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HIV Risk Reduction With Buprenorphine–Naloxone or Methadone: Findings From a Randomized Trial

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Objectives: Compare HIV injecting and sex risk in patients being treated with methadone (MET) or buprenorphine–naloxone (BUP).

Methods: Secondary analysis from a study of liver enzyme changes in patients randomized to MET or BUP who completed 24 weeks of treatment and had 4 or more blood draws. The initial 1:1 randomization was changed to 2:1 (BUP:MET) after 18 months due to higher dropout in BUP. The Risk Behavior Survey measured HIV risk before 30 days at baseline and weeks 12 and 24.

Results: Among 529 patients randomized to MET, 391 (74%) were completers; among 740 randomized to BUP, 340 (46%) were completers; 700 completed the Risk Behavior Survey. There were significant reductions in injecting risk ($P < 0.0008$) with no differences between groups in mean number of times reported injecting heroin, speedball, other opiates, and number of injections; or percent who shared needles; did not clean shared needles with bleach; shared cookers; or engaged in front/back loading of syringes. The percent having multiple sex partners decreased equally in both groups ($P < 0.03$). For males on BUP, the sex risk composite increased; for males on MET, the sex risk decreased resulting in significant group differences over time ($P < 0.03$). For females, there was a significant reduction in sex risk ($P < 0.02$) with no group differences.

Conclusions: Among MET and BUP patients who remained in treatment, HIV injecting risk was equally and markedly reduced; however, MET retained more patients. Sex risk was equally and significantly reduced among females in both treatment conditions, but it increased for males on BUP and decreased for males on MET.

Key Words: HIV, risk reduction, buprenorphine, methadone

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INTRODUCTION

Research over the past 20 years has shown that methadone (MET) maintenance reduces opioid use and is an effective HIV risk reduction intervention.[1–8] This finding has been observed when MET patients are compared with their community counterparts who are not in treatment[9–11] and when opioid use during treatment is compared with pre treatment and posttreatment use.[3] Furthermore, significantly lower rates of opioid use have been observed when patients with regular MET program attendance are compared with those with poor attendance[12] and when patients receiving minimal ancillary services are compared with those receiving more intensive services.[13,14]

Consistent with these reductions in opioid use, MET maintenance markedly reduces opioid injection and needle sharing. This finding has been reported in cross-sectional, prospective, and retrospective designs comparing MET patients with heroin users who are not in treatment[5,9,11,15,16] and in studies measuring changes among MET patients during treatment.[14,17] Findings have also been reported (Fig. 1) showing significantly lower rates of injection among patients who remain in treatment when compared with patients who left treatment.[10,18]

Importantly, previous research demonstrates strong associations between participation in MET maintenance and lower rates of HIV prevalence and incidence. For example, heroin users who remained in MET treatment during periods of rapid HIV transmission in their local communities had a dramatically lower prevalence of infection.[19–21] In both prospective and retrospective studies, the incidence of HIV infections has been associated with participation[7,10,12] and time receiving MET treatment.[7,22,23] Although none of these

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Trial registration of the parent study was initiated and maintained on clinicaltrials.com (NCT00315341).

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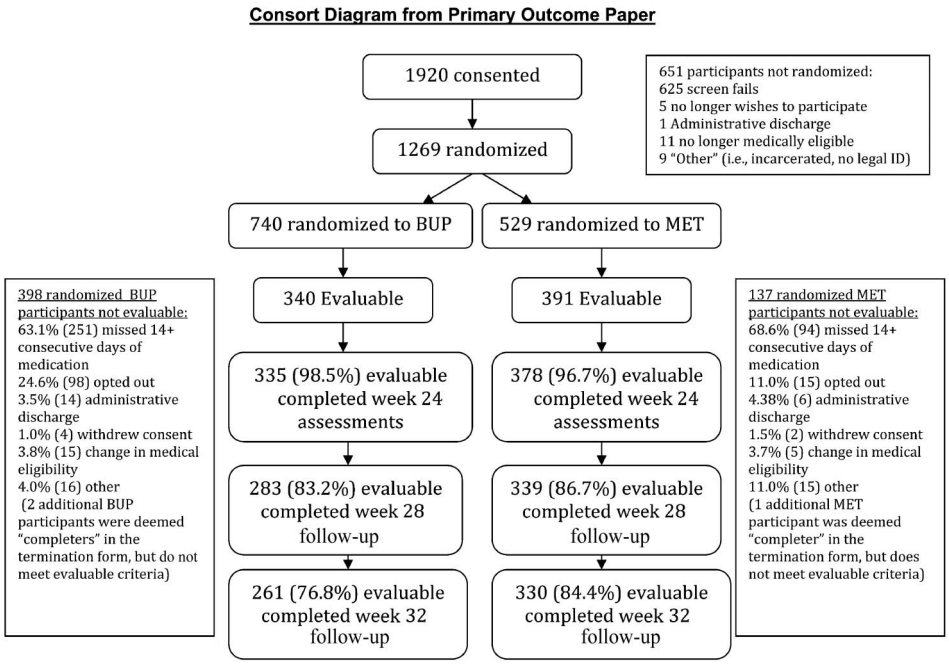

FIGURE 1. Consort diagram from the primary outcome article.

studies were randomized trials, the strength and consistency of the findings indicate that participation in MET maintenance is strongly associated with protection from HIV infection and that MET treatment reduces the risk behaviors that can spread HIV.[10,24–26] This risk reduction occurs both directly through reduction of injecting behaviors, but also by facilitating adherence to antiretroviral medication and reducing the viral load among persons who are infected.[27]

Buprenorphine is a schedule III μ-opioid partial agonist with a greater margin of safety and a less intensive withdrawal.[28,29] It is available in the United States as a tablet or film with 4 parts buprenorphine to 1 part naloxone in an attempt to reduce abuse if crushed and injected and is approved for treatment of opioid addicted individuals aged 16 years and older.[30–32] Like MET, treatment with buprenorphine–naloxone (BUP) appears to reduce HIV risk,[33,34] and we know of only 1 study that directly compared HIV risk in patients treated with buprenorphine vs. MET. It was conducted in Baltimore and randomized 47 patients to buprenorphine and 51 to MET. MET doses ranged from 60 to 100 mg/day; buprenorphine doses were 16–32 mg on Mondays and Wednesdays with a 50% higher dose on Fridays. HIV risk was assessed at baseline and at weeks 1, 2, 3, and 18 using the Risk Behavior Interview.[35] Patients in both groups had marked and equal reduction in injecting risk, but only the MET group had consistent declines in sexual risk.[36] Here, we present the results of a similar comparison of a much larger sample in a secondary analysis of data from a study conducted by the National Institute on Drug Abuse in the Clinical Trials Network.[37]

METHODS

The main study ("START") was a randomized trial that evaluated transaminase changes in patients randomized to treatment with MET or BUP. Participants were consenting individuals who were applying for treatment at 1 of 8 MET programs located across the United States. Eligibility criteria included being age 18 or older, meeting the DSM-IV-TR criteria for opioid dependence, and not having an alanine aminotransferase or aspartate aminotransferase value >5 times or alkaline phosphatase >3 times above the upper limit of normal. Exclusion criteria included serious medical conditions that could make study participation unsafe or impractical, schizophrenia, bipolar I disorder, homicidal or suicidal ideation, cognitive impairment that made informed consent difficult to obtain, and poor venous access such that repeated blood samples to measure liver enzymes would be difficult to obtain. Recruitment occurred between May 2006 and October 2009 with follow-up assessments through August 2010.

The Food and Drug Administration (FDA) requested this study based on reports of elevated liver enzymes in patients treated with BUP and required a minimum of 300 "evaluable" participants on each medication. The criteria for evaluable were completing 24 weeks on the assigned medication and providing at least half of the 8 liver tests that were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24. Test windows included ±2 days for weeks 1 and 2, and ±7 days for all other weeks. Due to a higher dropout rate in the BUP condition, the initial 1:1 randomization was changed to 2:1 (BUP:MET) in December 2007.

The initial BUP dose ranged from 2 to 8 mg with increases for persistent withdrawal to a maximum of 16 mg on the first day. Dosing was flexible and based on clinical response with further increases up to a maximum of 32 mg; the mean maximum daily dose among study participants was 22.1 mg (SD = 8.2; median = 24 mg). The maximum initial MET dose was 30 mg with an additional 5–10 mg if

needed on day 1 after 3 or more hours to suppress withdrawal symptoms. As with BUP, MET dosing was based on clinical response and could be increased in 5 to 10 mg increments with no maximum dose specified; the mean maximum MET dose was 93.2 mg (SD = 42.2; median = 90 mg).

Observed dosing occurred daily except on Sundays and holidays or when take-homes were permitted by local regulations. BUP participants were titrated to a maintenance dose, typically over the first few days; MET participants were titrated over several weeks. Both groups remained on study medication for 24 weeks and then tapered to 0 over ≤8 weeks or were referred for continuing treatment. Assessments were done at prespecified intervals and included urine drug tests, self-reported drug use, HIV risk, and blood samples for liver tests.

The analyses presented here were obtained from the HIV Risk Behavior Survey (RBS), an interviewer-administered measure of injecting and sexual HIV risk behavior.[38] It takes 6–10 minutes, was administered at baseline and at weeks 12 and 24, and collects information about drug and sexual behaviors over the past 30 days. Questions include number of times injected; sexual activity; condom use; times exchanged sex for drugs, money, or both; and HIV testing history. For these analyses, individual questions were used to create composite scores of injecting and sex risk. The injecting risk composite was defined as reporting at least 1 risk behavior [sharing needles, not using bleach to clean needles, sharing cooker, front/back loading of syringes (eg, pulling out the barrel of 1 syringe and filling it with another or vice versa)]. The sexual risk composite was defined as reporting more than 1 sexual partner and/or sex without a condom. Injection risk outcomes were modeled as count data and negative binomial distribution was specified in GENMOD procedure. Needle sharing and sexual behavior outcomes were modeled as Yes/No, and the PROC GENMOD/GEE option was used to compare the data.

RESULTS

There were 731 evaluable participants (BUP = 340, MET = 391) who completed the baseline RBS, and of these, 700 (95.8%) completed the 12-week RBS and 705 (96.4%) completed the 24-week RBS. At baseline, BUP participants reported more past 30-day nonheroin opioid use than MET participants (9.3 vs. 7.3 days; $P = 0.043$), but MET participants had a higher percentage of cocaine-positive urine tests (39.0 vs. 29.7; $P = 0.006$) and a higher percentage reported injecting drug use in the past 30 days (69.3 vs. 61.8; $P = 0.03$). Average age and all other baseline characteristics showed no statistically significant differences between groups (Table 1).

TABLE 1. Baseline Characteristics of Evaluable Participants

Demographic Characteristics	BUP (n = 340)	MET (n = 391)
Mean, age (SD)	39.3 (11.3)	38.4 (11.3)
Gender		
Male	71.2 (242)	64.7 (253)
Female	28.8 (98)	35.3 (138)
Ethnicity/Race		
Hispanic	15.6 (53)	14.3 (56)
White	72.9 (248)	79.3 (310)
Black or African American	12.1 (41)	10.7 (42)
American Indian/Alaskan Native	0.9 (3)	0.5 (2)
Asian	0.9 (3)	0.3 (1)
Native Hawaiian/Pacific Islander	0.3 (1)	0.0 (0)
Other	12.7 (43)	8.7 (34)
Unknown	0.3 (1)	0.5 (2)
Self-reported mean days of drug use in the past 30 days (SD)		
Cocaine	3.0 (6.3)	2.9 (5.9)
Heroin	24.3 (9.9)	24.2 (9.8)
Nonheroin opioids*	9.3 (12.0)	7.3 (11.0)
Amphetamines	0.8 (2.5)	1.0 (3.2)
Self-reported mean days of injection drug use (SD)		
Heroin by injection	20.0 (12.9)	20.6 (12.3)
Nonheroin opioids by injection	0.8 (4.0)	0.9 (3.9)
Percent positive urine drug test (n)		
Opiates (morphine)	85.3 (290)	86.7 (339)
Oxycodone	14.7 (50)	15.1 (59)
Cocaine†	29.7 (101)	39.4 (154)
Benzodiazepines	19.7 (67)	18.7 (73)
Cannabis	25.3 (86)	20.5 (80)
HIV risk behaviors reported for last 30 days		
Mean times injected with shared needles	2.1 (6.1)	4.8 (25.7)
% Reporting multiple sex partners (n)	6.8 (23)	8.2 (32)
% Reporting injection drug use past 30 days‡ (n)	61.8 (210)	69.3 (271)
Laboratory results		
Hepatitis B surface antibody	32.6 (97)	35.3 (138)
Hepatitis C core antibody	1.5 (5)	1.5 (6)
Hepatitis B surface antigen	0.3 (1)	0.5 (2)
Hepatitis C antibody	43.5 (148)	43.5 (170)
HCV RNA	32.9 (112)	28.4 (111)
HIV positive	1.2 (4)	0.5 (2)

Values are expressed as % (n) unless otherwise specified.
*t = 2.03, $P = 0.043$.
†$\chi^2 = 7.5$, $P = 0.0062$.
‡$\chi^2 = 4.60$, $P = 0.0320$.

Follow-up assessments showed significant reductions from baseline ($P \leq 0.0008$) in the mean number of times heroin, speedball, or other opioids were injected in the last 30 days, and the overall number of injection events. Significant reductions ($P < 0.0001$) were also noted in the percentage who shared needles, did not clean shared needles with bleach, shared cookers, engaged in front/back loading, and the needle risk composite score. There were no significant differences between groups on any of these outcomes. The only significant group difference on injecting risk was for amphetamines in which the mean number of times injected rose from 0.05 at baseline to 1.9 at 24 weeks in BUP participants vs. a decrease from 0.29 to 0.22 in MET participants ($P < 0.05$). The mean number of times

TABLE 2. Injection Drug Use and Needle Risk Behavior

	BUP			MET			*P*		
Variable	Baseline (n = 340)	12-Week Follow-up (n = 326)	24-Week Follow-up (n = 330)	Baseline (n = 391)	12-Week Follow-up (n = 374)	24-Week Follow-up (n = 375)	Tx	Time (Visit)	Tx × Time
Mean number of times injected cocaine	1.8	1.1	0.77	2.2	1.5	1.2	0.8813	0.1861	0.7585
Mean number of times injected heroin	64.6	1.9	2.7	65.3	3.9	4.4	0.6695	<0.0001	0.4797
Mean number of times injected speedball	2.3	0.69	0.22	4.1	0.74	0.42	0.5375	<0.0001	0.9633
Mean number of times injected other opiates	1.0	0.02	0.01	1.7	0.01	0.02	0.9919	0.0008	0.7064
Mean number of times injected amphetamines	0.05	0.07	1.9	0.29	0.02	0.22	0.0497	0.6135	0.0363
Mean number of times injected total	69.7	3.83	5.6	73.5	6.2	6.2	0.8756	<0.0001	0.9407
Shared needles, %	14.4	2.5	2.4	14.1	2.9	4.8	0.2008	<0.0001	0.1029
Did not clean shared needles with bleach, %	10.3	1.8	1.8	9.9	1.6	3.2	0.3692	<0.0001	0.3009
Shared cooker, %	17.1	2.5	3.0	18.9	4.8	4.5	0.7262	<0.0001	0.2959
Front/back load (any), %	21.2	3.1	4.6	20.5	5.9	4.5	0.7049	<0.0001	0.5311
Needle risk composite, %	25.0	4.2	5.2	24.8	7.2	6.9	0.4022	<0.0001	<0.1923

cocaine was injected dropped approximately equally in both groups but did not meet the threshold for statistical significance (Table 2).

Sexual risk behaviors in the last 30 days (>1 partner, sex without a condom), and sex risk composite were compared across time (baseline, 12, and 24 weeks) and between treatment groups. There was a significant reduction in sex with more than 1 partner over time and no group differences. Percent having multiple sex partners decreased equally in both groups ($P < 0.03$); however, MET participants reported greater reduction in the sex risk composite score than BUP participants ($P < 0.05$) (Table 3).

Sexual risk behavior was analyzed separately for males and females (Tables 4 and 5, respectively), and time effect and interactions were found. For males on BUP, the sex risk composite increased over time, whereas for males on MET, there was a reduction in sex risk over time and a significant difference between groups with more overall sex risk reduction on MET. For females, there was a significant reduction in the sex risk composite over time with no differences between groups.

DISCUSSION

These findings show marked and approximately equal reductions in injection and injection-related risk among participants who remained in their assigned treatment condition and completed 4 or more blood draws over 24 weeks. Reasons for the small but significant increase in amphetamine use in BUP participants are unclear and may be an incidental finding because it has not been previously reported.

The much smaller but significant decrease in the sexual risk composite among MET as compared with BUP participants could be the result of a greater impact on sexual hormone production among patients taking MET, particularly males. This would be consistent with reports from the 1970s that MET decreases gonadal hormone secretion during the first months of treatment with accompanying reductions in sexual activity[39,40] and with a more recent study that found much lower total testosterone levels in 83 men on MET maintenance as compared with 19 on buprenorphine.[41] The decrease in sex risk composite among males on MET, and the absence of a decrease in males on BUP (Table 4), is consistent with these data and with another study that also found lower testosterone levels in patients on MET as compared with BUP.[42] These differences in sexual effects could be a reflection of the full opioid agonist effects of MET vs. the partial agonist effects of BUP.

The higher dropout rate among participants assigned to BUP[37] suggests that MET may be more generally effective than BUP at reducing HIV risk over time, at least among individuals who enroll in treatment at MET clinic

TABLE 3. Sexual Risk Behavior

	BUP			MET			*P*		
Variable	Baseline (n = 340)	12-Week Follow-up (n = 326)	24-Week Follow-up (n = 330)	Baseline (n = 391)	12-Week Follow-up (n = 374)	24 Week Follow-up (n = 375)	Tx	Time (Visit)	Tx × Time
Multiple (>1) partners, %	6.8	7.9	5.2	8.2	4.3	5.1	0.6750	0.0329	0.3539
Unsafe sex (without condom), %	40.9	40.2	43.0	44.5	40.9	41.3	0.1602	0.2063	0.0914
Sex risk composite, %	44.4	45.7	46.7	49.6	43.6	44.5	0.0894	0.0490	0.0272

TABLE 4. Sexual Risk Behavior for Male

	Male								
	BUP			MET			*P*		
Variable	Baseline (n = 242)	12-Week Follow-up (n = 234)	24-Week Follow-up (n = 234)	Baseline (n = 253)	12-Week Follow-up (n = 243)	24-Week Follow-up (n = 245)	Tx	Time (Visit)	Tx × Time
Multiple (>1) partners, %	5.79	8.12	5.13	5.53	3.29	3.27	0.9728	0.1370	0.2931
Unsafe sex (without condom), %	39.26	39.32	44.02	42.29	40.74	41.22	0.2472	0.8370	0.1279
Sex risk composite, %	41.32	45.30	47.44	46.25	42.39	44.08	0.1575	0.5554	0.0318

sites. Despite these differences in dropout rates, the data clearly show that injecting risk was markedly and equally reduced regardless of medication assignment among those who remained in treatment. This finding indicates that BUP, like MET, is a successful HIV risk reduction intervention for patients who remain in treatment, but with the added advantage of being accessible in settings other than MET programs in the United States. For individuals who drop out of MET or BUP, naltrexone, residential treatment, or intensive self-help group participation could be helpful, depending on patient choice and available resources.

In addition to the differential dropout rate, a study limitation was that approximately 75% of the participants were Caucasian; thus, these findings may not apply to populations with higher representations of minorities. Findings may also differ in populations with higher rates of amphetamine, cocaine, or benzodiazepine use.

Overall, these findings further support the importance of expanding availability of evidence-based medical treatments for opioid addiction.[43] At the same time, it is often difficult to balance expanded access with diversion control. In the case of MET, one approach that current US law permits but is rarely used is to involve local pharmacies as medication dispensing stations. Another is to involve primary care providers in MET treatment as was done in one RCT where stable MET patients were transferred to primary care for ongoing treatment; however, the current US law does not allow primary care providers to prescribe MET for opioid dependence.[44] In contrast, such a development has occurred in the United Kingdom over the past 10 years with apparent success in reducing overdose deaths.[45,46]

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TABLE 5. Sexual Risk Behavior for Female

	Female								
	BUP			MET			*P* Values		
Variable	Baseline (n = 98)	12-Week Follow-up (n = 92)	24-Week Follow-up (n = 96)	Baseline (n = 138)	12-Week Follow-up (n = 131)	24-Week Follow-up (n = 130)	Tx	Time (Visit)	Tx × Time
Multiple (>1) partners, %	9.18	7.61	5.21	13.04	6.11	8.46	0.6989	0.1292	0.9470
Unsafe sex (without condom), %	44.90	42.39	40.63	48.55	41.22	41.54	0.5750	0.1055	0.5598
Sex risk composite, %	52.04	46.74	44.79	55.80	45.80	45.38	0.5489	0.0245	0.5433

REFERENCES

1. Haverkos HW. HIV/AIDS and drug abuse: epidemiology and prevention. *J Addict Dis.* 1998;17:91–103.
2. Hubbard RL, Marsden ME, Rachal JV, et al. *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill: University of North Carolina Press; 1989.
3. Ball JC, Lange WR, Myers CP, et al. Reducing the risk of AIDS through methadone maintenance treatment. *J Health Soc Behav.* 1988;29:214–226.
4. Ball JC, Ross A. *The Effectiveness of Methadone Maintenance Treatment*. New York: Springer Verlag; 1991.
5. Hubbard RL, Craddock SG, Flynn PM, et al. Overview of one-year follow-up outcomes in the substance abuse treatment outcome study (DATOS). *Psychol Addict Behav.* 1997;11:261–268.
6. Gowing L, Farrell R, Bornemann R, et al. Methadone treatment of injecting opioid users for prevention of HIV infection. *J Gen Intern Med.* 2006;21:193–195.
7. Hartel DM, Schoenbaum EE. Methadone treatment protects against HIV infection: two decades of experience in the Bronx, New York City. *Public Health Rep.* 1998;113:107–115.
8. Lawrinson P, Ali R, Buavirat A. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. *Addiction*. 2008;103:1484–1492.
9. Caplehorn JR, Ross MW. Methadone maintenance and the likelihood of risky needle-sharing. *Int J Addict.* 1995;30:685–698.
10. Metzger DS, Woody GE, McLellan AT, et al. Human immunodeficiency virus seroconversion among in-and out-of-treatment intravenous drug users: an 18-month prospective follow-up. *J Acquir Immune Defic Syndr.* 1993;6:1049–1056.
11. Qian HZ, Hao C, Ruan Y, et al. Impact of methadone on drug use and risky sex in China. *J Subst Abuse Treat*. 2008;34:391–397.
12. Wong KH, Lee SS, Lim WL, et al. Adherence to methadone is associated with a lower level of HIV-related risk behaviors in drug users. *J Subst Abuse Treat.* 2003;24:233–239.
13. McLellan AT, Arndt IO, Metzger DS, et al. The effects of psychosocial services in substance abuse treatment. *JAMA*. 1993;269:1953–1959.
14. Avants SK, Margolin A, Sindelar JL, et al. Day treatment versus enhanced standard methadone services for opioid-dependent patients: a comparison of clinical efficacy and cost. *Am J Psychiatry.* 1999;156:27–33.
15. Booth RE, Crowley TJ, Zhang Y. Substance abuse treatment entry, retention and effectiveness: out-of-treatment opiate injection drug users. *Drug Alcohol Depend.* 1996;42:11–20.
16. Kwiatkowski CF, Booth RE. Methadone maintenance as HIV risk reduction with street-recruited injecting drug users. *J Acquir Immune Defic Syndr.* 2001;26:483–489.
17. Gossop M, Marsden J, Stewart D, et al. Reduced injection risk and sexual risk behaviors after drug misuse treatment: results from the National Treatment Outcome Research Study. *AIDS Care*. 2002;14:77–93.
18. Thiede H, Hagan H, Murrill CS. Methadone treatment and HIV and hepatitis B and C risk reduction among injectors in the Seattle area. *J Urban Health.* 2000;77:331–344.
19. Centers for Disease Control. Antibodies to a retrovirus etiologically associated with acquired immunodeficiency syndrome (AIDS) in populations with increased incidences of the syndrome. *MMWR Morb Mortal Wkly Rep.* 1984;33:377–379.
20. Novick DM, Joseph H, Croxon T, et al. Absence of antibody to human immunodeficiency virus in long-term, socially rehabilitated methadone maintenance patients. *Arch Intern Med.* 1990;150:97–99.
21. Blix O, Gronbladh L. Impact of methadone maintenance treatment on the spread of HIV among IV heroin addicts in Sweden. In: Loimer N, Schmid R, Springer A, eds. *Drug Addiction and AIDS*. Wien, New York: Springer-Verlag; 1991;200–205.
22. Moss AR, Vranizan K, Gorter R, et al. HIV seroconversion in intravenous drug users in San Francisco, 1985-1990. *AIDS.* 1994;8:223–231.
23. Serpelloni G, Carrieri MP, Rezza G, et al. Methadone treatment as a determinant of HIV risk reduction among injecting drug users: a nested case-control study. *AIDS Care.* 1994;6:215–220.
24. Sorenson JL, Copeland AL. Drug abuse treatment as an HIV prevention strategy: a review. *Drug Alcohol Depend.* 2000;59:17–31.
25. Farrell M, Gowing L, Marsden J, et al. Effectiveness of drug dependent treatment in HIV prevention. *Int J Drug Policy.* 2005;16S:S67–S75.
26. Sullivan L, Metzger DS, Fudala PJ, et al. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injection drug users. *Addiction*. 2005;100:150–158.
27. Berg KM, Litwin A, Li X, et al. Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: a randomized controlled trial. *Drug Alcohol Depend.* 2011;113:192–199.
28. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry.* 1978;35:501–516.
29. Walsh SL, Preston KL, Stitzer ML, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther.* 1994;55:569–580.
30. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA.* 1992;267:2750–2755.
31. Strain EC, Stitzer ML, Liebson IA, et al. Buprenorphine versus methadone in the treatment of opioid dependence: self-reports, urinalysis, and addiction severity index. *J Clin Psychopharmacol.* 1996;16:58–67.
32. Fudala PJ, Yu E, Macfadden W, et al. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend.* 1998;50:1–8.
33. Sullivan LE, Fiellin DA. Buprenorphine: its role in preventing HIV transmission and improving the care of HIV-infected patients with opioid dependence. *Clin Infect Dis.* 2005;41:891–896.
34. Sullivan LE, Moore BA, Chawarski MC, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. *J Subst Abuse Treat.* 2008; 35:87–92.
35. Brooner RK, Greenfield L, Schmidt CW, et al. Antisocial personality disorder and HIV infection among intravenous drug abusers. *Am J Psychiatry.* 1993;150:53–58.
36. Lott DC, Strain EC, Brooner RK, et al. HIV risk behaviors during pharmacologic treatment for opioid dependence: a comparison of levomethadyl acetate, buprenorphine, and methadone. *J Subst Abuse Treat.* 2006;31:187–194.
37. Saxon AJ, Ling W, Hillhouse M, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. *Drug Alcohol Depend.* 2013;128:71–76. PMC3543467.
38. Needle R, Fisher DG, Weatherby N, et al. Reliability of self-reported HIV risk behaviors of drug users. *Psychol Addict Behav.* 1995;9: 242–250.
39. Hanbury R, Cohen M, Stimmel B. Adequacy of sexual performance in men maintained on methadone. *Am J Drug Alcohol Abuse.* 1977;4: 13–20.
40. Crowley TJ, Simpson R. Methadone dose and human sexual behavior. *Int J Addict.* 1978;13:285–295.
41. Hallinan R, Byrne A, Agho K, et al. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. *Int J Androl.* 2009;32:131–139.
42. Bliesener N, Albrecht S, Schwager A, et al. Plasma testosterone and sexual function in men receiving buprenorphine maintenance treatment for opioid dependence. *J Clin Endocrinol Metab.* 2005;90:203–206.
43. Nosyk B, Anglin MD, Brissette S, et al. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff (Millwood).* 2013;32:1462–1469.
44. Fiellin DA, O'Connor PG, Chawarski M, et al. Methadone maintenance in primary care: a randomized controlled trial. *JAMA*. 2001; 286:1724–1731.
45. Strang J, Manning V, Mayet S, et al. Does prescribing for opiate addiction change after national guidelines? Methadone and buprenorphine prescribing to opiate addicts by general practitioners and hospital doctors in England, 1995-2005. *Addiction*. 2007;102:761–770.
46. Strang J, Hall W, Hickman M, et al. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland. *BMJ.* 2010;341: c4851. doi: 10.1136/bmj.c4851.