textbook explanation of the genome, simplified: 3 genes are universally present in the genomes of replication-competent retroviruses. The *gag* (group antigen) gene, *env* (envelope) and *pol* (polyprotein) which encode, respectively, the viral core proteins inside the envelope, the envelope glycoproteins (gp) that bind to receptors on T-cells, and the nonstructural proteins required for replication (protease, integrase and reverse transcriptase). All retroviruses possess, in their RNA genome, two ending long term repeat (LTR) sequences at either end of the viral genome. These are the sequences recognized by integrase, and that are involved in insertion into the host DNA (Gladwin & Trattler, 2004). Besides these basic properties of all retroviruses, the viruses are distinct from one another by the action of their accessory genes, unique to each, many of which have been identified, although their functions are not entirely known. HTLV contains several accessory genes that regulate genome expression or replication and are not present in simple retroviruses, particularly *tax* or transactivating protein, thought to be involved in leukemic transformation and other pathologic effects of the virus.

Biologic features. HTLV-I and –II are closely related C-type human complex delta retroviruses (genus) of the family Retroviridae. The two types have a similar genome structure and share approximately 70% nucleotide sequence homology (Feuer & Green, 2005). They have a single-stranded RNA genome that is approximately 8,900 base pairs in length. The HTLV-I and-II genomes encode structural proteins, including core proteins (p)19 and p24, as well as envelope proteins gp46 and p21e. Like other human replication-competent retroviruses, HTLV-I and -II encodes a *pol* gene for a reverse transcriptase to allow transcription of its RNA genome into a complementary DNA strand that is then incorporated into the host genome by an HTLV-encoded integrase. There is also a protease gene for an enzyme responsible for cleaving the large precursor proteins into the smaller structural subunits of the *gag* (viral core) and *env* (envelope) regions. The virus also includes a transactivator *tax* gene that induces viral replication under certain circumstances. Other genes such as *rex* influence the balance of transcription between structural and regulatory gene products (Gladwin & Trattler, 2004).

Comparison of the HTLVs to HIV, from (Beilke & Murphy, 2006). Although HTLV-I and -II are only distantly related to HIV, they share a number of biologic properties. Viruses from both groups preferentially infect T lymphocytes, with the CD4+ cell as primary host for HIV and HTLV-I and CD8+ cell as primary host for HTLV-II, although B cells, endothelial cells, glial cells and monocytes can also be infected (Levy et al., 1985). A major difference is that in vitro HTLV-I and HTLV-II induce neoplastic transformation and cell proliferation, whereas HIV infection causes cell death (HIV destroys T-lymphocytes, ultimately resulting in devastating immunodeficiency, while HTLV-I causes CD8+ cells to proliferate).

HTLV-I and -II can be differentiated from HIV morphologically (Orenstein, 1992). HIV has a bullet-shaped nucleocapsid, while the HTLV viruses contain a central round nucleocapsid structure, characteristic of delta retroviruses.

The genomes of HTLV-I and HTLV-II also share some distinctive features with HIV. The overall genetic structure of the three viruses is similar, in that they contain the structural (*gag, env*) and enzymatic (*pol, pro, in*[tegrase]) genes (Matsuoka, 2003). The principle differences reside in the characteristics and function of the non-structural genes. HIV possesses a number of accessory genes that facilitate viral replication within host cells at very high levels (Haseltine, 1991). HIV has a very high replication error rate, leading to HIV strains resistant to reverse transcriptase inhibitor medications. This heterogeneity protects the virus from the human immune system and vaccine induced antibodies. These accessory genes are lacking in the HTLVs.

Viral replication. Retroviruses follow the same general steps in their replication cycles that are common to other viruses (i.e., attachment, penetration, uncoating, replication, assembly, release and maturation). The steps that differ from other viruses involve the retroviral reverse transcriptase, an enzyme discovered simultaneously by Howard Temin and David Baltimore in 1970 for which they were awarded the Nobel Prize in 1975. Reverse transcriptase converts the single-stranded, positive-polarity RNA genome of a retrovirus into double-stranded DNA, thereby reversing the typical flow of genetic information (which is from DNA to RNA). The DNA copy is transported into the nucleus of the host cell, circularized, and integrated into the host chromosome (Varmus, 1982).

The initial targets of HTLV-I and -II infections are mucosal surfaces, just as for HIV. Beyond initial sites of viral replication, it is presumed that initial infection occurs locally within the regional lymphatics. The resulting infection is capable of inducing malignant, autoimmune, and neurological illnesses. A latent infection, in which the virus is dormant, or persistent infections, in which low-levels of the virus are continuously produced, is also possible. These capabilities explain the life-long nature of retroviral infections, and render the diseases induced by HTLV extremely difficult to treat (Varmus, 1982).

Viral load. Because there are no validated biomarkers of disease for HTLV, viral load has the most data supporting its relationship with possible disease course (Oh & Jacobson, 2008). Viral load is a measure of the severity of a viral infection and can be calculated by estimating the amount of viral RNA in an involved body fluid. Health care providers are familiar with viral load as an indicator of progression of disease and the effectiveness of antiviral drug therapy against deadly viruses, such as HIV, hepatitis B (HBV), and hepatitis C (HCV). It is known that asymptomatic HIV-infected people with high viral loads progress to clinical AIDS faster than individuals with low viral loads. In HIV viral load can be measured in plasma, CSF, genital secretions and breast milk, but in HTLV the virus cannot be detected in cell-free fluids as the virus is highly cell-associated, therefore studies have focused on HTLV proviral load in peripheral blood mononuclear cells (PBMCs). HTLV-I proviral load is determined as the amount of integrated HTLV provirus, measured by real-time quantitative polymerase chain reaction (PCR) assay and typically expressed as the number of copies of HTLV-I proviral DNA per number of PBMC (Oh & Jacobson, 2008).. The relationship between proviral load

and pathogenesis for HTLV-I and -II is not well understood, although increased proviral load is associated with disease progression with HTLV-I infection (Nagai et al., 1998), (Ono et al., 1998) in (Lee, Chafets, Busch, & Murphy, 2004). Three studies have found that persons with HTLV-I and HAM have significantly higher viral loads than those without HAM (Manns et al., 1999), (Nagai et al., 1998), (Orland et al., 2003). In one recent study, the data do not support the hypothesis that HTLV-I or -II proviral load increases over time in infected humans. Instead, the data suggest that the chronic level of proviral load in each individual is established at a specific set point, perhaps due to immunologic response or the infectious dose of the virus (Kwaan et al., 2006).

Serologic detection. HTLV-I and -II infection may be diagnosed by tests detecting the presence of specific anti-HTLV-I and -II antibody. In the United States, the most widely used test is the enzyme immunoassay (EIA), which has high sensitivity and specificity but does not distinguish between HTLV-I and HTLV-II (due to cross-reactive antibodies) (Madeleine et al., 1993). EIA is the screening test; a specimen initially reactive by EIA is retested in duplicate to minimize the chance that reactivity is due to technical error. Specimens that are reactive in either of the duplicate tests are considered repeatably reactive. Specimens that do not react to either of the duplicate repeat tests are considered nonreactive (CDC, 1988). Repeat reactive EIA screened specimens are followed by Western Blot (WB) or immunofluorescence (IFA) testing to confirm the presence of antibodies and differentiate between HTLV-I and –II.

The presence of antibodies to HTLV-I or HTLV-II indicates that a person is infected with the virus. It is known that infection with HTLV-I results in development of antibodies within 1 to 2 months, after which levels of antibody persist at a stable level for

life (Okayama et al., 1991). Comparable data on HTLV-II antibodies have not been established.

Natural History of Retroviruses

In many animal species, retroviruses are the etiologic agents of leukemias and lymphomas (Teich N, 1985) in (Pierik & Murphy, 1991). The discovery during the 1950s of mammalian retroviruses triggered intensive efforts to find human retroviruses. In 1970, Howard Temin and David Baltimore discovered the RNA-to-DNA transcription of retroviruses (Temin, 1970).This discovery led the way to finding other retroviruses by following the path of reverse transcriptase (Edlich, Arnette, & Williams, 2000). By the mid-1970s, retroviruses had been discovered in many vertebrate species, including apes. The hypothesis that humans may also be infected with retroviruses led to a search that ultimately resulted in the isolation of a retrovirus from the cell lines and blood of patients with adult T-cell leukemia. That retrovirus was HTLV-I, first isolated in 1980 by Drs. Bernard Poiesz and Francis Ruscetti and their co-workers in the laboratory of Robert Gallo at the National Cancer Institute (NCI), from a viral sample from Luc Montagnier's group at the Pasteur Institute in Paris. A second, closely related virus, HTLV-II, was found in 1982 in a patient with a somewhat different disease, a T-cell variant of the relatively benign hairy cell leukemia (Kalyanaraman et al., 1982).

In the early days of the AIDS epidemic, HTLV-I was hypothesized to have been etiologically associated with AIDS. In 1983 the cause of AIDS was ascribed to a virus which was examined in three different locales and given three different names: Lymphadenopathy virus (LAV) by Luc Montagnier's lab at the Pasteur Institute in Paris, AIDS Related Virus (ARV) independently identified by Jay Levy at the University of

California San Francisco, and HTLV-III by Robert Gallo at the NCI in 1984. This virus appears to have come from a sample sent to Gallo's lab from Montagnier's lab. Although the hypothesis of an etiological association between HIV and HTLV was later proved incorrect, the technology gained through the study of the HTLVs led directly to discovery of the responsible agent, HIV (Pierik & Murphy, 1991). For example, almost identical methods for isolation of HTLV-I were used for the isolation of HIV (Takatsuki, 1995).

HTLV is closely related to primate T-lymphotropic viruses, and is thought to be an ancient infection of humans. The viruses are found in different groups of people around the globe, although each virus is concentrated more in some geographic locations than others. HTLV-I is found mostly in Southern Japan, the Caribbean basin and in some regions of Africa and the Americas. HTLV-II is found primarily among injection drug users and their sexual partners in the United States and Europe with prevalence estimates ranging from 3-18% (Khabbaz et al., 1992). Both HTLV-I and HTLV-II are also found among sex partners and children of people who are infected with the virus (Murphy, Watanabe et al., 1999). HTLV-II is endemic in certain North (Hjelle et al., 1994), Central (Reeves et al., 1990), and South American Indian tribes (Maloney et al., 1992) with prevalence estimates ranging from 2-30% (Vitek et al., 1995); some of the highest seroprevalence estimates are documented in tribes with the least contact with contemporary civilization. This has led to the hypothesis that HTLV-II was already endemic in these tribes before they migrated across the Bering land bridge over 10,000 years ago.

The Importance of Blood Banks in the Epidemiology of HTLV. In the early 1980s, blood transfusion was identified as a major source of HIV transmission. The first report

of the transmission of AIDS by transfused blood appeared in December 1982 (CDC, 1983). However, there was a technology gap between the time HIV was identified and the time an HIV antibody test was developed. In March 1985, an enzyme-linked immunosorbent assay (ELISA) for HIV antibodies was licensed for use in screening blood donors. As the risks HIV posed to the blood supply became clarified, evidence emerged that HTLV was also transmitted by transfusions (Okochi, Sato, & Hinuma, 1984). Then, following a gap in time from virus identification to antibody test, blood donations in the U.S. were screened for antibodies to HTLV-I and HTLV-II starting in November 1988 (Zuck et al., 1995).

After the introduction of antibody screening, the risk of acquiring one of the four major blood-borne viruses (HIV, HTLV, HCV, HBV) following transfusion declined. The risk continues to decline with the use of new and more sensitive viral-antigen or nucleic acid screening tests. Using data from five U.S. blood centers between 1991 and 1993, the risk was estimated to be 1 in 641,000 for HTLV-I or -II, 1 in 493,000 for HIV, 1 in 103,000 for hepatitis C, and 1 in 63,000 for hepatitis B (Schreiber, Busch, Kleinman, & Korelitz, 1996). As of 2003 the transfusion related risks declined even further: 1 in 2,993,000 for HTLV-I or-II, 1 in 1,215,000 for HIV, 1 in 1,935,00 for HCV and 1 in 205,000 for HBV (Pomper, Wu, & Snyder, 2003).

The sensitivity and specificity of testing for viruses in donated blood products has greatly improved in the last decade. The 1999 licensed nucleic acid testing (NAT) is a good example. The NAT system is capable of detecting more infectious donations because it detects viral RNA rather than antibodies or antigens. Detection of viral RNA permits detection earlier in the infection since the appearance of antibodies requires time

for the donor to develop an immune response, and since the detection of antigens requires time for a higher level of virus to appear in the bloodstream. NAT of all U.S. blood donors has further reduced the risk of transfusion-transmitted HIV and hepatitis C, but NAT has not been introduced for HTLV-I or –II, probably because current NAT systems test plasma and not white cells, and because the disease risk of HTLV-I and –II is underappreciated (Beilke & Murphy, 2006).

Every year blood banks discover donors who are unknowingly infected with HTLV. Long-term studies of blood donors were established in the early 1990s in response to a call from the National Heart, Lung and Blood Institute (NHLBI) to develop a multicenter epidemiologic study of the human retroviruses HIV-I, HIV-2, HTLV-I, and HTLV-II in volunteer blood donors in the United States. The umbrella term for the five community blood banks participating in the study is REDS (Retrovirus Epidemiology Donor Study). Over the years, the REDS database has provided a framework that allows for rapid response to research questions of critical importance to the safety of the blood supply (Zuck et al., 1995).

The HTLV Outcomes Study (HOST), started under REDS but now independently funded by NHLBI, is a prospective cohort of HTLV-I and II seropositive blood donors, with a control group of seronegative donors, designed to investigate HTLV transmission risk factors and disease outcomes. It is the only cohort study of HTLV in the United States. HOST researchers took inspiration from the Miyazaki Cohort Study (MCS), which was established in 1984 to evaluate HTLV-I infection in an endemic population in Southern Miyazaki Prefecture on the island of Kyushu in Japan. MCS is an international collaboration between the Miyazaki Medical School and the Harvard School of Public

Health, which is funded by the NCI. HOST and MCS have provided a foundation of knowledge of the natural history of HTLV.

Prevalence estimates. World wide, it is estimated that roughly 15 to 25 million people are infected with HTLV-I (de The & Kazanji, 1996) and several million are infected with HTLV-II. Numbers of HTLV-II infected persons are only an approximation. Population-based prevalence estimation tools such as the Center for Disease Control's National Health and Nutrition Examination Survey have not thus far included measurements of HTLV prevalence (Orland et al., 2003). In 2003 the principal investigator of HOST estimated that there are approximately 46,000 persons with HTLV-I and 220,000 with HTLV-II infection in the United States (Orland et al., 2003). This estimate was based on the prevalence of infection among blood donors, injection drug users (IDU), American Indians and other specific populations.

Modes ofTransmission. The primary routes of HTLV-I and -II transmission include: from mother to child primarily via ingestion of infected lymphocytes in breast milk; through sexual intercourse with probably lower efficiency than for HIV; and via contaminated blood or cellular blood products through transfusion or by contaminated needles among IDU. Risk factors related to the primary routes are environmental (e.g., birthplace and/or ancestry in a viral endemic area, blood transfusion prior to the institution of HTLV antibody screening of donors) and sexual (e.g., having large numbers of male sexual partners, a steady sexual relationship with a seropositive partner, or being coinfected with a sexually transmitted disease) (W. Blattner, 1990).

Mother to child. Vertical transmission, and mostly through breast-feeding (ingestion of milk-borne lymphocytes) contributes to the high seroprevalence rates

observed in HTLV-I and -II endemic populations (Hino et al., 1985). The duration of breast-feeding appears to be important, suggesting a possible dose effect (Wiktor et al., 1997). High maternal HTLV-I antibody titer and HTLV-I proviral load have also been associated with transmission (Wiktor et al., 1997), (Ureta-Vidal et al., 1999). In Japan, efforts to eliminate breastfeeding by seropositive mothers or at least reduce its duration to less than 6 months may significantly reduce HTLV-I transmission to children (Hino et al., 1997). Few studies have focused on mother to child transmission of HTLV-II, but the virus has been isolated from breast milk of infected mothers, and children born to infected mothers have a higher seropositivity compared with those born to seronegative mothers (Vitek et al., 1995), (Heneine et al., 1992). In the absence of breast-feeding, several studies have indicated that the risk of perinatal transmission of HTLV-II is quite low, suggesting that the predominant source of infection occurs via breast-feeding (Kaplan et al., 1992), (D. Gallo, Petru, Yeh, & Hanson, 1993).

S*exual Transmission.* Sexual transmission of HTLV-I has been well-documented by cross-sectional studies showing higher sexual activity to be a risk factor, studies of discordant couples, and prospective observation of seroconversion in sexual partners of known HTLV-I seropositives (Kajiyama et al., 1986), (Murphy, Figueroa et al., 1989), (Iga et al., 2002). HTLV-I carriers infect their spouses at low rates; however, longer termed relationships and lower rates of condom use were associated with increased transmission efficiency (Iga et al., 2002). Another study showed no difference in male to female versus female to male transmission for both HTLV-I and-II (Roucoux & Murphy, 2004). In contrast to HTLV-I, sexual transmission of HTLV-II has been less well studied, but cross-sectional studies have identified sexual transmission of HTLV-II as an

important route of infection in several populations, including Native Americans, blood donors, patients attending sexually transmitted disease clinics, and prostitutes. (Beilke & Murphy, 2006).

Blood-borne Transmission. In both HTLV-I and-II, blood transfusion is a very efficient mode of transmission, requiring preventive measures from blood banks. Among blood donors found to be infected with HTLV-I or -II soon after the initiation of blood screening in the U.S. in 1988, previous receipt of a blood transfusion was significantly more common than in HTLV-seronegative controls (Schreiber et al., 1997), (Eble, Busch, Guiltinan, Khayam-Bashi, & Murphy, 1993). Transmission of HTLV-I/II by blood transfusion occurs with transfusion of cellular blood products (i.e., whole blood, red blood cells, and platelets) but not with the plasma fraction or plasma derivatives from HTLV-I infected blood (CDC, 1993). The probability of transmission from red blood cells appears to diminish with longer product storage (Sullivan et al., 1991) (Donegan et al., 1994).

Injection Drug Use (IDU). Both HTLV-I and-II are clearly transmitted by drug injection, presumably via blood contamination of shared needles and syringes (Beilke & Murphy, 2006). HTLV-I is not common among IDUs in the areas where type I is concentrated (i.e., Southwestern Japan, the Caribbean basin and Central Africa), perhaps because injection drug use is not widespread in those regions. HTLV-II is currently more prevalent among IDUs in the U.S., Italy, Spain, Brazil and Argentina than HTLV-I (Gotuzzo, 2000).

While HIV and HTLV viruses share common modes of transmission, the dynamics of transmission differ for each virus. HIV probably gained a foothold in the

U.S. during the 1970s (Hessol et al., 1989) and rapidly increased in risk groups such as men who have sex with men (MSM) and IDU. HTLV-II has apparently infected injection drug users but not MSM since the 1960s, and increased steadily in that risk group until HIV prevention measures took hold. HTLV-II is highly prevalent among certain populations of IDU and is associated with long duration of heroin injection, suggesting transmission of this virus through the practice of needle sharing (Feigal et al., 1991). Evidence supporting these transmission modes for HTLV-I and HTLV-II has accumulated primarily through cross-sectional and family studies in humans.

Diseases Associated with HTLV-I

From its discovery, HTLV-I was associated with adult t-cell leukemia/lymphoma (ATLL), (Poiesz et al., 1980; Yoshida, Seiki, Yamaguchi, & Takatsuki, 1984) and subsequently with HTLV-I associated myelopathy/ tropical spastic paraparesis (HAM/TSP), uveitis, polymyositis, synovitis, thyroiditis, and bronchoalveolar pneumonia (Beilke & Murphy, 2006). The two most important diseases most discussed in connection to HTLV-I are ATLL and HAM/TSP.

ATLL. ATLL is endemic in some regions of the world, especially in southwestern Japan (Tajima, 1990), the Caribbean islands (W. A. Blattner et al., 1982), (Catovsky et al., 1982), and parts of Central Africa, South and Central America (R. C. Gallo, Blattner, Reitz, & Ito, 1982) and Iran (Safai et al., 1996), (Abbaszadegan et al., 2003). More than 700 cases of ATLL are diagnosed each year in Japan alone (Yamaguchi & Watanabe, 2002). Despite this wide geographical distribution, reliable data concerning prevalence and incidence are available mostly from Japan, some Caribbean areas and Brazil (Mahieux & Gessain, 2003).

ATLL is an aggressive malignancy of mature CD4+, CD25+ T-lymphocytes. It is a spectrum of diseases that is generally categorized in four forms: acute, chronic, smoldering and lymphoma-type. Acute and lymphoma types each account for >40% of all ATLL (Manns et al., 1993). One of the distinguishing characteristics that led to the discovery of this disease entity is the presence of "flower cells", i.e., lymphocytes with convoluted, cleaved nucleus, in the peripheral blood. Flower cells are most commonly seen in acute ATLL, but are present also in other subtypes at a low level. Another hallmark of ATLL is the presence of cutaneous involvement (skin lesions) in over one-third of the cases (Beilke & Murphy, 2006).

ATLL develops after a long incubation period, with an estimated lifetime risk of approximately 2-4% in individuals infected before the age of 20 (Murphy, Hanchard et al., 1989). Males appear to be at an increased risk of ATLL as compared to women (Hisada, Okayama, Spiegelman, Mueller, & Stuver, 2001), (Arisawa et al., 2000) in the Japanese. However, this trend is not evident in the Black population in the Caribbean basin and Brazil. The risk of acquiring ATLL appears to be greatest in individuals who acquire HTLV-I via mother-to-child transmission (Maguer, Casse-Ripoll, Gazzolo, & Dodon, 1993), (Wilks et al., 1993).

ATLL presents a wide range of clinical diversity, making the diagnosis difficult at the onset of the disease (Mahieux & Gessain, 2003). In a study of 187 patients with ATLL (Takatsuki, 1995), the predominant physical findings were peripheral lymph node enlargement (72%), hepatomegaly (47%), splenomegaly (25%) and skin lesions (53%). Other findings at onset were abdominal pain, diarrhea, pleural effusion, ascities, cough, sputum and an abnormal shadow on chest x-ray. Hypercalcemia is a common

complication (Edlich et al., 2000), (Kiyokawa et al., 1987). Diagnostic criteria have been defined as: 1) Histologically and/or cytologically proven lymphoid malignancy with t-cell surface antigens, mostly CD2, CD3, and CD4 + 2) Abnormal T-lymphocytes always present in the peripheral blood, except in the lymphoma type of ATLL. These abnormal T-lymphocytes include not only typical ATL cells, but also the small immature T-lymphocytes with incised or lobulated nuclei that are characteristic of the chronic or smoldering type ("flower-cells") 3) Antibodies to HTLV-I must be present in the patient serum at diagnosis (Mahieux & Gessain, 2003; Takatsuki, 1995).

The survival rate of ATLL patients, especially those who develop the acute leukemic or lymphomas forms, is very poor (Mahieux & Gessain, 2003). Treatment of ATLL using conventional lymphoma chemotherapy has limited benefit, but treatment with alpha interferon and zidovudine (AZT) has shown promise (Hermine, Wattel, Gessain, & Bazarbachi, 1998), (Bazarbachi & Hermine, 2001), (Siegel, Gartenhaus, & Kuzel, 2001) in (Mahieux & Gessain, 2003).

HAM/TSP. Epidemiologic evidence suggests sexual transmission is the predominant mode of transmission leading to the later development of HAM/TSP (Maloney et al., 1998) (Kramer et al., 1995) in (Beilke & Murphy, 2006).The majority of patients are females aged 40-50. It is a chronic inflammatory disease of the central nervous system usually characterized by the development of slowly progressive spastic paraparesis, often associated with a neurogenic bladder (Edlich et al., 2000). The initial symptoms are typically back pain, gait disturbance, and bladder/bowel or sexual dysfunction (Oh & Jacobson, 2008). Complaints of burning, pins and needles, cramps, numbness, and tingling exist in approximately 50% of the cases (Beilke & Murphy,

2006). Clinical signs include weakness of the legs, spasticity, hyperreflexia, gait ataxia, and loss of vibratory sense (Oh & Jacobson, 2008). The principle disability is weakness and spasticity of the lower legs, and patients will frequently require a walker or a wheelchair (Beilke & Murphy, 2006). The most prominent pathologic feature includes chronic inflammatory changes in the spinal cord, most notably a meningomyelitis of the lower thoracic cord (Beilke & Murphy, 2006). HAM/TSP can be misdiagnosed as multiple sclerosis; other differential diagnosis include hereditary spastic paraplegias, degeneration due to vitamin B12 deficiency myelopathy, syphilis and Lyme disease (Oh & Jacobson, 2008).

There is no definitive therapy to alter long-term disability associated with HAM/TSP. Clinical improvements have been reported with corticosteroids, plasmapheresis, danazol (Harrington et al., 1991), pentoxifylline (Shirabe et al., 1997), and interferon (Oh & Jacobson, 2008). There is a controversy over the efficacy of antiviral nucleoside analog drugs like AZT (zidovudine and lamivudine), which could possibly help in reducing viral replication and associated direct cell injury. In one study, in a randomized, double-blind, placebo-controlled study of 6 months of combined therapy with zidovudine and lamivudine in 16 patients there was no significant change in HTLV-I proviral load and no significant clinical changes (Taylor et al., 2006). The authors admit that irreversible nerve damage in patients with a long clinical history could explain the lack of clinical improvement, and that nucleoside analogs may not act against HTLV-I reverse transcriptase. In a second study, an analysis of 20 ATLL patients in Iran reported a high response rate and potentially prolonged survival with minimal side effects using zidovudine (AZT) and interferon (Kchour et al., 2007).

Diseases Associated with HTLV-II

Whereas both ATLL and HAM/TSP are associated with HTLV-I, only HAM/TSP is found in persons with HTLV-II. In HOST, the signs and symptoms of HAM (HAM/TSP is called HAM when seen outside of tropical areas) with HTLV-II are milder, and the patients have viral loads that are the same or lower than patients with HAM and HTLV-I (Orland et al., 2003). Other possible disease associations with HTLV-II need more research. HOST cohort data have demonstrated an association between HTLV-II and an increased incidence of pneumonia, bronchitis, tuberculosis, bladder or kidney infection, and skin abscess (Murphy et al., 1997), (Murphy, Glynn et al., 1999), (Murphy et al., 2004), (Modahl, Young, Varney, Khayam-Bashi, & Murphy, 1997). These findings need to be replicated by other long-term cohort studies.

Health Care Approach to HTLV

In the U.S., blood donation is the primary way persons with HTLV are identified. Approximately 2,000 HTLV-I/II –infected volunteer blood donors were identified in 1988, the first year of blood donor screening in the United States; approximately one half are infected with HTLV-I and one half with HTLV-II (CDC, 1990). These donors are counseled and permanently deferred from donating blood. Other HTLV seropositive persons may be identified in the clinical setting during sperm or egg donation in fertility clinics, or in the differential diagnosis for leukemia (to rule out ATLL) or lower limb paralysis (to rule out HAM). Regardless of the mode of discovery, health care providers may come in contact with persons seropositive for HTLV-I or-II and should be informed about HTLV screening tests, the natural history of the virus and the clinical presentation

of HTLV- related disease, to know how to recognize the manifestations of this infection in order to correctly diagnose them and offer their patients appropriate guidance and treatment.

It is important to know which type of HTLV an individual has since HTLV-I and HTLV-II are each associated with slightly different transmission rates and disease outcomes. Initial screening tests for HTLV, done by ELISA, are generally not specific for HTLV-I or HTLV-II, but instead test for the presence of antibodies to either virus. Confirmatory testing is needed to determine the viral type. Provirus amplification by PCR, some Western Blot (WB) tests or Immunofluorescence (IFA) may be needed to differentiate between HTLV-I and HTLV-II, but occasionally they cannot (indeterminate test result). The vast majority of people with indeterminate western blot results are not infected with HTLV-I/II. In a small percent of cases (<2%), a person may have been recently infected with HTLV-I/II and are in the process of seroconverting (i.e., the test cannot adequately detect the presence of antibody in serum yet). However, most of these individuals have known risk factors for HTLV, or have had recent high-risk drug use or sexual behaviors. Persons without risk factors testing indeterminate on one occasion should be offered retesting in 3 months. If they have the same test result, they should be reassured they that are unlikely to be infected with HTLV-I or -II.

After seropositivity and viral type have been established, there are several frequently asked questions that health care providers should be prepared to answer. The reassuring information to convey is that HTLV-I or -II is not HIV, it is not spread by casual contact, and that most infected persons are healthy, asymptomatic carriers. The lifetime risk of developing either ATLL or HAM is low, under 5% (Oh & Jacobson,

2008) depending on mode of transmission and other factors. The negative information is that it is a lifelong infection, and that, because it is transmissible by blood, infected persons can no longer donate blood or be an organ donor.

Why some people with HTLV-I/II develop disease and others do not is unknown. Currently, there are no tests that allow us to predict which people with HTLV-I/II will become ill and which people will not. There is no known way to reduce the risk of developing disease, but it is important to remember most people infected with HTLV-I or HTLV-II live without serious health problems caused by these viruses.

Another frequent asked question is "how did I get HTLV?", especially if a person knows that they have no link to an endemic area, never received a transfusion or shared a needle. They can be told that sometimes the virus spreads outside of recognized risk groups. Many people do not realize that they had a blood transfusion in the past, or that a previous sex partner was HTLV positive.

Becoming pregnant is not contraindicated by HTLV seropositivity. There is current information on ways to minimize vertical transmission. Because of the high rate of mother to child transmission of HTLV-I among children breast-fed for longer than 3-6 months, many studies have advised HTLV-I carrier mothers to bottle feed their infants. Alternatives to breast-feeding would need to be discussed.

CDC recommendations for counseling. These recommendations, written in 1993 with revisions in 1998, were developed by CDC and a U.S. Public Health Service working group for counseling HTLV-I and HTLV-II infected persons. The website can be found at: wonder.cdc.gov/wonder/prevguid/p0000295/p0000295.asp

Persons found to be seropositive for HTLV-I or HTLV-II by confirmatory testing should be informed that they are infected with HTLV-I. They should be told that HTLV-I is not the AIDS virus, that it does not cause AIDS, and that AIDS is caused by a different virus called HIV. They should be told that HTLV-I is a lifelong infection. They should be given information regarding modes and efficiency of transmission, disease associations, and the probability of developing disease. In particular, persons infected with HTLV-I should be advised to: share the information with their physician, refrain from donating blood, semen, body organs or other tissues; refrain from sharing needles or syringes with anyone, refrain from breast-feeding infants; consider the use of latex condoms to prevent sexual transmission.

If the HTLV positive person is in a mutually monogamous sexual relationship, testing of the sex partner should be recommended to help formulate specific counseling advice. If the sex partner is also positive, no further recommendations are indicated. If the sex partner is negative, the couple should be advised that the use of latex condoms can help prevent transmission of HTLV-I or II to the negative partner, male or female. Male-infected, female-noninfected couples desiring pregnancy should be made aware of a finite risk for sexual transmission of HTLV-I during attempts at pregnancy, and of a small risk of vertical transmission from mother to infant unrelated to breast-feeding. Such couples might be advised to use latex condoms at all times except the fertile period while attempting pregnancy. The use of latex condoms is strongly recommended for HTLV-I positive individuals with multiple sex partners engaging in non-mutually monogamous sexual relationships. These individuals should be reminded of the risk for acquiring other sexually transmitted infections, including HIV.

In addition to those recommendations provided by the CDC, other considerations are appropriate. A periodic medical evaluation by a physician knowledgeable about these viruses is recommended. This evaluation should include a physical examination, including examination of the lymph nodes and spleen, and a complete blood count (CBC) with differential.

An HTLV-seropositive patient may have emotional issues (i.e., feeling stigmatized as socially undesirable by having a life-long infection, fear of the future in regards to the progression to HTLV-related disease, fear of transmitting the virus to others) that require some understanding by the health care provider. For blood donors who receive unexpected notification of abnormal laboratory results, lasting psychological stress may be one unfortunate outcome of their altruistic act (Guiltinan et al., 1998). Psychological stress has been identified as a cofactor for many serious health problems such as cardiac illness (Daubenmier et al., 2007) the progression of cancer (Reiche, Nunes, & Morimoto, 2004), (Armaiz-Pena, Lutgendorf, Cole, & Sood, 2008), and immune-related diseases (i.e, viral infections, chronic auto-immune diseases and tumors) (Kemeny & Schedlowski, 2007). The health care provider can let seropositive patients know that you understand the issues of a life-long infection with a little known virus. For many of these HTLV-seropositive patients, you may be one of the few in their lives that they can talk openly with about having the infection and what it is like for them. Be prepared to listen with acceptance and without judgment, and refer to psychotherapy if needed to help contain feelings of fear or shame.

In conclusion, the confusion about the similarities and differences between HIV and HTLV persists in the public consciousness, and it is up to health care providers to be

informed about the HTLVs and be equipped to advise patients by knowing the natural history, clinical presentation and counseling guidelines. It is a challenge to counsel or expect long term follow up in patients with a viral infection known for its long latency period and lacking definitive biomarkers. Seropositive persons can be encouraged to take an interest in their status as a carrier of a little-known virus by working with their primary care physician to schedule yearly neurologic examinations and CBCs.

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CHAPTER 3

Determinants of Subject Visit Participation in a Prospective Cohort Study of HTLV Infection

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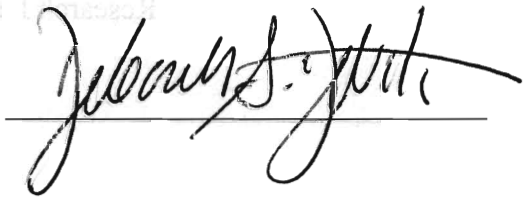
AUTHORSHIP NOTE

This paper was submitted in publication form with additional authors, including E. Murphy, the principal investigator for HOST, whose data were used in the analysis; Z. Kaidarova, the HOST statistician who produced the analytic dataset from SAS files created by the Westat Corporation in 1991-2004; X. Zhao who advised on statistical methods, and M.C. White who is my faculty advisor and advised me on the statistical analysis and interpretation of the data.

The paper, however, is my work. The idea for the research question came directly from my work managing the HOST prospective cohort and my struggles to get subjects to continue or renew their participation every two years over a long time period. I wanted to write a paper that would help me to understand how to deal with repeated measures and missing data, and that would allow me to analyze the differences in the behaviors of the seropositive and seronegative cohort subjects.



ABSTRACT

Background: Understanding participation in a prospective study is crucial to maintaining and improving retention rates. In 1990-92, following attempted blood donation at five blood centers, we enrolled 154 HTLV-I, 387 HTLV-II and 799 HTLV seronegative persons in a long-term prospective cohort. Health questionnaires and physical exams were administered at enrollment and 2-year intervals through 2004. To examine factors influencing attendance at study visits of the cohort participants we calculated odds ratios (OR's) with generalized estimated equations (GEE) to analyze fixed and time-varying predictors of study visit participation.

Results: There were significant independent associations between better visit attendance and female gender (OR=1.31), graduate education (OR=1.86) and income > $75,000 (OR=2.68). Participants at two centers (OR= 0.47, 0.67) and of Black race/ethnicity (OR= 0.61) were less likely to continue. Higher subject reimbursement for interview was associated with better visit attendance (OR= 1.84 for $25 vs. $10). None of the health related variables (HTLV status, perceived health status and referral to specialty diagnostic exam for potential adverse health outcomes) significantly affected participation after controlling for demographic variables.

Conclusions: Increasing and maintaining participation by minority and lower socioeconomic status participants is an ongoing challenge in the study of chronic disease outcomes. Future studies should include methods to evaluate attrition and retention, in addition to primary study outcomes, including qualitative analysis of reasons for participation or withdrawal.

Determinants of Subject Visit Participation in a Prospective Cohort Study of HTLV Infection

BACKGROUND

Understanding participation in a prospective study is crucial to maintaining and improving retention rates [1, 2]. A high participant loss rate will impact the ability to draw valid conclusions. This is particularly relevant in longitudinal studies where loss of data points within or between visits can distort the relationships between measurements [3, 4]. Many strong predictors of attrition, such as health problems and socioeconomic factors [5], race/ethnicity [6], and substance abuse [7] have been explored in efforts to develop strategies to maintain participation in a long term cohort study. Most studies evaluate retention by employing a survival approach, looking at the time to loss to follow-up; some have explored positive and negative predictors of retention in long-term prospective studies using mixed model statistical techniques [8]. But few have examined drop-out of study participants followed by return after missing at least one visit. Although newer statistical techniques allow analysis of data with missing data points, minimization of attrition still remains important for drawing valid research conclusions [9].

The purpose of this paper was to examine factors influencing the continued or renewed participation of subjects in a prospective longitudinal cohort study of human T-cell lymphotropic virus (HTLV) outcomes. By analyzing the large HTLV Outcomes Study (HOST) data set, we had the opportunity to investigate some uncommon but

possible reasons for long-term study participation. The HTLV positive donors, with matched controls, followed in HOST since the early 1990s, permitted the examination of three research questions: first, does diagnosis with a relatively obscure virus in healthy adults impact study retention; second, does poorer health status influence participants to continue in a study, and third, does referral for specialty physician diagnostic examination, an indication of possible development of HTLV-associated disease or other adverse health outcome, contribute to long-term study enrollment. Our hypothesis was that healthy persons diagnosed with HTLV would be more likely to continue in a longitudinal study that included regular health assessments compared to HTLV negative controls. Further, we hypothesized that changes toward poorer health status regardless of HTLV status would increase the likelihood of staying in or reengaging in the study.

METHODS

Sample. Beginning in 1990 through 1992, 154 HTLV-I seropositive, 387 HTLV-II seropositive and 799 seronegative participants were enrolled from populations of blood donors from five sites across the United States. Participants were aged 18 and older, testing either positive or negative for HTLV at the time of attempted donation. HOST data have been the source of many publications on the transmission, natural history and health outcomes of HTLV infection [10-15]. HOST is an extension of the cohort enrolled previously under the Retrovirus Epidemiology Study (REDS) and the details of HOST study design have been described elsewhere [16].

To improve the comparability of the groups, seronegative subjects were matched to HTLV seropositive subjects by age (5 year groups), sex, race/ethnicity, type of blood donation (whole blood, autologous or platelet pheresis) and blood center. A ratio of 1.5 seronegatives to HTLV seropositives was attempted, anticipating lower follow-up success with seronegative subjects. All participants were HIV seronegative. The HOST cohort included some sexual partners of HTLV seropositive donors, but they are excluded from analysis in this paper.

Setting. HOST is a multi-center, longitudinal prospective cohort study of the health effects of infection with HTLV-I and HTLV-II occurring at five blood banks in United States cities. The five clinical and data collection sites include three American Red Cross (ARC) blood services centers: Chesapeake/Potomac (Washington/Baltimore), Southeastern Michigan (Detroit), and Southern California (Los Angeles), as well as two independent blood centers: Blood Centers of the Pacific in San Francisco, California and the Oklahoma Blood Institute in Oklahoma City, Oklahoma. Testing for HTLV was routinely done at the time of blood donation, and donors found to be seropositive were permanently deferred from blood donation prior to enrollment. Seropositive persons are not usually ill, as there is only a 1-2% risk of progressing to either of the two recognized HTLV related diseases: adult T-cell leukemia (ATL) and HTLV-associated myelopathy (HAM) [17].

Procedures. Following enrollment and baseline data collection in 1990-92, participants have been contacted every two years to complete the three activities that comprise each visit: a health questionnaire, a basic neurologic exam, and phlebotomy for

complete blood count and storage of specimens in the HOST biorepository. All activities and procedures were identical for seropostive and seronegative participants. Nurse counselors at each site were trained and monitored to perform all study activities in a standardized manner, but there was staff turnover during follow-up. The structured interview questions were asked by the study nurse and entered into a questionnaire booklet as the participant answered each question. Attempts were made to see all participants in person, but telephone interviews were accepted from participants who had moved out of state or who refused an in-person visit. An exception was the fourth study visit. Due to decreased resources, the fourth visit had a protocol modification which differed from the other visits. It consisted of an abbreviated health questionnaire completed by mail or telephone, no basic neurologic examination, and remote phlebotomy with the blood sample sent by courier to the central laboratory. The study reverted back to the original protocol when resources were restored for visits five and six.

During each visit, an effort was made to limit the number of participants lost to follow-up by updating subject information for possible changes of name, address or telephone number. Participants consented to allow study personnel to search telephone directory assistance, the U.S. Postal Service forwarding service, public use databases, and credit bureau records if their previous information had changed between visits. Additionally, at each visit, participants were asked to designate a relative or friend who could be contacted to provide updated contact information or knowledge of the subject's death. In cases where the participant and designated contact person were no longer valid

sources of information, a professional tracing expert was assigned to the participant with the purpose of discovering new contact information.

The health questionnaire, neurologic exam and phlebotomy were developed to screen for medical conditions or disease outcomes which might be associated with HTLV-I or HTLV-II, including ATL or HAM. Study clinicians developed an algorithm to identify abnormal responses in the health questionnaire, neurologic exam or phlebotomy results. A computer program was written to use the algorithm to screen all participant data (health questionnaire, basic neurologic exam, complete blood count and medical records) and identify/flag participants whose data was suggestive of clinical outcomes. A panel of three medical physicians with expertise in HTLV clinical and hematologic presentation met at regular intervals during each visit. The panel was blinded to participant serostatus and made decisions for participant referral to the local study physician and/or specialty physician for further diagnostic examinations in a uniform fashion.

Data

Dependent Variable. The outcome of interest for this analysis is the attendance of study participants at each of the visits 2, 3 5 and 6, following enrollment in the baseline visit 1. Data for visit 4 were excluded because of different procedures for that visit (see above). Study visit participation was defined as active if a participant completed at least a study health questionnaire either in person or by telephone, whether or not he or she completed the screening physical exam and phlebotomy.

Independent Variables. Our independent variables were related to health status in a natural history study. One was HTLV status (HTLV-I, HTLV-II or seronegative) measured at baseline. Perceived health status, measured by a five item Likert scale from excellent to poor, was measured at each visit. The third independent variable was referral to a specialty physician diagnostic examination, also determined at each visit. In addition to the main independent variables, another time-varying variable measured at each visit was reimbursement for interview, which changed from $10 to $25 for visits 4, 5 and 6.

Covariates. Fixed covariates measured at baseline were gender, age, race/ethnicity, education, annual income, ever use of injection drugs and study site. Race/ethnicity was recorded in detail (16 specific origins corresponding to risk groups for HTLV infection) but was collapsed to five for the analysis (White, Black, Hispanic, Asian and other). Educational achievement was collapsed from six categories (8^{th} grade or less; 9^{th} -12^{th} grade but no diploma; high school graduate or equivalent, such as GED; some college or technical school; bachelor's degree; master's or professional degree) to four (high school or less; some college; bachelor's degree; master's or professional degree). Income was collapsed from seven categories (<$10,000; $10,000 to 19,999; $20,000 to 29,000; $30,000 to 39,999; $40,000 to 49,999; $50,000 to 74,999 and $75,000 or more) to five (< $10,000; $10,000 to 29,000; $30,000 to 49,999; $50,000 to 74,999 and > $75,000).

Analysis. We first described the sample on baseline characteristics by HTLV status using chi-square tests comparing the percent in each category across HTLV status. In our initial analysis, we first categorized participants as taking part in visit 1 only (baseline only), in visit 1 and at least one other visit (some follow-up) or in all visits (all follow-up) by chi-square tests to compare proportions in each category.

We then used multivariate Generalized Estimating Equation (GEE) analysis to test the relationship between attendance at a study visit after baseline enrollment at visit1 and independent variables over time. The model included the fixed (HTLV status, gender, age, race/ethnicity, education, income, ever drug use and site) and time-varying (health status at previous visit, referral to a specialty physician diagnostic examination at previous visit and reimbursement at previous visit) variables. Variables were then sequentially removed, starting with the least statistically significant. We forced two variables (HTLV status and referral for further exam) into the final model for plausibility: our hypothesis is that they were associated with participation, although they were not statistically significant in our adjusted model. Time was entered in the model as visit, and attendance at each visit was used to predict attendance at the following visit. GEE analysis does not require a balanced design (i.e., observations at all measurements for each participant), and it accommodates correlated errors due to repeated measures. We used the binomial logit function to estimate the likelihood of participation and to present the results of these tests in the form of adjusted odds ratios (OR) with 95% confidence intervals (CI). All analyses were done with SAS, version 9.0 (SAS Institute, Inc., Cary, NC).

RESULTS

The characteristics of the 1341 participants at baseline are shown, by HTLV status, in Table 1. HTLV-I blood donors were more likely to be Black and HTLV-II donors to be Hispanic, and both HTLV seropositive groups were observed to have lower education and lower annual income than HTLV seronegative donors.

After recruitment and baseline data collection in visit 1, 88 (6.6%) participants were lost to follow-up and completed no further interviews or examinations; 51 (13.9%) after visit 2, 113 (30.9 %) after visit 3, 84 (22.9 %) after visit 5. Most of the 366 (27%) participants who dropped out were lost at the second or third visit. As some participants rejoined the study, a total of 1020 (76.0%) participants completed one or more follow-ups from visit 2 through visit 6, and 233 (17.3%) subjects completed all visits. Of the 1341 participants enrolled at baseline, 975 participated in visit 6 (73%). Characteristics in bivariate analysis by sociodemographic and health-related variables and study site, by these groupings of participation, are shown in Table 2.

Overall study participation by site is shown in the Figure. Visit 4 had a telephone rather than in-person interview, and demonstrated considerably lower study participation. Further, the visit 4 health questionnaire did not include the perceived health status question. Because of the resulting loss of data and statistical power and our interest in perceived health as a predictor of participation, we examined GEE results and found no differences in effect sizes with and without visit 4 data. Table 3 and Figure 1 therefore present results on study participation excluding visit 4.

Among health-related variables in the bivariate analysis, HTLV-seronegatives and those with excellent or good health status were more likely to attend study visits (Table 3). However, in multiple regression analysis, neither health status nor HTLV status was associated with participation after adjusting for relevant covariates. Referral for speciality physician diagnostic exam was not a significant predictor of participation. We examined health status, which was significant in bivariate analyses but not in the multivariate model. We found that education accounted for the apparent association between health status and visit participation seen in the bivariate model.

Of the protocol-related variables, higher subject reimbursement and study site were statistically significant predictors of participation at a subsequent visit. When reimbursement was increased from $10 to $25, participants were nearly twice as likely to continue (adjusted OR 1.84). As shown by the differences in proportions, participation by study site remained significant in the GEE analysis. In particular, compared to the San Francisco site, Detroit and Los Angeles were significantly less likely to participate (adjusted OR 0.47 and 0.67, respectively).

Of the sociodemographic variables examined, there was a clear trend for socioeconomic status. Those in higher income categories were increasingly more likely to continue in the study as compared to those in the lowest income group, with those reporting $75,000 or more in annual income 2.68 times as likely to continue as those making less than $10,000. A similar trend was seen for increasing education, with those in the highest education category 1.86 times as likely as those with high school or less education to participate in study visits. Women were more likely to participate compared to men (adjusted OR 1.31), and Blacks and “other race” subjects were less

likely to attend study visits as compared to Whites (adjusted OR 0.61 and 0.59, respectively).

DISCUSSION

The main findings of this study were that persons with higher incomes and more education were more likely to participate in study visits and men and persons of Black and other race/ethnicity were less likely to participate. Contrary to our hypothesis, HTLV seropositivity, poorer perceived health status, and referral to specialty diagnostic exam for potential adverse health outcomes did not significantly affect participation after controlling for demographic variables. Specific protocol-related characteristics did matter: study site and an increase in reimbursement were positively associated with participation.

Retention rates overall have remained high in this 12 year study of blood donors, 73% through visit 6. By virtue of selection criteria, blood donors are generally healthier than the general population. The diagnosis of a viral infection, with serious albeit rare consequences, is an unexpected consequence of blood donation. We hypothesized that being seropositive for HLTV, having poorer perceived health status, and referral for further physician examination because of possible HTLV-related disease would be associated with higher rates of overall participation and re-engagement in subsequent visits. Our data did not support these hypotheses: HTLV positive status, perceived health status, and referral for specialty physician diagnostic examination made no difference in

retention or reengagement of participants. This inability to reject the null hypothesis is reassuring for the HOST study's scientific validity. Loss to follow-up related to HTLV seropositivity and the presence of adverse health outcomes, whether perceived or as a result of changes in objective health measures, could be an important source of bias in this longitudinal study.

Instead, as previously reported in the literature, demographic factors were important predictors of retention in this cohort. Males, those with lower education and lower income, and persons of color were less likely to participate in study visits. There is controversy about the effect of gender on study participation. Some studies indicate women have been shown to be more likely to consent to study participation [18] and continue in studies over time [19], others say there is no difference in participation by gender [20].

What is novel in this research is that the health status of the participants did not appear to affect visit participation. These findings are difficult to compare with other studies because of the inherent difference of these essentially healthy participants with a diagnosis as positive with a virus yet not ill, compared to participants in longitudinal studies of chronic illness. Poor health is usually predictive of dropping out of longitudinal studies [5] [21, 22].

Increasing and maintaining participation by underrepresented groups, who are likely to be in lower socioeconomic strata as well, is an ongoing challenge for researchers

wanting to characterize health and disease for the general population [23-26]. While studies have shown that blood donors as a group have higher socioeconomic status [27], the persistent and independent influence of race/ethnicity, education and income demonstrates the continued and urgent need to develop and test strategies to encourage participation by under-represented groups.

In addition to well known sociodemographic factors, notable differences in the protocol and its implementation were important in study participation. As others have shown [28] the increase of monetary reimbursement (from $10 in visit 3 to $25 in visit 4) was positively associated with study participation. The most dramatic change in participation was seen in visit 4 when interviews were done by telephone or mail and phlebotomy was done remotely, instead of in-person interviews and phlebotomy by the study nurse. The modified approach resulted in profound decreases in participation at all centers and despite the increase in reimbursement, so for subsequent visits the study resumed in-person methods. Moreover, differences by site despite consistency in training and protocol management may have represented subtle differences in personnel and in implementation of the protocol. For example, the Los Angeles site reported that subjects moved often and required intensive tracing efforts, and that urban sprawl and the large, traffic-congested metropolitan area was cited by many subjects as a reason to drop out. Anecdotally, frequent changes in study nurses at some centers probably disrupted rapport essential to maintaining retention. These protocol and logistical observations, while consistent with common sense, remain crucial to the successful implementation of future prospective studies.

Strengths of this analysis are that the data concerned five different blood centers and a long follow-up period. HOST follows a uniform, well funded study protocol with a data coordinating center. The overall retention rate was high, allowing better measurement of differences among study groups. Limitations include the telephone follow-up in visit 4, which was addressed by excluding those data. In addition, few variables were collected specifically for the analysis of study participation. As is often the case, studies of retention are secondary analyses, peripheral to the primary research aim, and often do not have the depth or richness of data to examine the more subjective aspects of retention.

CONCLUSION

In future research, investigators may wish to study various strategies to minimize participant attrition. These have been categorized by others into three areas: competence, dedication and standardized training; communication and collaborative effort between participant and researcher; and expressions of appreciation to participants [29-33]. For future longitudinal, natural history studies, researchers should consider the collection of data specifically related to study participation, including characteristics of study personnel, protocol implementation process and outcomes, changes in the study environment that could affect collection efforts, and other factors directly related to retention. Such factors may include flexible staffing hours, recommended by some to insure that the research interviews are convenient for the participant [34] and home visits,

although time consuming and costly, that may have a positive impact on retention [21]. Qualitative research to better understand the range of interactions between subject and researcher may also be useful in developing testable hypotheses.

In conclusion, poor longitudinal visit participation is one of the major challenges to study validity. Our data have confirmed previous findings and suggested new insights. We recommend that future longitudinal studies incorporate specific measures of participant attrition and retention into their design, including qualitative analysis participant-researcher interactions. In this way, real progress may be made in understanding and improving participation in studies.

COMPETING INTERESTS

The author(s) declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

DAD conceived the study design and analytic methods and took overall responsibility for the paper, wrote the paper, assisted with data collection coordination, supervised data analysis and provided interpretation of the data. MCW advised on the statistical analysis and interpretation of the data, contributed to the writing and revision of the manuscript. XZ performed the statistical analysis and participated in the interpretation of findings. ZK created the analytic dataset and participated in the interpretation of the findings. ELM is

the principal investigator of the cohort study HOST from which the data were derived, and contributed to all aspects of the study. All authors read and approved the final manuscript.

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Table 1: Characteristics of the HOST study sample at baseline by HTLV status, 1990-1992

Characteristic (N)	HTLV-I N (%) N=155	HTLV-II N (%) N=387	HTLV-Negative N (%) N=799	Total N (%) N=1341
Gender (1341)				
Male	44 (28)	102 (26)	257 (32)	403 (30)
Female	111 (72)	285 (74)	542 (68)	938 (70)
Age (1341)				
18-29	10 (6)	23 (6)	68 (8)	101 (8)
30-39	31 (20)	157 (41)	241 (30)	429 (32)
40-49	66 (43)	136 (35)	269 (34)	471 (35)
50-59	22 (14)	49 (13)	131 (17)	202 (15)
≥60	26 (17)	22 (6)	90 (11)	138 (10)
Race/Ethnicity (1327)				
White	59 (39)	138 (36)	309 (39)	506 (38)
Black	61 (40)	124 (32)	243 (31)	428 (32)
Hispanic	9 (6)	104 (27)	152 (19)	265 (20)
Asian	20 (13)	6 (2)	50 (6)	76 (6)
Other	3 (2)	10 (3)	39 (5)	52 (4)
Education (1340)				
High school or less	54 (35)	155 (40)	147 (18)	356 (27)
Some college	63 (41)	179 (46)	362 (45)	604 (45)
Bachelor's degree	25 (16)	40 (10)	179 (23)	244 (18)
Master's or professional degree	12 (8)	13 (3)	111 (14)	136 (10)
Annual income (1328)				
<$10,000	13 (8)	40 (10)	30 (4)	83 (6)

$10,000-29,999	645 (30)	130 (34)	173 (22)	348 (26)
$30,000-49,999	47 (31)	121 (31)	243 (31)	411 (31)
$50,000-74,999	29 (19)	67 (17)	204 (26)	300 (23)
≥$75,000	18 (12)	26 (7)	142 (18)	186 (14)
Health status (1341)				
Excellent	87 (22)	313 (39)	44 (28)	444 (33)
Very good	129 (33)	329 (41)	42 (27)	500 (37)
Good	118 (30)	139 (17)	54 (35)	311 (23)
Fair & Poor	53 (14)	18 (2)	15 (10)	84 (6)
Ever used injection drugs (1338)				
No	152 (99)	294 (76)	788 (99)	1234 (92)
Yes	2 (1)	92 (24)	10 (1)	104 (8)
Site (1341)				
Chesapeake	32 (21)	51 (13)	122 (15)	205 (15)
Detroit	32 (21)	39 (10)	102 (13)	173 (13)
Los Angeles	44 (28)	206 (53)	345 (43)	595 (44)
Oklahoma City	16 (10)	23 (6)	74 (9)	113 (8)
San Francisco	31 (20)	68 (18)	156 (20)	255 (19)

Not all subjects answered every question; the number answering each question is listed with each characteristic. Percentages may not add to 100 because of rounding, and are based on those answering the question.

Table 2: Subject participation by HTLV status and baseline characteristics

Characteristic (N)[a]	Participated in All Follow-up N (%) N=233(17)	Participated in Some Follow-up N (%) N=1020(76)	Participated in Baseline only[b] N (%) N=88(7)	Total N (100%)[c] N=1341	*P*
Viral status (1341)					0.07
HTLV-I	30 (19)	110 (71)	15 (10)	155	
HTLV-II	70 (18)	285 (74)	32 (8)	387	
HTLV-Negative	133 (17)	625 (78)	41 (5)	799	
Gender (1341)					0.15
Male	59 (15)	313 (78)	31 (8)	403	
Female	174 (18)	707 (75)	59 (6)	938	
Age (1341)					0.25
18-29	15 (15)	77 (76)	9 (9)	101	
30-39	74 (17)	320 (75)	35 (8)	429	
40-49	92 (20)	351 (74)	31 (6)	471	
50-59	28 (14)	165 (81)	10 (5)	202	
≥60	24 (17)	109 (79)	5 (4)	138	
Race/Ethnicity (1330)					0.01
White	80 (16)	402 (79)	24 (5)	506	
Black	94 (21)	298 (70)	39 (9)	428	
Hispanic	38 (14)	211 (80)	16 (6)	265	
Asian	8 (10)	62 (82)	6 (8)	76	
Other	11 (21)	37 (71)	4 (8)	52	
Education (1340)					0.05
High school or less	70 (20)	252 (71)	34 (9)	356	
Some college	103 (17)	465 (77)	37 (6)	604	
Bachelor's degree	43 (18)	192 (79)	10 (4)	244	
Master's or professional degree	17 (12)	112 (82)	7 (5)	136	

Annual income (1328)					0.03
<$10,000	11 (13)	62 (75)	10 (12)	83	
$10,000-29,999	69 (20)	248 (71)	31 (9)	348	
$30,000-49,999	68 (16)	316 (77)	27 (6)	411	
$50,000-74,999	50 (17)	236 (77)	14 (5)	300	
≥$75,000	31 (17)	150 (81)	5 (3)	186	
Health status (1341)					0.02
Excellent	65 (15)	347 (78)	32 (7)	444	
Very good	92 (18)	383 (77)	25 (5)	500	
Good	57 (18)	235 (76)	19 (6)	311	
Fair & Poor	19 (22)	55 (64)	12 (14)	86	
Ever used IV drugs (1338)					0.21
Yes	17 (16)	76 (73)	11 (11)	104	
No	216 (18)	942 (76)	76 (6)	1234	
Site (1341)					<.001
Chesapeake	68 (33)	125 (61)	12 (6)	205	
Detroit	27 (16)	129 (75)	17 (9)	173	
Los Angeles	59 (10)	501 (84)	35 (6)	595	
Oklahoma City	27 (24)	82 (72)	4 (4)	113	
San Francisco	52 (20)	183 (72)	20 (8)	255	

[a] Not all subjects answered every question; the number who did is listed with each characteristic. Percents may not add to 100 because of rounding, and are based on those answering the question.

[b]These subjects provided data at baseline (Visit1) only.

[c] The total represents all who answered the question.

Table 3: Predictors of subject visit participation in HOST study by bivariate and multivariate GEE analysis.

Predictor	Crude OR (95% CI)	P^a	Adjusted OR (95% CI)	P^b
Site				
Chesapeake	0.72 (0.48, 1.09)	0.12	0.69 (0.45, 1.04)	0.08
Detroit	0.45 (0.30, 0.67)	<0.001	0.47 (0.31, 0.71)	<0.001
Los Angeles	0.73 (0.52, 1.03)	0.08	0.67 (0.48, 0.94)	0.02
Oklahoma City	0.88 (0.56, 1.40)	0.59	0.75 (0.47, 1.19)	0.22
San Francisco	Reference		Reference	
Phase				
Visit 3 vs. Visit 2	0.63 (0.54, 0.73)	<0.001	1.34 (1.00, 1.79)	0.05
Visit 5 vs. Visit 3	0.29 (0.24, 0.35)	<0.001	0.29 (0.22, 0.39)	<0.001
Visit 6 vs. Visit 5	0.28 (0.23,0.33)	<0.001	1.38 (0.90, 2.11)	0.14
Reimbursement for interview				
$25 vs. $10	1.14 (0.95, 1.47)	0.13	1.84 (1.22, 2.77)	0.004
Gender				
Female	1.25 (0.99, 1.57)	0.05	1.31 (1.04, 1.66)	0.02
Male	Reference		Reference	
Age				
One year increase	1.00 (0.99, 1.02)	0.69	1.00 (0.99, 1.01)	0.41
Race/Ethnicity				
Black	0.51 (0.40, 0.67)	<0.001	0.61 (0.47, 0.80)	0.004
Asian	0.74 (0.44, 1.24)	0.25	0.68 (0.42, 1.10)	0.11
Hispanic	0.71 (0.52, 0.96)	0.03	0.76 (0.56, 1.04)	0.09
Other	0.59 (0.35,0.99)	0.05	0.59 (0.36, 0.99)	0.05
White	Reference		Reference	
Education				
High school or less	Reference		Reference	
Some college	1.35 (1.05, 1.73)	0.02	1.14 (0.89, 1.47)	0.29

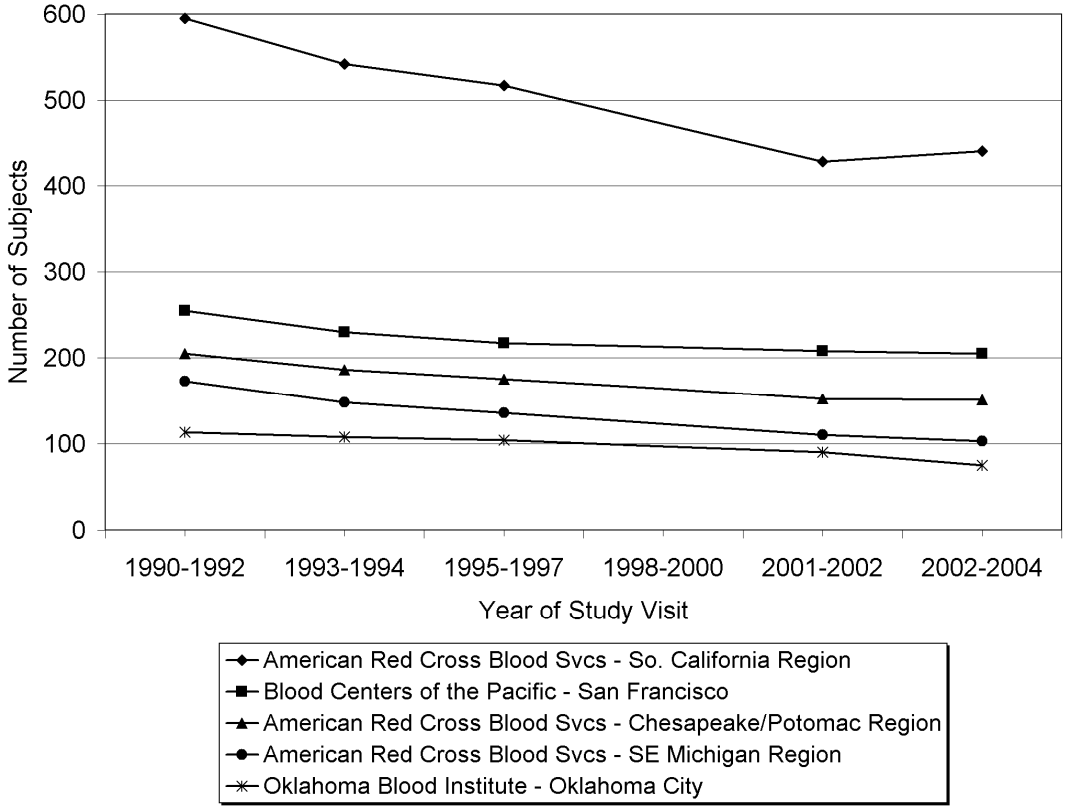
Bachelor's degree	2.01 (1.43, 2.28)	<0.001	1.56 (1.09, 2.23)	0.02
Master's or professional degree	2.31 (1.45, 3.67)	<0.001	1.86 (1.19, 2.92)	0.01
Annual income				
<$10,000	Reference		Reference	
$10,000-29,999	1.56 (1.04, 2.34)	0.03	1.47 (0.97, 2.28)	0.07
$30,000-49,999	1.74 (1.17, 2.59)	0.01	1.57 (1.04, 2.40)	0.03
$50,000-74,999	2.52 (1.64, 3.88)	<0.001	1.96 (1.24, 3.10)	0.004
≥$75,000	3.73 (2.25, 6.19)	<0.001	2.68 (1.58, 4.56)	0.003
Health status in previous Visit				
Excellent	1.72 (1.18,2.50)	0.01	1.20 (0.80, 1.81)	0.38
Very good	1.75 (1.22,2.52)	0.003	1.33 (0.91, 1.96)	0.14
Good	1.18 (081,1.72)	0.38	1.12 (0.85, 1.47)	0.14
Fair or Poor	Reference		Reference	
Ever used IV drugs				
Yes	1.57(1.08,2.26)	0.02	1.08 (0.83,1.42)	0.55
No	Reference		Reference	
HTLV status				
HTLV-I	0.64 (0.46, 0.89)	0.01	1.12 (0.85,1.47)	0.42
HTLV-II	0.70 (0.55, 0.88)	0.003	1.01 (0.70, 1.45)	0.96
HTLV-Negative	Reference		Reference	
Referral for further exam in previous visit				
Yes	0.86 (0.68, 1.09)	0.22	1.08 (0.83,1.42)	0.55
No	Reference		Reference	

Note: OR = odds ratio; CI= confidence interval.

[a]bivariate analysis

[b]multivariate analysis, controlling for all other values shown in the table

Figure 1. Number of subjects in 6 visits: (1990-1992 through 2002-2004) by study site



CHAPTER 4

Living with HTLV: Insights from a prospective cohort

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ABSTRACT

Living with HTLV: Insights from a prospective cohort

Background. Most HTLV-I positive persons remain asymptomatic carriers with 5% or less developing adult-cell leukemia/lymphoma (ATL) or HTLV-associated myelopathy (HAM). Given the small risk of progression to life-threatening disease (ATL) or physically debilitating disorder (HAM), it is interesting to consider the outlook of the HTLV infected person.

Methods. This was a cross sectional survey nested within the 8th visit of the HTLV Outcomes Study (HOST), which follows former blood donors infected with HTLV- I and II. We asked HTLV-I and -II seropositive subjects two questions: "How often do you think about having HTLV?" and "What is the worst thing about having HTLV?". Data analysis used the chi square test for variance in a normal population (SAS procedure GENMOD).

Results. A total of 92 HTLV-I, 263 HTLV-II (including 8 HAM subjects) participated in the survey. The distribution of responses to how often subjects thought about having HTLV did not differ significantly between the HTLV-I and II subjects (about 50% of each group "never thought about HTLV") but HAM patients thought about HTLV more often. Subjects responded that "the worst thing about having HTLV" was current physical symptoms, fear of future progression to HTLV-related disease, fear of transmitting HTLV, feeling stigmatized, and not being able to donate blood or organs, although the largest proportion of subjects answered "none" (35% HTLV-I, 41% HTLV-

II, 37% HAM). HTLV-I subjects were more likely than HTLV-II subjects to report fear of the future (36% vs 26%; $p<0.05$), while15% of HTLV-I and 20% of HTLV-II subjects reported fear of transmitting HTLV to others. There was a statistically significant difference between the HTLV-I and II carriers and HAM subjects on self-reported current health status, with the HAM subjects reporting poorer health ($p=0.03$) and more concern about their current physical symptoms ($p= 0.04$).

Conclusions. Many HTLV-I and HTLV-II participants rarely thought about their HTLV infection, but this was not the case for HAM patients. However when asked, a majority of subjects reported specific concerns such as fear of future progression to HTLV-related disease and fear of transmitting HTLV to others. HTLV health care providers need to inquire about the fears and concerns of their patients.

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Living with HTLV: Insights from a prospective cohort

Background

Human t-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are little known viruses outside of the fields of retrovirology, hematology, neurology and transfusion medicine. An ancient infection of humans, they were discovered after a long search that began in the 1950s with intensive efforts to find human counterparts to cancer-causing animal retroviruses, helped along by the 1970s breakthrough discovery of reverse transcriptase, and finally isolated in 1979 (HTLV-I) (Poiesz et al., 1980) and 1981 (HTLV-II) (Kalyanaraman et al., 1982) from the cell lines and blood of patients with adult t-cell leukemia (ATL).

The three major routes of HTLV transmission are mother to child, sexual contact and infected blood. The 1988 introduction of systematic blood screening in the United States greatly reduced the incidence of infection by transfusion (Schreiber, Busch, Kleinman, & Korelitz, 1996). In developing countries, however, blood transfusions remain a major risk factor for HTLV infection transmission. Efforts to stop breastfeeding by HTLV seropositive mothers has significantly decreased transmission to children in endemic areas (Hino et al., 1997). Intravenous drug abuse and sexual activity, although amenable to prevention efforts, continue to be efficient transmitters of HTLV infection (Feigal et al., 1991; Roucoux et al., 2005)

World wide, it is estimated that roughly 5 to 10 million people are infected with HTLV-I, and several million are infected with HTLV-II (Oh & Jacobson, 2008). A lifelong infection, most HTLV-I infected persons remain asymptomatic carriers with a 2% to 4% chance of developing adult t-cell leukemia/lymphoma (ATL), and 1% to 2%

chance of HTLV-associated myelopathy /tropical spastic paraparesis (HAM/TSP), the two most important diseases associated with HTLV (Murphy et al., 1989), (Orland et al., 2003). Other possible consequences of HTLV-I are uveitis, polymyositis, synovitis, thyroiditis, persistent lymphadenopathy and bronchoalveolar pneumonia (Beilke & Murphy, 2006). Disease associations with HTLV-II are less clear than those with HTLV-I, although there is accumulating evidence showing a link to HAM, as well as other neurological abnormalities (Araujo & Hall, 2004). The risk of developing disease is related to age, route of infection and the immune competency of the host, and there are no biomarkers to predict disease progression. The time from seroconversion to disease can vary from years to decades (Tajima & Kuroishi, 1985).

Despite recent improvements in chemotherapy regimens for ATL, there is a poor prognosis with survival rates of 6 to 24 months. Patients with HAM/TSP endure a nonremitting progressive spasticity and lower extremity weakness (Osame et al., 1987) often resulting in the inability to stand or walk, along with urinary incontinence and impotence in men (Gessain & Gout, 1992), (Shibasaki et al., 1988).

Purpose

Given the small risk of progression to life threatening disease (ATL) or physically debilitating disorder (HAM), the long latency period of the virus, no biomarkers for disease progression and no known way to reduce the risk of developing disease, it is important for clinicians caring for patients with HTLV infection to try to understand their perspectives and outlook regarding living with this virus. Is this population uniquely affected by psychological and social problems related to living with HTLV? There is a wealth of literature studying the psychological stress of being HIV positive related to

disease progression (Leserman, 2003), stigma (Herek, Capitanio, & Widaman, 2002), coping mechanisms and self-care (Anderson & Spencer, 2002). Little has been written about living with HTLV either as an asymptomatic carrier or person with HAM. A study in 1998 indicated that psychological distress was associated with knowledge of positive HTLV-I or - II tests among blood donors (Guiltinan et al., 1998).

Using data from a longterm prospective cohort study, the purpose of this paper is to describe feelings about having HTLV by asking questions about how often a subject thinks about their seropositivity and concerns associated with being HTLV positive. Our hypothesis was that subjects with diagnosed HTLV-associated myelopathy (HAM) would think about it more often and be more likely to express a fear of the future, fear of transmitting HTLV to others, or stigmatized feeling than the asymptomatic carriers of either HTLV-I or HTLV-II.

Methods

Sample. Data are from the HTLV Outcomes Study (HOST). Beginning in 1990 through 1992, 155 HTLV-I seropositive, 387 HTLV-II seropositive and 799 seronegative participants were enrolled from populations of blood donors from five sites across the United States. Participants were aged 18 and older, testing either positive or negative for HTLV at the time of attempted donation. All participants were HIV negative. For this paper, only data from the HTLV-I and HTLV-II seropositive participants were used.

HOST data have been the source of many publications on the transmission, natural history and health outcomes of HTLV infection (Kaplan et al., 1996; Murphy et al., 1993; Murphy et al., 1997; Murphy et al., 2004; Orland et al., 2003) HOST is an

extension of the cohort enrolled previously under the Retrovirus Epidemiology Study (REDS) and the details of HOST study design have been described elsewhere (Zuck et al., 1995).

Setting. HOST is a multi-center, longitudinal prospective cohort study of the health effects of infection with HTLV-I and HTLV-II occurring at five blood banks in United States cities. The five clinical and data collection sites include three American Red Cross (ARC) blood services centers: Chesapeake/Potomac (Washington/Baltimore), Southeastern Michigan (Detroit), and Southern California (Los Angeles), as well as two independent blood centers: Blood Centers of the Pacific in San Francisco, California and the Oklahoma Blood Institute in Oklahoma City, Oklahoma. Testing for HTLV was routinely done at the time of blood donation, and donors found to be seropositive were counseled according to Centers for Disease Control and Prevention (CDC) guidelines and permanently deferred from blood donation prior to enrollment.

Procedures. Following enrollment and baseline data collection in 1990-92, the general procedures for HOST included participant contact every two years to complete the three activities that comprise each visit: a health questionnaire, a basic neurologic exam, and phlebotomy. Attempts were made to see all participants in person, but telephone interviews were accepted from participants who had moved out of state or who refused an in-person visit.

The health questionnaire, neurologic exam and phlebotomy were developed in HOST to screen for medical conditions or disease outcomes which might be associated with HTLV-I or HTLV-II, including ATL or HAM. The health questionnaire asked about physical condition in general since their last visit, including questions to determine if they

had developed symptoms related to possible progression to HAM or other diseases associated with HTLV.

Data. From the HOST dataset, sociodemographic data that were collected at enrollment, and clinical data gathered at each visit to measure changes in general health and HTLV-related health outcomes over time were used for this analysis. The identification of those who developed disease and the onset of HTLV-related outcomes were noted from the clinical data of the visit when progression was first detected.

During the most recent visit, (July 2007- February 2009, the eighth visit), two questions, to be asked of the HTLV-I and –II seropositive participants only, were added to the health questionnaire, and these comprise the focus for this analysis. The first question "how often do you find yourself thinking about being positive for HTLV?" could be answered as never, rarely (25% of the time), sometimes (50% of the time), usually (75% of the time) or always (100% of the time). Concerns about HTLV were measured by responses and subjects could answer affirmatively to more than one choice. "What is the worst thing about having HTLV?" had 4 possible answers: current physical symptoms, fear of the future regarding progression to HTLV-related disease, fear of transmitting HTLV to others such as family members or sex partners, and feeling stigmatized by having a life long infection. A fifth possible answer was "other" and required a response from the participant that would be written in by the nurse interviewer. If the response was a variant of "nothing about having HTLV bothers me", the nurse interviewer was instructed to write "none" as the response.

Analysis

This was a cross sectional survey nested within the eighth visit of HOST. We first described the sample on baseline characteristics by HTLV type (HTLV-I, HTLV-II) and diagnosis of HTLV-associated myelopathy (HAM) using chi-square tests comparing the percent in each category. We then looked at the frequency of answers to "How often do you think about having HTLV" and performed chi-square tests for variance in a normal population (SAS procedure GENMOD) to compare how HTLV-I, HTLV-II and HAM participants answered the question. Finally, due to diverse original statements, responses to "What is the worst thing about having HTLV?" were categorized into six separate variables, because of the nonexclusivity of responses to the single question. They were: current physical symptoms, fear of the future, fear of transmitting HTLV, feeling stigmatized, not being able to donate organs or blood, and none. Chi-square tests compared the percents responding positive to each by HTLV-I, HTLV-II and HAM categories.

In order to look at comparisons within the subset of individuals with HAM, we constructed a line listing of the HAM participants to describe the severity of their symptoms and their perspective on living with HTLV. HOST neurology specialist physicians use the HTLV-associated myelopathy (HAM) Disability Scale Summary Form when performing the bi-annual assessment of HAM subjects. The HAM Disability Scale was adapted from an Expanded Disability Scale Summary (EDSS) in use for rating impairment in multiple sclerosis (Kurtzke, 1983), (Tindall et al., 1982). The HAM Disability Scale has four sections: overall neurologic disability and three categories of activities of daily living (walking, hygiene, and dressing). The criteria are lengthy and are

condensed here as they apply to the 8 participants in HOST. HAM is classified as “mild” if there is no or minimal signs of neurological dysfunction, normal unassisted walking or slightly deviant gait, hygiene is maintained normally by self or minimal difficultly unassisted and the person is self-reliant or has minimal difficulty dressing unassisted; “moderate” if there is moderate ataxia or paresis, frequent urinary incontinence or disturbing sensory loss, moderately poor gait or moderately limited walking unaided, hygiene is maintained with difficulty and some assistance is needed, and the person dresses with difficulty and some assistance; and “severe” if there is severe ataxia, marked paresis, loss of sensation in one or two limbs, loss of bladder function with need for catheterization, severe limitation or inability to walk, hygiene necessitates complete assistance, and the person needs complete assistance with dressing.

Results

Retention rates overall were high in this 18 year study of blood donors, with 73% completing visit 6 (DeVita, White, Zhao, Kaidarova, & Murphy, 2009). By visit 8, participants were lost to follow-up for many documented reasons: death (118, 8 % of enrollees) and active or passive refusal to continue (204, 14% of enrollees). Of the 155 HTLV-I seropositives enrolled at visit 1, 92 (59%) attended visit 8, as did 263 (68%) of the 387 enrolled HTLV-II seropositives, 65% overall. Of the HTLV-I seropositives, 6 had been diagnosed with HAM, of whom 4 participated in visit 8. Of the 263 HTLV-II seropositives in visit 8, 4 had been diagnosed with HAM and all participated in visit 8.

Table 1 describes the sample on characteristics by HTLV status and diagnosis: HTLV-I, HTLV-II and HAM. The distribution of responses to how often subjects

thought about having HTLV did not differ significantly between the HTLV-I and II subjects (about 50% of each group reported they never thought about HTLV) but HAM patients thought about HTLV more often. Although some responded that they had fears and concerns related to HTLV, many in both asymptomatic and the HAM groups responded "none" (35% HTLV-I, 41% HTLV-II, 37% HAM). HTLV-I subjects were more likely than HTLV-II subjects to report fear of the future (36% vs 26%; $p<0.05$), while 15% of HTLV-I and 20% of HTLV-II subjects reported fear of transmitting HTLV to others. There was a statistically significant difference between the HTLV-I and II carriers and HAM subjects on self-reported current health status, with the HAM subjects reporting poorer health ($p=0.03$) and more concern about their current physical symptoms ($p= 0.04$).

Table 2 describes the participants with HAM in more detail with respect to progression and their perspectives on living with HTLV and shows how they answered the two questions. Two of the HAM cases (1 and 3) are complicated with co-existing morbidities (obesity and diabetic neuropathy) that make it difficult to determine if their performance of activities of daily living (ADL) was hindered by HAM or other conditions. Despite the differences in their ability to perform ADL, mild HAM case number 2 had identical answers to severe HAM case number 6. The other three mild HAM cases (3, 4 and 8) and two moderate HAM cases did not express strong fears about their diagnosis.

Discussion

Although diagnosed HTLV-related illness remains uncommon among individuals infected with HTLV, people living with the virus are affected in psychological and social

ways related to the infection. A case study review of the HOST cohort (464 HTLV-I and- II positive donor subjects and 735 HTLV-I and- II negative donor controls) was done three years after seropositive notification using a subjective analysis of emotional and social difficulties, the General Well-Being scale (GBW) (Guiltinan et al., 1998). The GWB scale is a standardized, self-administered measure consisting of questions concerning the "presence, severity, or frequency of some clinical symptoms that are generally considered important in making assessments of subjective well-being" (Wan & Livieratos, 1978). To our knowledge, this is the only publication addressing the psychological well-being of HTLV-infected individuals. Not surprisingly, the seropositive subjects reported significantly more anxiety than did the seronegative controls, and despite the large sample size (464 HTLV-I/II positive donor subjects and 735 HTLV-I/II negative donor controls) the study only suggested implications for quality of life issues for persons with a clinical diagnosis in which there is no known treatment and minimal knowledge about long term effects.

In the present study, there were no important differences in response to the first question (how often do you think about having HTLV?) between the asymptomatic carriers of HTLV-I or-II and those participants diagnosed with HAM. For the second question (what is the worst thing about having HTLV?), the HAM subjects did have more concern for their current physical symptoms and reported poorer health, as might be expected. The fact that they did not think about having HTLV more frequently could suggest that they are coping with the knowledge of their disease. It is difficult to know how significant having HAM is to each participant without an extensive biographical case-history and assessment of the personal experience and environment of each person.

If coping refers to the thoughts and behaviors a person uses to regulate distress (Folkman & Greer, 2000), perhaps the progression from being an asymptomatic carrier to being diagnosed with HAM takes away uncertainty and the stress associated with uncertainty, making it possible to develop and sustain a sense of psychological well-being despite unfavorable circumstances.

In this study of former blood donors, it is of interest to note that 7% of HTLV-I (including 1 HAM subject) and 5% of HTLV-II participants (including 1 HAM subject) responded that they regret their ineligibility to donate blood now that they have a permanently deferrable risk factor. There is research suggesting that blood donors gain an actual psychological benefit (emotional gratification, feelings of heroism and heightened self-esteem) from their altruistic behavior (Piliavin, 1990). Although now deferred from donating, subjects can view their participation in HOST as a valuable philanthropic activity; this may be a substitute for the psychological benefit lost because of the prohibition against donating blood or organs.

A limitation of this study is the small number and diversity of the HAM cases, which limits the generalizability of the findings and conclusions that can be drawn from it. The addition of the questions related to concerns about HTLV only at visit 8, independent of the progression to symptoms and/or diagnosis of HAM, limits interpretation of any temporal relationships.

Ongoing access to adequate counseling and information about having a lifelong viral infection, particularly related to transmission within sexual relationships, feelings about being marked or stigmatized by society, long-term effects on the family, guilt or fear surrounding the unintended sexual transmission of the virus, and obstacles to

establishing or maintaining a sexual relationship with a seronegative partner are part of standard practice for persons who are HIV-positive. In this study the continued participation in the cohort, with regular attention paid to the infected or diseased person, despite strict study protocols, may have been viewed as comparable care, resulting in fewer concerns and less difference between positives and diseased than we expected. What are the emotional consequences of being labeled with an early- and unexpected, discovered after performing the altruistic act of donating blood- diagnosis of HTLV? Can harm be done by labeling, that is, from telling someone who feels well that he or she is sick or may become sick? These general questions frame the discussion of potential qualitative approaches that are needed to expand knowledge in this area.

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Table 1: Characteristics of the HTLV seropositive subjects by HTLV type and HTLV-associated myelopathy (HAM) diagnosis in HOST at visit 8, 2007-2009

Characteristic	HTLV-I N (%) N=92 (25%)	HTLV-II N (%) N=263 (72%)	HAM N (%) N=8 (2%)	Total N (%) N=363
Gender (363)				
Male	21 (23)	60 (23)	0 (0)	81 (22)
Female	71 (77)	203 (77)	8 (100)	282 (78)
Age (363)				
<39	2 (2)	8 (3)	0 (0)	10 (3)
40-49	11 (12)	46 (18)	0 (0)	57 (16)
50-59	31 (34)	129 (49)	3 (38)	163 (45)
≥60	48 (52)	80 (30)	5 (62)	133 (37)
Race/Ethnicity (360)				
White	34 (37)	101 (38)	5 (63)	140 (39)
Black	37 (40)	80 (30)	1 (12)	118 (33)
Hispanic	4 (4)	70 (27)	2 (25)	76 (21)
Asian	14 (15)	5 (2)	0 (0)	19 (5)
Other	2 (2)	5 (2)	0 (0)	7 (2)
Education (363)				
High school or less	25 (27)	75 (29)	2 (25)	102 (28)
Some college	38 (41)	137 (52)	3 (37)	178 (49)
BA, BS or higher	29 (32)	51 (19)	3 (37)	83 (23)
Annual income (360)				
$10,000-29,999	18 (20)	61 (23)	4 (50)	83 (23)
$30,000-49,999	17 (18)	54 (21)	0 (0)	71 (20)
$50,000-74,999	21 (23)	61 (23)	1 (12)	83 (23)
≥$75,000	30 (33)	65 (25)	2 (25)	97 (27)
Refused	6 (6)	19 (7)	1(12)	26 (7)
Health status (363)				

Excellent	19 (21)	37 (14)	0 (0)	56 (15)
Very good	27 (29)	86 (33)	2 (25)	115 (32)
Good	38 (41)	92 (35)	2 (25)	132 (36)
Fair or Poor	8 (9)	48 (18)	4 (50)	60 (17)

Not all subjects answered every question; the number answering each question is listed with each characteristic. Percentages may not add to 100 because of rounding, and are based on those answering the question.

Table 2: Characteristics of HOST subjects diagnosed with HAM

HAM subject	HTLV type	Severity of HAM	Age at diagnosis	Duration Of HAM* (years)	How often think about HTLV	Concerns about Having HTLV	Activities of Daily living
1.	II	moderate	47	18	never (0%)	none	moderate neuro dysfunction, urinary incontinence, complicated by obesity
2.	II	mild	43	17	usually (50%)	fear of the future	normal
3.	II	mild	51	12	rarely (25%)	none	normal but complicated by diabetic neuropathy
4.	II	mild	54	7	rarely (25%)	can't donate	normal
5.	I	severe	51	17	usually (50%)	current physical symptoms	assistance with all ADL, unable to stand/walk, loss of bladder function
6.	I	severe	43	17	usually (50%)	fear of the future	assistance with all ADL, unable to stand/ walk, loss of bladder function
7.	I	moderate	54	7	never (0%)	none	needs assistance, uses cane to stand/walk
8.	I	mild	50	8	rarely (25%)	can't donate	normal

* Duration of HAM was based on the year the diagnosis was made to 2009.

CHAPTER 5

Dissertation Conclusion:

Cohort Study of Persons with human t-cell lymphotropic virus (HTLV)

Deborah A. DeVita RN, MS, PhDc

Dissertation Conclusion:

Cohort Study of Persons with human t-cell lymphotropic virus (HTLV)

The purpose of this dissertation was to familiarize the reader with HTLV and the research of the HOST cohort. The three papers for publication address different aspects of the virus, the study of persons with a long-term condition enrolled in a prospective cohort, and the impact of being seropositive for asymptomatic carriers and those who have progressed to HTLV-associated myelopathy (HAM).

The review of the literature, Chapter 2, identified the importance of investigating the relatively obscure HTLV as part of the larger field of retrovirology and presented the public health relevance of HTLV by comparing it with and contrasting it to its notorious cousin, human immunodeficiency virus (HIV). While alike in some aspects, differences between HTLV and HIV in both presentation and outcome are considerable: HIV is a highly mutable virus and almost everyone infected will become ill and die after a long latency period, while HTLV-I and- II are characterized by their high genomic stability and low pathogenicity. It is hoped that health care providers will become familiar with the clinical presentation of HTLV-related disease (HAM) in order to correctly diagnose them and offer their patients appropriate guidance and treatment.

The prospective cohort is one of the most powerful designs available for use in analytic epidemiology. The HTLV Outcomes Study (HOST) was determined to be an appropriate resource for this dissertation because it contained a large, diverse cohort followed over eighteen years with a well funded study protocol, measured many

demographic and health related variables, had low amounts of missing data, and low loss to follow-up. It is well known that minimizing loss to follow-up in long-term cohort studies is essential for reducing bias and maintaining statistical stability. There is great variability in retention among longitudinal cohorts, and it was of interest to investigate why HOST had better than average retention. For Chapter 3, the study of subject follow-up, the HOST data were amenable to General Estimating Equation (GEE) analysis that provided some uncommon but possible reasons for long-term study participation. The results confirmed the findings of other researchers that the persistent and independent influence of race/ethnicity, education and income demonstrates the continued and urgent need to develop and test strategies to encourage participation by under-represented groups. And, although the researcher has no control over participant demographic characteristics, we can incorporate specific measures of subject attrition and retention into study design, including the assessment of subject motivation at enrollment and qualitative analysis subject-researcher interactions.

The concerns of HTLV seropositive persons, aware that there is a small chance their infection may progress to a physically debilitating disorder (HTLV-associated myelopathy, known as HAM) or a life threatening blood disease (adult t-cell leukemia lymphoma, known as ATLL) but also aware that there is no known way to reduce their risk, have been overlooked by researchers working with this population. Chapter 4 provides some insights into the thoughts and concerns of the HTLV seropositive subjects in HOST. A chi-square analysis was done of two psycho-social questions added to the HOST questionnaire at the most recent visit. The results showed that subjects diagnosed with HAM had more concern for their current physical symptoms, not an unexpected

finding. Of more interest was that there were no important differences between asymptomatic subjects and diagnosed subjects on how often they think about having HTLV, suggesting that coping mechanisms may be in place.

In conclusion, although there is a wealth of information to be obtained from the HOST cohort, there remains a gap in the literature about seropositive persons, asymptomatic or diagnosed with HAM or ATLL. In my experience with the study and the subjects, one HOST participant's experience with HTLV provides evidence of this gap in knowledge. This participant was diagnosed with HAM in 1993 and has reported losing her marriage, her job, and many friends as the virus increasingly impaired her ability to perform activities of daily living. Her balance, strength and mobility are now severely diminished, as she cannot stand or walk. She has lost bowel and bladder control. She needs help with almost every activity, from putting away the groceries to bathing and dressing. Although fortunate in that she had bought a home before she lost her job, her walker and later wheelchair confined her to the first floor of her home and she could no longer enter into or tend to her back yard garden. She has been able to get a stair lift that allows her to access the upper floor of her home, but other home modifications like a roll-in shower to accommodate her wheelchair are beyond her means and not paid by Medi-Cal. She has spoken candidly about the gradual loss of sexual sensation. The HTLV literature has reported on impotence in men diagnosed with HAM, but nothing on the sexual dysfunction of women with HAM. Her emotional damage is in every way equal to the physical. She has isolated herself from intimate relationships because of worries about transmitting the virus, and this isolation coupled with decreasing mobility and difficulty experiencing sexual sensation has led to intense feelings of sadness, guilt,

shame, anger, fear and resentment. After many years of depression she got out of her home and connected with disability organizations and activities that have become a valued social milieu and support network, enhancing her ability to cope with her disability. She has become a counselor and finds consolation and strength in helping other disabled persons. At our most recent visit in 2008 she told me she has made peace with her disease and is the happiest she has ever been in her life.

The goal of this study was to encourage HTLV researchers and clinicians to pay attention to the development and maintenance of psychological well-being in the face of the threat of disease progression. The three papers are a start in the education of health care providers about the virus and the disease, and serve to highlight the long-term burden of disease faced by those who progress to illness.

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