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Biomedical HIV prevention including pre-exposure prophylaxis and opiate agonist therapy for women who inject drugs: State of research and future directions

Kimberly Page[1], **Judith Tsui**[2], **Lisa Maher**[3], **Kachit Choopanya**[4], **Suphak Vanichseni**[4], **Philip A. Mock**[5], **Connie Celum**[6], and **Michael Martin**[5,7]

[1]Epidemiology, Biostatistics and Preventive Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA [2]Department of Medicine, University of Washington, Seattle, WA, USA [3]Kirby Institute for Infection and Immunity, UNSW Australia, Sydney, Australia [4]Bangkok Tenofovir Study Group, Taksin Hospital, Bangkok, Thailand [5]Thailand MOPH - U.S. Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand [6]Department of Global Health and Medicine, University of Washington, Seattle, WA, USA [7]Centers for Disease Control and Prevention, Division of HIV/AIDS Prevention, Atlanta, USA

Abstract

Women who inject drugs are at higher risk of HIV compared to their male counterparts as a result of multiple factors including biological, behavioral and socio-structural, yet comparatively little effort has been invested in testing and delivering prevention methods that directly target this group. In this paper, we discuss the need for expanded prevention interventions for women who inject drugs, focusing on two safe, effective, and approved, yet underutilized biomedical prevention methods: opiate agonist therapy (OAT) and oral pre-exposure prophylaxis (PrEP). While both interventions are well researched they have not been well examined in the context of gender. We discuss the drivers of women injectors' higher HIV risk, review the effectiveness of OAT and PrEP interventions among women, and explain why these new HIV prevention tools should be prioritized for women who inject drugs. There is substantial potential for impact of

Corresponding author: Kimberly Page, Ph.D., MPH, Epidemiology, Biostatistics and Preventive Medicine, Dept. of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA, MSC10 5550, 1 University of New Mexico, Albuquerque, NM 87131-0001, Tel: 1-505-272-4180, Fax: 1-505-272-2570, Pagek@salud.unm.edu.
Judith Tsui, M.D., Department of Medicine, University of Washington, Box 359780, 325 Ninth Ave, Seattle, WA 98104-2499, tsuij@uw.edu
Lisa Maher, Ph.D., Kirby Institute for Infection and Immunity, Faculty of Medicine, UNSW Australia, Sydney, NSW, 2051, Australia, Lmaher@kirby.unsw.edu.au
Kachit Choopanya, MD, MPH, Bangkok Tenofovir Study Group, Taksin Hospital, 543 Somdet Chaophraya Road, Bangkok 10600, Thailand, Tel: +02 863 2121, Fax: +02 863 2129, kachitc@gmail.com
Suphak Vanichseni, MD, MPH, Bangkok Tenofovir Study Group, Taksin Hospital, 543 Somdet Chaophraya Road, Bangkok 10600, Thailand, Tel: +02 863 2121, Fax: +02 863 2129, suphakv@yahoo.com
Philip A. Mock, MAppStats, DDC 7, Ministry of Public Health, Nonthaburi 11000, Thailand, Tel: +02 580 0669, Fax: +02 580 0712, pgm6@cdc.gov
Connie Celum, M.D., Department of Medicine, University of Washington, Box 359780, 325 Ninth Ave, Seattle, WA 98104-2499, ccelum@uw.edu
Michael Martin, MD, MPH, DDC 7, Ministry of Public Health, Nonthaburi 11000, Thailand, Tel: +02 580 0669, Fax: +02 580 0712, Znd9@cdc.gov

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OAT and PrEP programs for women who inject drugs in the context of broader gender-responsive HIV prevention initiatives. While awaiting efficacy data on other biomedical approaches in the HIV prevention research 'pipeline', we propose that the scale up and implementation of these proven, safe, and effective interventions are needed now.

INTRODUCTION

Preventing HIV infection remains a challenge thirty-two years after the recognition of the virus. New effective prevention strategies are needed, and the implementation of strategies that have been shown to be safe and effective must be accelerated. Globally, injection drug use remains a key route of HIV transmission, and in areas where HIV is driven by injection drug use, women who inject drugs (WWID) play an increasingly important role in the growth and evolution of the HIV epidemic (1–3). Compared to men who inject, WWID have a modest but measurable increased risk of HIV infection (1). This increased risk is likely the result of multiple biological, behavioral and socio-structural factors, yet comparatively little effort has been invested in the evaluation and delivery of effective HIV prevention methods directly targeting this group. In this paper we discuss the need for expanded prevention interventions for women who inject drugs, focusing on two safe, effective, and approved, yet underutilized biomedical prevention methods: opiate agonist therapy (OAT) and oral pre-exposure prophylaxis (PrEP). While both interventions are well researched, they have not been well examined in the context of gender.

We reviewed published data on the efficacy and effectiveness of OAT and PrEP interventions among women and their potential impact on HIV-associated risk behaviors and incidence in this population and examine the reasons why these new HIV prevention tools should be prioritized for women who inject drugs.

Despite widespread knowledge of how HIV is transmitted, as well as inexpensive and effective methods to prevent HIV infection, 2.1 million people worldwide were estimated to have contracted HIV in 2013 (4). Injection drug use contributes to a significant fraction of these new HIV infections; the World Health Organization (WHO) estimates that on average at least 10% of new infections globally result from injection drug use (5), more than 200,000 new HIV infections a year. In 2008, it was estimated that just over two-thirds of the estimated 3 million HIV-infected people who inject drugs (PWID) were in Eastern Europe, East and Southeast Asia, and Latin America (6). These numbers likely underestimate the burden of HIV infections caused by drug use because injecting populations are difficult to enumerate, and HIV surveillance in PWID is less systematic than among other risk groups (6, 7). We are not aware of any global reviews of HIV among PWID that stratify by gender. One study examining trends in the population prevalence of PWID across 96 U.S. metropolitan service areas between 1992 and 2007 examined prevalence of WWID (8). The 2007 estimate of HIV prevalence among WWID (per 10,000) was 74.3 in comparison with an estimated prevalence among men of 132.94, for a male: female ratio of 1.78 to 1. More recently, Lansky et al.(9) estimated that the population proportion of WWID (any lifetime use) in the U.S. was 1.6% (95% CI 1.1, 2.0%) corresponding to 2,059,709 women (range: 1,513,969–2,606,450). In comparison, estimates for men were more than double those for

women: prevalence 3.6% (95% CI 2.4, 4.8%), corresponding to 4,532,348 men who had ever injected (range 3,040,447–6,024,250). If we assume that women make up between one-third and a half of all HIV infections among PWID worldwide, then over one million are living with HIV and 82,000 to 125,000 become newly infected each year (based on 2013 estimates). UNAIDS, WHO, the World Bank and other systematic reviews that discuss HIV risk associated with injection drug use do not report gender-specific estimates of population size, and discussion of women's risk is strictly in terms of their childbearing age, or sexual risk in association with heterosexual sex or transactional sex (4, 6).

Due to concomitant sexual and injecting exposures, PWID are at incrementally higher risk of HIV than other key populations. In a review of 117 studies conducted in 14 countries, Des Jarlais et al., (1) found that female injectors had higher odds of HIV infection compared to male injectors (OR 1.18; 95% CI 1.10, 1.26). Studies have shown that female injectors are more likely to have higher risk behaviors, including sexual and injection risks, than their male counterparts (10–13). Some WWID engage in sex work (14–17), potentially exposing themselves to other sexually transmitted diseases (18), and increasing their risk for HIV infection. Women in overlapping injecting and sexual relationships often have little or no control over partners' condom use and injecting equipment (19, 20). Other key issues include access to clean needles and syringes, which remains a challenge and is mired in political and moral debates in many parts of the world, including in the U.S. (21). The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that only "two of 32 reporting countries provide the recommended minimum of at least 200 sterile syringes per year for each person who injects drugs." (4). While condoms are easily available and widely promoted, women have limited power to control their use. The disproportionate sexual and injection risks experienced by WWID are further exacerbated by stigma/discrimination, and violence (19, 22–24). Women are more likely to conceal their injection risk and as a result, are harder to reach, count and engage in prevention programs(22). Drug users, including both injection and non-injection users, may not be prioritized as a key population in some areas, and women in particular may fall through the HIV prevention 'cracks'. In many locations, sex work and injection drug use are co-occurring exposures, and prevention programs for these groups need to consider these intersecting risks. Reliable surveillance data on PWID, in general, and WWID in particular is lacking in many settings due to legal barriers preventing access to these populations.

In addition to condom distribution and needle and syringe programs, the current "combination" HIV prevention package proposed for PWID by the WHO includes HIV counseling and testing, linkage to HIV care, access to opiate agonist therapy (OAT), and evidence based psychosocial interventions (25, 26). With persistently high rates of new infection, ongoing risk and limited access to prevention, WWID need access to effective HIV prevention technologies. Biomedical HIV prevention approaches, defined as "strategies that use medical and public health approaches to block infection, decrease infectiousness, and reduce susceptibility" (27), are now available and should be included as a part of combination prevention approaches. Currently, "biomedical HIV prevention" includes effective biomedical strategies including diagnosis and treatment of sexually transmitted infections, male circumcision, pharmacologic therapy for substance abuse treatment (including OAT), and daily oral PrEP (28–30). For women, vaccines and topical protections,

including microbicides and vaginal gels such as 1% tenofovir (topical PrEP) are high priority research areas (31). Vaccines remain elusive, and topical 1% vaginal tenofovir, used before and after sex as PrEP, has shown promise in one study but requires confirmatory evidence of efficacy for regulatory approval (53,76,77). Research into long-acting injectable PrEP is progressing, but this research is in the early stages (32, 33). Two important HIV prevention tools that deserve more attention and expanded availability are OAT and PrEP. Both have been shown to be safe and effective and are approved for use – yet both are underutilized.

OAT and HIV prevention in women who inject drugs

Untreated substance use disorders (particularly opioid use disorders) are a major source of HIV transmission, particularly in developing countries (34). Injection drug use is frequently a consequence of untreated opiate addiction, for which there are effective pharmacotherapies. Methadone and buprenorphine have been shown to be effective in reducing opiate use (35), reducing injecting and sexual risk behaviors (36), and preventing HCV and HIV (37–41). Both methadone and buprenorphine have opioid agonist properties, which reduce craving for illicit opiate use. However, buprenorphine, which was approved for use by the U.S. Food and Drug Administration in 2002, is a partial mu-opioid receptor agonist, and therefore has a ceiling that limits side effects such as sedation and respiratory depression. Maintenance therapy with long-acting oral medications that reduce craving can break the cycle of intoxication and withdrawal from heroin use and ongoing injection drug use. Longer courses of OAT in general have been associated with better health and social outcomes (42).

Both methadone and buprenorphine have been demonstrated in randomized controlled trials to lead to reductions in illicit opioid use. A 2009 Cochrane review found 11 randomized trials of methadone maintenance compared to non-pharmacological treatment for opioid dependence. Overall, methadone maintenance was shown to be associated with a 44% (RR 0.66; 95% CI 0.56, 0.78) improvement in retention and suppression of heroin use (measured by self-report and biomarkers) (43). A subsequent review of methadone and buprenorphine maintenance therapy which included 31 trials, showed that both of these pharmacological interventions were significantly associated with reductions in illicit opioid use as measured by urine drug tests (37). Additionally, risk behaviors associated with HIV declined, including the number of participants reporting injection drug use, frequency of injection, and sharing of equipment (although these effects were difficult to disentangle from the effects of decreased injecting overall) (38). The reductions seen in transactional sex, including exchanging sex for money or drugs, with OAT (38) may be due to a reduction of the need for income to purchase illicit drugs.

A recent systematic review and meta-analysis of data on 819 incident HIV infections over 23,608 person-years (py) of observation found that OAT was associated with a 54% reduction in the risk of HIV infection among PWID (RR=0.46; 95% CI: 0.32–0.67; $p<0.0001$). No gender-specific estimates were provided, and most studies included had modest sample sizes with the majority of participants being male, consistent with a male predominance among PWID (8, 9). OAT has also been shown to be effective in preventing

HCV (39–41). WWID report higher rates than men for both injecting and sexual HIV risk behaviors (10–12). Thus, the risk of infection with blood-borne viruses including HIV and HCV is likely increased among WWID (1, 12, 44).

Access and retention in substance use treatment that includes OAT should be a priority HIV prevention area for WWID. Women are disproportionately under-represented in inpatient and outpatient substance abuse treatment programs, suggesting a disparity in access to OAT (45), although this may not be true in all settings (46). Women may delay presentation for treatment. For example, a national multi-site study conducted in the U.S. found that among opioid-dependent patients presenting for treatment, women not only demonstrated a more severe clinical profile than men did, as evidenced by higher Addiction Severity Index scores in multiple domains, but also reported higher opioid craving (47) and comorbid mental health diagnoses (48). The data on retention in OAT by gender is mixed; the U.S. Substance Abuse and Mental Health Administration reports that gender is not a good predictor of retention, in part because of the complex interaction of multiple demographic, psychosocial, psychiatric, and health-status factors (49). It should be recognized that not all WWID use opioids, and treatment strategies for other drug dependencies are also urgently needed. To date, pharmacotherapy for non-opiate drug dependence has shown some promise but no evidence of effectiveness in clinical trials (50). Furthermore, the importance of social, cultural and personal barriers in preventing women from accessing drug treatment in general are substantial and should not be overlooked(51). Stigma, fear of inter-partner violence or abandonment, and fear of loss of custody of children are all well-documented barriers that may impede WWID from accessing drug treatment, including OAT (52–54).

Pre-Exposure prophylaxis (PrEP) in women who inject drugs

Seven large randomized controlled trials have been conducted assessing HIV PrEP (28, 55–60). Four have provided compelling evidence that when used, it prevents or substantially reduces the risk of HIV acquisition among women (56, 57, 59, 61). Two of the trials had sufficient data to assess the impact of PrEP on women and showed statistically significant decreases in the risk of HIV infection (54, 55). Trials of oral PrEP have shown reductions in HIV incidence ranging from 49.4% to 78.6% (57, 59, 61). In the CAPRISA study, topical PrEP reduced HIV risk by 38.5% among women (56); however, two other large randomized trials, VOICE (62) and FACTS 001 (63) did not show a reduction in HIV risk among women using topical PrEP. Collectively, these studies enrolled a geographically diverse group of women in different risk settings. The Bangkok Tenofovir Study (BTS) (61) specifically enrolled PWID, and included women. Strong dose–response relationships have been shown between adherence to PrEP pill-taking (52,54,55) or gel-use (53) and HIV protection in the studies where PrEP was effective, whilst no protective effect was demonstrated in studies with overall low study drug adherence (60, 64). Based on the results of these trials, the U.S. Centers for Disease Control and Prevention (CDC) has issued guidance on the use of PrEP to limit sexual and parenteral HIV transmission (65, 66).

The BTS assessed the safety and efficacy of oral PrEP in HIV-uninfected men and women, aged 20 to 60 years, who reported injecting drugs in the year before enrollment; trial results and a review of participant risk behavior have been published (61, 67). The trial was

conducted at 17 Bangkok Metropolitan Administration (BMA) drug treatment clinics. Participants were not required to have attended the BMA clinics prior to the study. Thailand's narcotics law prohibits the distribution of needles to inject illicit drugs and needles are not provided in the clinics. However, sterile needles and syringes are available to the public over the counter at low cost in pharmacies in Bangkok. A total of 2413 participants were randomly assigned in a 1:1 ratio to receive daily oral tenofovir 300 mg or placebo.

We analyzed BTS data limited to women participants using chi-square for baseline data and generalized estimating equations. Table 1 provides the baseline characteristics of the 489 WWID enrolled in the BTS trial: median age 30 (Interquartile range [IQR] 26, 36) years, 260 (53.2%) with primary (6 years) education or less, and 101 (20.7%) with self-report of being in police custody in the 12 weeks prior to enrollment. There were no differences between the group receiving Tenofovir compared to placebo with respect to reported drug use or sexual behavior risks, with 62 (12.7%) women enrolled in methadone programs, and over half (54.4%, n=266) reported injecting drugs in the 12 weeks before enrollment. Women were followed for a total of 1990 person-years (py) (maximum 6.9 years). Among the 489 women, the 11 who became HIV infected included 9 in the placebo group (incidence, 0.92/100 py) and 2 in the Tenofovir group (incidence, 0.20/100 py) indicating a 78.6% reduction in risk (95% CI, 16.8, 96.7; p=0.03). This protective effect was almost twice that seen in men (37.6%), though the 95% CIs overlap. The number and proportion of women reporting injection drug use, and needle sharing during the previous 3 months decreased significantly during follow-up (Table 2). Reported sexual risk behaviors also decreased, including the proportion reporting sex with more than one partner during the previous 3 months and sex with casual partners (Table 2). Controlling for age, adherence (average/mean of days based on study diaries) was better in women (median 95.6%, IQR 81.1, 98.9) compared with men (median 93.8%; IQR 78.8, 98.7; p=0.04). In summary, these results support the efficacy of PrEP in WWID. Along with a good safety profile, the protective effect of PrEP was high, and participant reports of drug use and needle sharing decreased, demonstrating that with appropriate risk-reduction counseling and access to methadone maintenance support, risk compensation can be limited or avoided. All of these findings suggest that PrEP should be scaled up among WWID.

DISCUSSION/CONCLUSIONS

Several commentaries have been published about the need to integrate HIV biomedical prevention into practice (30, 68, 69), particularly with interventions for high-risk women (29). These discussions are important because they note the difficulties associated with behavior change and the limitations of current mainstream (non-biomedical) prevention approaches. However, few reviews address the needs of PWID, and little attention is given to WWID despite their high risk of HIV infection (23, 70). There is an important need to better quantify the population of WWID globally. Gender-specific population estimates could greatly inform planning and HIV prevention activities. While there is agreement within the HIV prevention field on the importance of implementing HIV biomedical interventions as part of a 'combined' and strengthened response to the HIV epidemic that includes integration of behavioral, structural and community-based efforts (68, 71–74), there

has been limited focus on the needs of women who inject drugs. The CDC has recommended PrEP use for PWID and has issued guidance (66); however, the WHO has not (25). Globally, it is widely acknowledged that existing interventions for PWID, including needle and syringe programs and OAT, need to be scaled up (21). Despite support for OAT by many countries there is a significant unmet need for this intervention, with an estimated 90% of opiate users lacking access(4). A recent review, Degenhardt et al., (75) notes progress in access to OAT in China and some Southeast Asian countries, but little progress in the U.S. or Russia, two countries with the largest numbers of PWID. There are also gaps in needle and syringe coverage, access to antiretroviral therapy, and ongoing adverse effects of stigmatization and incarceration of PWID. In summary, OAT has been demonstrated to be effective in preventing HIV among men and women who inject drugs. WWID may be at increased risk for acquiring HIV because of higher levels of risk taking associated with sexual activity and drug injection; therefore, OAT may be particularly effective among women, as it has been linked to both improved sex and drug risk behaviors. However, gender-specific estimates of the impact of OAT on HIV incidence are not known. Further research is needed to assess barriers women face accessing and consistently using OAT. There is also a significant need to address non-opioid injection drug use among women.

The results of the BTS study provide important information for WWID. Although the study was not powered to assess efficacy by subgroup, the results among women showed high levels of protection against incident HIV infection and significant reductions in drug use. These combined effects are important. The availability of directly observed therapy (DOT) delivery likely facilitated adherence, and ongoing counseling and access to OAT likely contributed to reduced risk behaviors. Although the study did not supply syringes and needles, participants could purchase them at low cost without a prescription from pharmacies in Bangkok. These factors suggest that oral PrEP, currently recommended as daily FTC/TDF (61), can have a substantial impact on the risk of HIV infection among women who inject.

The evidence reviewed here supports the expansion of programs to make OAT and PrEP more accessible to WWID in the context of HIV prevention using gender-responsive approaches to enhance impact. It is well recognized that women benefit from women-centered services. Several “gender-based” HIV prevention interventions focused on women have been successfully developed with the aim of reducing sexual risks in women, including increasing condom use and reducing sex client and partner violence, promoting gender empowerment, community mobilization and micro-enterprise (76, 77). Gender-specific services, including ‘women only’ needle and syringe programs (60) have been shown to appeal to WWID. Gender-based approaches can reduce HIV incidence, are cost-effective, and, in some cases cost-saving (78). The U.S.-based Center for Substance Abuse and Mental Health Services Administration has published a report assessing the needs of women in drug treatment that is a useful guide for gender-based biomedical HIV prevention (49), and the United Nations Development Programme has issued new guidance stressing the value and need for synergistic investment in integrating gender-responsive HIV programming (79). While the latter report (79) is more focused on promoting gender equality and violence reduction in general, than on specific HIV prevention strategies among women, it is encouraging that UN agencies are recognizing the importance of gender-specific

programming. In a recent commentary on scaling up PrEP, Katz (69) asks pertinent questions regarding ‘who’ and ‘how many’ receive PrEP. WWID represent a highly impacted and large proportion of the population at risk for HIV that is often overlooked. There are important opportunities to access this hard-to-reach population, including working with community-based groups, syringe and needle exchange programs, OAT programs, and possibly HCV treatment clinics. Providers, including clinicians providing primary care and reproductive health services, and prevention educators should be aware of the findings and recommendations of these two important prevention approaches (62). Further evidence including modeling and cost-effectiveness studies of the impact of expanded access to OAT and PrEP is needed to inform policy-makers and HIV programs globally. Programs designed to provide social and behavioral support for women using OAT and PrEP are needed to maintain good adherence and retention. Considerable energy is currently being focused on new technologies for women at risk of HIV (53,76,77). However, it is important to not lose sight of the fact that two highly effective interventions for preventing HIV (OAT and PrEP) exist. Successfully implementing these safe and effective HIV prevention tools will limit new HIV infections among women who inject drugs and help inform subsequent HIV prevention efforts.

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References

1. Des Jarlais DC, Feelemyer JP, Modi SN, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: an international systematic review of high seroprevalence areas. Drug Alcohol Depend. 2012; 124(1–2):95–107. [PubMed: 22257753]
2. Strathdee SA, Galai N, Safaiean M, Celentano DD, Vlahov D, Johnson L, et al. Sex differences in risk factors for HIV seroconversion among injection drug users: a 10-year perspective. Arch Intern Med. 2001; 161(10):1281–8. [PubMed: 11371255]
3. Thomas K. Female injection drug users in Vancouver face higher risks of HIV infection. Canadian HIV/AIDS policy & law review / Canadian HIV/AIDS Legal Network. 2002; 7(1):36. [PubMed: 14765487]
4. UNAIDS. [Accessed, January 5, 2015] Global Report: UNAIDS report on the global AIDS Epidemic. 2013. http://wwwunaidsorg/sites/default/files/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_enpdf
5. Organization. WH. [Accessed January 7, 2015] HIV/AIDS: Injecting drug use. http://www.who.int/hiv/topics/idu/en/
6. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet. 2008; 372(9651):1733–45. [PubMed: 18817968]
7. Topp L, Day CA, Iversen J, Wand H, Maher L. Collaboration of Australian N. Fifteen years of HIV surveillance among people who inject drugs: the Australian Needle and Syringe Program Survey 1995–2009. AIDS. 2011; 25(6):835–42. [PubMed: 21192232]
8. Tempalski B, Pouget ER, Cleland CM, Brady JE, Cooper HL, Hall HI, et al. Trends in the population prevalence of people who inject drugs in US metropolitan areas 1992–2007. PLoS One. 2013; 8(6):e64789. [PubMed: 23755143]

9. Lansky A, Finlayson T, Johnson C, Holtzman D, Wejnert C, Mitsch A, et al. Estimating the number of persons who inject drugs in the united states by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. PLoS One. 2014; 9(5):e97596. [PubMed: 24840662]
10. Bennett GA, Velleman RD, Barter G, Bradbury C. Gender differences in sharing injecting equipment by drug users in England. AIDS Care. 2000; 12(1):77–87. [PubMed: 10716020]
11. Evans JL, Hahn JA, Page-Shafer K, Lum PJ, Stein ES, Davidson PJ, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). J Urban Health. 2003; 80(1):137–46. [PubMed: 12612103]
12. Davey-Rothwell MA, Latkin CA. Gender differences in social network influence among injection drug users: perceived norms and needle sharing. J Urban Health. 2007; 84(5):691–703. [PubMed: 17682947]
13. El-Bassel N, Gilbert L, Terlikbayeva A, Beyrer C, Wu E, Shaw SA, et al. HIV risks among injecting and non-injecting female partners of men who inject drugs in Almaty, Kazakhstan: implications for HIV prevention, research, and policy. Int J Drug Policy. 2014; 25(6):1195–203. [PubMed: 24556208]
14. Cleland CM, Des Jarlais DC, Perlis TE, Stimson G, Poznyak V. and the WHO Phase II Drug Injection Collaborative Study Group. HIV risk behaviors among female IDUs in developing and transitional countries. BMC Public Health. 2007; 7:271. [PubMed: 17908299]
15. Benotsch EG, Somlai AM, Pinkerton SD, Kelly JA, Ostrovski D, Gore-Felton C, et al. Drug use and sexual risk behaviours among female Russian IDUs who exchange sex for money or drugs. Int J STD AIDS. 2004; 15(5):343–7. [PubMed: 15117506]
16. Asher AK, Hahn JA, Couture MC, Maher K, Page K. People who inject drugs, HIV risk, and HIV testing uptake in sub-Saharan Africa. The Journal of the Association of Nurses in AIDS Care : JANAC. 2013; 24(6):e35–44. [PubMed: 23164598]
17. Baral S, Beyrer C, Muessig K, Poteat T, Wirtz AL, Decker MR, et al. Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis. 2012; 12(7):538–49. [PubMed: 22424777]
18. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations between herpes simplex virus type 2 and HCV With HIV among injecting drug users in New York City: the current importance of sexual transmission of HIV. Am J Public Health. 2011; 101(7):1277–83. [PubMed: 21566021]
19. Razani N, Mohraz M, Kheirandish P, Malekinejad M, Malekafzali H, Mokri A, et al. HIV risk behavior among injection drug users in Tehran, Iran. Addiction. 2007
20. Morris MD, Evans J, Montgomery M, Yu M, Briceno A, Page K, et al. Intimate injection partnerships are at elevated risk of high-risk injecting: a multi-level longitudinal study of HCV-serodiscordant injection partnerships in San Francisco, CA. PLoS One. 2014; 9(10):e109282. [PubMed: 25286346]
21. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010; 375(9719):1014–28. [PubMed: 20189638]
22. [Accessed January 5, 2015] The Global Coalition on Women and AIDS. Women who use drugs, harm reduction and HIV. 2011. http://womenandaids.net/CMSPages/GetFile.aspx?guid=74d74180-8cba-4b95-931e-90bd0c4abef4&disposition=inline
23. El-Bassel N, Terlikbaeva A, Pinkham S. HIV and women who use drugs: double neglect, double risk. Lancet. 2010; 376(9738):312–4. [PubMed: 20650519]
24. Simmonds L, Coomber R. Injecting drug users: a stigmatised and stigmatising population. Int J Drug Policy. 2009; 20(2):121–30. [PubMed: 17981451]
25. Organization. WH. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva Switzerland: 2014. http://apps.who.int/hiv/pub/guidelines/keypopulaitons/ [Accessed Jan 5, 2015]
26. Dutta, A.; Wirtz, A.; Stanciole, A.; Oelrichs, R.; Semini, I.; Baral, S., et al. The Global HIV Epidemics among People Who Inject Drugs. Washington DC: World Bank; 2013.

27. USAID. [Accessed January 7, 2015] AIDSTAR-One (AIDS Support and Technical Assistance Resources) HIV Prevention Knowledge Base. http://www.aidstar-one.com/focus_areas/prevention/pkb/biomedicalinterventions
28. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015; 372(6): 509–18. [PubMed: 25651245]
29. Bekker LG, Johnson L, Cowan F, Overs C, Besada D, Hillier S, et al. Combination HIV prevention for female sex workers: what is the evidence? Lancet. 2015; 385(9962):72–87. [PubMed: 25059942]
30. Coffin PO, Rowe C, Santos GM. Novel Interventions to Prevent HIV and HCV Among Persons Who Inject Drugs. Curr HIV/AIDS Rep. 2015
31. Chirenje ZM, Marrazzo J, Parikh UM. Antiretroviral-based HIV prevention strategies for women. Expert Rev Anti Infect Ther. 2010; 8(10):1177–86. [PubMed: 20954882]
32. Spreen WR, Margolis DA, Pottage JC Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. Curr Opin HIV AIDS. 2013; 8(6):565–71. [PubMed: 24100877]
33. Radzio J, Spreen W, Yueh YL, Mitchell J, Jenkins L, Garcia-Lerma JG, et al. The long-acting integrase inhibitor GSK744 protects macaques from repeated intravaginal SHIV challenge. Sci Transl Med. 2015; 7(270):270ra5.
34. Sullivan LE, Metzger DS, Fudala PJ, Fiellin DA. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injection drug users. Addiction. 2005; 100(2):150–8. [PubMed: 15679744]
35. Fullerton CA, Kim M, Thomas CP, Lyman DR, Montejano LB, Dougherty RH, et al. Medication-assisted treatment with methadone: assessing the evidence. Psychiatr Serv. 2014; 65(2):146–57. [PubMed: 24248468]
36. Saxon AJ, Hser YI, Woody G, Ling W. Medication-assisted treatment for opioid addiction: methadone and buprenorphine. Journal of food and drug analysis. 2013; 21(4):S69–S72. [PubMed: 24436573]
37. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014; 2:CD002207. [PubMed: 24500948]
38. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011; (8):CD004145. [PubMed: 21833948]
39. Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users. JAMA Intern Med. 2014; 174(12):1974–81. [PubMed: 25347412]
40. White B, Dore GJ, Lloyd AR, Rawlinson WD, Maher L. Opioid substitution therapy protects against hepatitis C virus acquisition in people who inject drugs: the HITS-c study. Med J Aust. 2014; 201(6):326–9. [PubMed: 25222455]
41. Nolan S, Dias Lima V, Fairbairn N, Kerr T, Montaner J, Grebely J, et al. The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users. Addiction. 2014; 109(12): 2053–9. [PubMed: 25041346]
42. Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014; 174(12):1947–54. [PubMed: 25330017]
43. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009; (3):CD002209. [PubMed: 19588333]
44. Tracy D, Hahn JA, Fuller Lewis C, Evans J, Briceno A, Morris MD, et al. Higher risk of incident hepatitis C virus among young women who inject drugs compared with young men in association with sexual relationships: a prospective analysis from the UFO Study cohort. BMJ Open. 2014; 4(5):e004988.

45. Greenfield SF, Brooks AJ, Gordon SM, Green CA, Kropp F, McHugh RK, et al. Substance abuse treatment entry, retention, and outcome in women: a review of the literature. Drug Alcohol Depend. 2007; 86(1):1–21. [PubMed: 16759822]
46. Gjersing L, Bretteville-Jensen AL. Gender differences in mortality and risk factors in a 13-year cohort study of street-recruited injecting drug users. BMC Public Health. 2014; 14:440. [PubMed: 24886464]
47. Back SE, Payne RL, Wahlquist AH, Carter RE, Stroud Z, Haynes L, et al. Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am J Drug Alcohol Abuse. 2011; 37(5):313–23. [PubMed: 21854273]
48. Du J, Huang D, Zhao M, Hser YI. Drug-abusing offenders with co-morbid mental disorders: gender differences in problem severity, treatment participation, and recidivism. Biomedical and environmental sciences : BES. 2013; 26(1):32–9. [PubMed: 23294613]
49. Treatment. CfSA. Treatment Improvement Protocol (TIP) Series 51. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009. Substance Abuse Treatment: Addressing the Specific Needs of Women. HHS Publication No. (SMA) 09–4426
50. Brensilver M, Heinzerling KG, Shoptaw S. Pharmacotherapy of amphetamine-type stimulant dependence: an update. Drug Alcohol Rev. 2013; 32(5):449–60. [PubMed: 23617468]
51. Roberts, A.; Mathers, B.; Degenhardt, Lbot. [Accessed Mar 22, 2015] Women who inject drugs: a review of their risks, experiences and needs. Reference Group to the United Nations on HIV and Injecting Drug Use. 2011. http://wwwunodcorg/documents/hiv-aids/Women_who_inject_drugspdf
52. Copeland J. A qualitative study of barriers to formal treatment among women who self-managed change in addictive behaviours. J Subst Abuse Treat. 1997; 14(2):183–90. [PubMed: 9258863]
53. El-Bassel N, Gilbert L, Witte S, Wu E, Chang M. Intimate partner violence and HIV among drug-involved women: contexts linking these two epidemics--challenges and implications for prevention and treatment. Subst Use Misuse. 2011; 46(2–3):295–306. [PubMed: 21303249]
54. Wilke DJ, Kamata A, Cash SJ. Modeling treatment motivation in substance-abusing women with children. Child Abuse Negl. 2005; 29(11):1313–23. [PubMed: 16263166]
55. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363(27):2587–99. [PubMed: 21091279]
56. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329(5996):1168–74. [PubMed: 20643915]
57. Baeten JM, Celum C. Antiretroviral preexposure prophylaxis for HIV prevention. N Engl J Med. 2013; 368(1):83–4. [PubMed: 23293791]
58. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013; 381(9883):2083–90. [PubMed: 23769234]
59. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012; 367(5):423–34. [PubMed: 22784038]
60. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367(5):411–22. [PubMed: 22784040]
61. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013; 381(9883):2083–90. [PubMed: 23769234]
62. Marrazzo JM, del Rio C, Holtgrave DR, Cohen MS, Kalichman SC, Mayer KH, et al. HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA. 2014; 312(4):390–409. [PubMed: 25038358]

63. Rees, H.; Delany-Moretiwe, S.; Baron, D.; Lombard, C.; Gray, G.; Myer, L., et al. ACTS 001 Phase III Trial of Pericoital Tenofovir 1% Gel for HIV Prevention in Women. CROI; 2015; Seattle, Washington. 2015. Abstract number: 26LB
64. van der Straten A, van Damme L, Haberer JE, Bangsberg D. Microbicide Trials Network. Statement on decision to discontinue use of oral tenofovir tablets in VOICE, a major HIV prevention study in women. AIDS. 2012; 26:F13–19. http://www.mtnstopshiv.org/node/3619. [PubMed: 22333749]
65. Centers for Disease C, Prevention. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012; 61(31):586–9. [PubMed: 22874836]
66. Centers for Disease C, Prevention. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for injecting drug users. MMWR Morb Mortal Wkly Rep. 2013; 62(23):463–5. [PubMed: 23760186]
67. Martin M, Vanichseni S, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Risk behaviors and risk factors for HIV infection among participants in the Bangkok tenofovir study, an HIV pre-exposure prophylaxis trial among people who inject drugs. PLoS One. 2014; 9(3):e92809. [PubMed: 24667938]
68. Mathers BM, Cooper DA. Integrating HIV prevention into practice. JAMA. 2014; 312(4):349–50. [PubMed: 25038352]
69. Katz MH. Preexposure Prophylaxis: A Path Forward. JAMA Intern Med. 2014
70. El-Bassel N, Wechsberg WM, Shaw SA. Dual HIV risk and vulnerabilities among women who use or inject drugs: no single prevention strategy is the answer. Curr Opin HIV AIDS. 2012; 7(4):326–31. [PubMed: 22498480]
71. Zorrilla CD, Rabionet SE, Mosquera AM, Ramirez de Arellano AB. Biomedical HIV prevention strategies: state of the art and implications for public health policy in the Caribbean. P R Health Sci J. 2012; 31(3):170–9. [PubMed: 23038893]
72. Ellen JM, Wallace M, Sawe FK, Fisher K. Community engagement and investment in biomedical HIV prevention research for youth: rationale, challenges, and approaches. J Acquir Immune Defic Syndr. 54(Suppl 1):S7–11. [PubMed: 20571425]
73. Dallabetta G, Chandrasekaran P, Wheeler T, Das A, Ramakrishnan L, Kumta S, et al. Rolling out new biomedical HIV prevention tools: what can be learned from Avahan, the India AIDS initiative? Sex Health. 2014; 11(2):207–16. [PubMed: 24990515]
74. Brown JL, Sales JM, DiClemente RJ. Combination HIV Prevention Interventions: The Potential of Integrated Behavioral and Biomedical Approaches. Curr HIV/AIDS Rep. 2014; 11(4):363–75. [PubMed: 25216985]
75. Degenhardt L, Mathers BM, Wirtz AL, Wolfe D, Kamarulzaman A, Carrieri MP, et al. What has been achieved in HIV prevention, treatment and care for people who inject drugs, 2010–2012? A review of the six highest burden countries. Int J Drug Policy. 2014; 25(1):53–60. [PubMed: 24113623]
76. Raj A, Saggurti N, Battala M, Nair S, Dasgupta A, Naik DD, et al. Randomized controlled trial to test the RHANI Wives HIV intervention for women in India at risk for HIV from husbands. AIDS Behav. 2013; 17(9):3066–80. [PubMed: 23921584]
77. Wingood GM, Reddy P, Lang DL, Saleh-Onoya D, Braxton N, Sifunda S, et al. Efficacy of SISTA South Africa on sexual behavior and relationship control among isiXhosa women in South Africa: results of a randomized-controlled trial. J Acquir Immune Defic Syndr. 2013; 63 (Suppl 1):S59–65. [PubMed: 23673889]
78. Remme M, Siapka M, Vassall A, Heise L, Jacobi J, Ahumada C, et al. The cost and cost-effectiveness of gender-responsive interventions for HIV: a systematic review. J Int AIDS Soc. 2014; 17:19228. [PubMed: 25373519]
79. UNDP. United Nations Development Program. One United Nations Plaza; New York, NY 10017: 2014. Checklist for integrating gender into the new funding model of the Global Fund to fight AIDS, TB and Malaria. http://wwwundporg/content/dam/undp/library/HIV-AIDS/HIVMDGsand Development Planning/UNDP-Checklist for Integrating Gender-May21-2014pdf

Table 1

Baseline characteristics of women participating in the Bangkok Tenofovir Study, 2005–2012 (n=489).

Characteristics	Tenofovir N=246	Placebo N=243	Total N=489	p-value
Age				
Median (IQR*)	30 (26–35)	30 (26–38)	30 (26–36)	0.18
Education level				
Primary or less (<6 years)	127 (51.6)	133 (54.7)	260 (53.2)	
Secondary or more	119 (52.0)	110 (48.0)	229 (46.8)	0.49
Risk factors				
Incarceration				
In police holding cell past 12 weeks	52 (21.1)	49 (20.2)	101 (20.7)	0.79
In prison in the past 12 weeks	37 (15.0)	30 (12.4)	67 (13.7)	0.39
Drug use				
Currently in methadone program	28 (11.4)	34 (14.0)	62 (12.7)	0.39
Injected drugs in past 12 weeks	132 (53.7)	134 (55.1)	266 (54.4)	0.74
Heroin	28 (11.4)	32 (13.2)	60 (12.3)	0.55
Methamphetamine	87 (35.4)	77 (31.7)	164 (33.5)	0.39
Midazolam	35 (14.2)	33 (13.6)	68 (13.9)	0.84
Other	9 (3.7)	15 (6.2)	24 (4.9)	0.20
Injection frequency in past 12 weeks				
Every day	16 (6.5)	11 (4.5)	27 (5.5)	0.34
Every week	45 (18.3)	49 (20.2)	94 (19.2)	0.60
Less frequent than every week	71 (28.9)	74 (30.5)	145 (29.7)	0.70
Shared needles in past 12 weeks	38 (15.5)	40 (16.5)	78(16.0)	0.76
Sexual behaviors				
Number of opposite sex sexual partners in past 12 weeks				
0	79 (32.1)	67 (27.6)	146 (29.9)	0.27
≥1	167 (67.9)	176 (72.4)	343 (70.1)	0.27
Reported sexual intercourse with live-in partner in past 12 weeks	134 (54.5)	142 (58.4)	276 (56.4)	0.38
Reported sexual intercourse with casual partner in past 12 weeks	48 (19.5)	58 (23.9)	106 (21.7)	0.24

Data are n/N (%) or n (%);

* Interquartile range (IQR)

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Table 2

Risk behaviors reported by female participants in the Bangkok Tenofovir Study by study visit, Thailand, 2005–2012[a].

	Enrollment n=489 n (%)	Month 12 n=392 n (%)	Month 24 n=358 n (%)	Month 36 n=317 n (%)	Month 48 n=275 n(%)	Month 60 n=213 n (%)	Month 72 n=147 n (%)	P value
Drug injection practices in past 3 months								
Injected drugs	266 (54.4)	49 (12.5)	44 (12.3)	30 (9.5)	26 (9.5)	17 (8.0)	12 (8.2)	<0.001
Shared needles	78 (16.0)	7 (1.8)	7 (2.0)	3 (1.0)	1 (0.4)	1 (0.5)	1 (0.7)	<0.001
Injected daily	27 (5.5)	8 (2.0)	11 (3.1)	8 (2.5)	6 (2.2)	8 (3.8)	8 (5.4)	0.85
Drugs injected in past 3 months								
Methamphetamine	164 (33.5)	20 (5.1)	14 (3.9)	13 (4.1)	9 (3.3)	7 (3.3)	2 (1.4)	<0.001
Midazolam	68 (13.9)	32 (8.2)	23 (6.4)	21 (6.6)	16 (5.8)	11 (5.2)	11 (7.5)	<0.001
Heroin	60 (12.3)	12 (3.1)	8 (2.2)	9 (2.8)	6 (2.2)	6 (2.8)	3 (2.0)	<0.001
Incarceration in past 3 months								
In jail	101 (20.7)	32 (8.2)	29 (8.1)	29 (9.2)	21 (7.6)	23 (10.8)	9 (6.1)	0.005
In prison	67 (13.7)	33 (8.4)	28 (7.8)	35 (11.0)	22 (8.0)	25 (11.7)	8 (5.4)	0.71
Sexual activity in past 3 months								
More than one sexual partner	44 (9.0)	17 (4.3)	15 (4.2)	15 (4.7)	15 (5.5)	10 (4.7)	3 (2.0)	0.04
Sex with casual partner	106 (21.7)	46 (11.7)	50 (14.0)	37 (11.7)	24 (8.7)	22 (10.3)	12 (8.2)	<0.001

[a]Risk behaviors reported at annual visits are shown in the table; data from all 3-monthly visits through month 72 were used in the generalized estimating equations logistic regression analysis.