



The potential uses of preexposure prophylaxis for HIV prevention among people who inject drugs

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Purpose of review

Oral preexposure prophylaxis (PrEP) has shown HIV preventive efficacy for several key populations at risk for HIV infection including MSM and heterosexual men and women in HIV serodiscordant relationships. An efficacy trial of daily oral tenofovir among people who inject drugs (IDU) is underway in Thailand.

Recent findings

Although efficacy data is pending, there is emerging biological and public health plausibility data suggesting the utility of PrEP as an effective component of combination HIV prevention for IDU. Drawing from studies characterizing adherence to antiretroviral therapy for IDU, there are a range of scientific and operational considerations for the potential use of PrEP for IDU. We review here the available literature on the potential use of PrEP for IDU, barriers to uptake and adherence, and potential implementation science questions, which could address, and potentially increase, the effectiveness of this intervention.

Summary

IDU remain the most underserved population in the HIV response worldwide, and have a marked gap in prevention services, making PrEP a potentially promising addition to the prevention toolkit for people who use drugs and, for those already living with HIV infection, for their spouses and other sexual partners.

Keywords

HIV, injecting drug user, preexposure prophylaxis, prevention

INTRODUCTION

Daily oral chemoprophylaxis with Truvada has shown efficacy in the reduction of HIV-1 acquisition risk among MSM, heterosexual men and women in discordant couples, and daily oral tenofovir alone has shown efficacy among heterosexual men at risk for HIV infection [1,2^{***},3]. There is an ongoing efficacy trial of daily oral tenofovir among people who inject drugs (categorized here by convention as IDU) in Thailand started in June, 2005 that has fully enrolled and being conducted by the Bangkok Metropolitan Authority (BMA), the Royal Thai Ministry of Public Health, and the US Centers for Disease and Control and Prevention (CDC4370) [4^{***}]. This trial of daily oral PrEP, among 2413 largely male IDUs attending 17 BMA drug treatment centers across Bangkok, has been continued through interim Data and Safety Monitoring Board (DSMB) reviews and results will likely be available at the end of 2012 [4^{***}]. There are a range of scientific and implementation questions to be answered regarding the efficacy, effectiveness, and optimization of PrEP for IDU [5].

The need for additional HIV prevention tools for IDU populations is clear. The Eastern European and

Central Asian regions, where HIV epidemics are largely driven by IDU risks, HIV epidemics are expanding in 2012, and there remain huge unmet needs for HIV prevention [6]. Ongoing public policy resistance to medication-assisted therapy with methadone, buprenorphine, and another opioid agonists with known efficacy as HIV preventive interventions across this vast region have limited prevention options and may make PrEP, if it is shown to be effective, an important alternative approach [7]. But clearly, as in so many other settings, including in the USA, structural barriers,

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Curr Opin HIV AIDS 2012, 7:563–568

DOI:10.1097/COH.0b013e328358e49e

KEY POINTS

- There is a single ongoing randomized controlled trial evaluating the efficacy of tenofovir in preventing HIV acquisition among IDUs in Bangkok that is fully enrolled with results expected in late 2012.
- There is biological and public health plausibility that PrEP could be an important biomedical component of an effective package of HIV prevention services for IDU including biomedical, behavioral, and structural approaches.
- There are several structural barriers to the effective implementation of PrEP for IDU such as incarceration, although there is emerging evidence of innovative programs that can support adherence to ART in difficult contexts.
- PrEP for IDU could be implemented in the context of existing services such as needle and syringe exchange programs and medically assisted therapy.
- There is a clear need for an implementation science agenda to evaluate the effectiveness of PrEP for IDU, should the ongoing randomized controlled trial prove PrEP efficacious in IDU.

including stigma and discrimination against persons who use drugs, will likely challenge PrEP use implementation as much as they have limited access to other interventions, from needle and syringe exchange to decriminalization of drug dependency [8].

Adherence is the Achilles heel of PrEP efficacy and effectiveness, and this has been true in both oral and vaginal chemoprophylaxis trials [1,9]. How will adherence challenges be addressed for IDU? The population most in need of PrEP among drug users would arguably be those who are actively injecting, those who inject cocaine (due to more frequent injecting per day and the current lack of effective treatments for cocaine dependency), who have dual sexual and injecting risks, and men and women who are the sexual partners of HIV-positive drug users. All are challenging populations to reach, engage, serve, and maintain in care in many settings [10]. Yet, numerous studies have demonstrated that active injectors will use clean needles if they are available, and are as willing as other populations at risk for HIV infection to take steps to reduce acquisition risks [11,12,13]. PrEP may be a useful intervention for some IDU and their sex partners, and it will most likely be a part of a menu of preventive options where a range of effective services are available [14]. It may also be of utility where few options are available to drug users to protect themselves, and for those periods of high exposure risk in their lives [15].

THE PLAUSIBILITY OF EFFECTIVE PRE-EXPOSURE PROPHYLAXIS AMONG PEOPLE WHO INJECT DRUGS

There is significant biological and public health plausibility supporting PrEP as an effective component of combination HIV prevention interventions for IDU. Recent in-vivo research has demonstrated the plausibility of PrEP in protection against parenteral exposure with HIV [16]. Humanized bone marrow/liver/thymus susceptible to HIV infection were challenged with either intravenously administered HIV through the tail vein or rectal administration of HIV after a 7-day course of daily intraperitoneal injections with emtricitabine/tenofovir (FTC/TDF). Protection against HIV seroconversion was highly significant irrespective of route of HIV exposure demonstrating the in-vivo biological plausibility of PrEP for parenteral exposure of HIV [16].

IDU also have significant acquisition risks related to sexual practices. This is especially the case among dual risk gay men and other MSM who also use drugs [17–19]. The per-act HIV transmission probability during anal intercourse is approximately 1.4% with an approximate 40% per-partner HIV transmission probability with unprotected receptive anal intercourse [20,21]. Other populations of IDU that would benefit from PrEP to prevent sexual acquisition of HIV include male-to-female transgender people who are often the receptive partner during anal intercourse and have also been demonstrated to carry a high burden of HIV across several settings [22]. Sex workers who use drugs including women, men, and transgender women also have high HIV sexual acquisition risks from higher numbers of partners and unprotected sex [23].

PrEP also has potential for significant benefit in the context of serodiscordant couples where the person living with HIV is a drug user [24,25, 26²⁷,27,28]. HPTN 052 enrolled only few couples in which one or both members of the couple were IDU, limiting the efficacy data supporting treatment as prevention in the context of drug use [29,30]. However, there is efficacy data in the context of serodiscordant heterosexual couples and this could be relevant especially where the couple is trying to conceive, and thus using barrier methods as an HIV prevention strategy is often not acceptable [2²⁷].

OPPORTUNITIES AND CHALLENGES FOR ADHERENCE TO PREEXPOSURE PROPHYLAXIS FOR PEOPLE WHO INJECT DRUGS

There will clearly be both opportunities and challenges to achieve the necessary levels of adherence required for PrEP to be an effective HIV prevention

strategy for IDU and their sex partners who choose to use it [27]. There have been numerous studies of adherence to antiretroviral therapy (ART) among IDUs living with HIV [31–33]. A large recent systematic review examined adherence rates among IDUs and characterized pooled adherence to be approximately 60% [95% confidence interval (CI) 0.52–0.68], which is similar to nondrug using populations living with HIV [34]. A recent study from Spain demonstrated that using a multidisciplinary approach to the provision of ART for active drug users living with HIV, time to and maintenance of virologic suppression was similar to study participants that were infected through sexual risks, even though the drug using patients presented with more advanced disease. At 48 weeks, 92.9% (95% CI 87.1–99.1) of PUD had less than 50 copies of HIV per millilitre and this was relatively sustained at 96 weeks with 87.3% (95% CI 78.7–95.2) remaining virologically suppressed [35]. A recent systematic review also demonstrated that PUD are no more likely to develop de-novo HIV resistance than non-IDU (odds ratio 1.04, 95% CI 0.74–1.45) supporting the ability to effectively provide ART to this population [36,37]. Although ART adherence in patients is not an ideal proxy for potential PrEP use among seronegative persons with similar risks, these findings do suggest that poor adherence to daily regimens among active drug users is not a given.

There is also likely some value in extrapolating results from studies evaluating increasing adherence to ART for IDU who are living with HIV to interventions that could be co-implemented with PrEP to increase adherence for drug users who are at high risk for HIV acquisition. A number of programs have demonstrated benefits including medical interventions such as methadone maintenance to behavioral interventions such as peer education and mentoring, directly observed therapy (DOT), and adherence counseling using motivational interviewing and cognitive behavioral strategies [38]. Opioid maintenance therapy, now generally referred to as medically assisted therapy (MAT) is the mainstay of support for opioid dependence and relies on daily administration of methadone, buprenorphine and methadone, or buprenorphine–naloxone. There is evidence from six randomized controlled trials that methadone maintenance programs can increase retention in treatment and suppression of heroin use (relative risk [RR] = 0.66, 95% CI 0.56–0.78) as measured both through biological and behavioral indicators [39]. More recently, there is emerging data on the use of heroin prescribed with methadone to support the drug users' refractory to methadone therapy alone. Data from four studies were available

demonstrating a risk ratio of 1.44 (95% CI 1.19–1.75) for patients to remain in therapy and to use less illicit drugs [40]. Although MAT remains at the core of interventions to increase treatment adherence, counseling has also shown to be of significant benefit with each hour of counseling resulting in a 20% increase in postcounseling adherence [41]. A recent RCT of DOT for drug users attending MAT was shown to significantly increase adherence to 86% as compared to 56% in the group with self-administered therapy ($P < 0.0001$) [42]. Patients under DOT were significantly more likely to have undetectable viral load (VL) [43]. However, the benefit of DOT in this randomized controlled trial was subject to decay with decreasing adherence and increasing rates of detectable viral loads [44]. Although these data relate to ART for those living with HIV, they highlight the need for sustained adherence interventions that are required to ensure sustained adherence for PrEP.

Barriers to drug and HIV treatment are likely to be all too similar to those to PrEP for this population [45,46]. A recent systematic review evaluated barriers to treatment among IDUs and found these barriers to be more commonly higher order risk factors outside of the control of the individual [31]. These structural associations with HIV disease progression among IDUs include incarceration, inadequate housing, and lack of a legal income [47,48]. Given the criminalization of drug use and drug users, incarceration constitutes an important potential barrier to the implementation of daily PrEP for people actively using drugs [49]. Recent data highlighted the potential causal and dose-dependent relationship of nonadherence to ART and incarceration events, with more incarceration events being independently associated with higher odds of nonadherence to ART [50]. Incarceration was also independently associated with an 83% increase (95% CI 33–252%) in virologic rebound among drug users previously virologically suppressed [51]. In addition, in the AIDS VAX B/E HIV vaccine trial in Thai IDU, incarceration was significantly associated with HIV seroconversion ($P < 0.04$) [52]. Although incarceration has been found to be a barrier, a recent systematic review of MAT in prison studies found 21 studies, including six experimental studies, demonstrating the benefits of MAT in prison [53]. These included increased treatment uptake and decreased heroin usage [53]. A recent prospective study found that opioid-dependent people living with HIV recently released from prison were more than five times (aOR 5.37, 95% CI 1.15–25.1) more likely to achieve virological suppression if they were provided buprenorphine/naloxone [54]. These studies suggest that if

programs in prison link effectively to those offered in the community, IDU could be safely maintained on PrEP [55]. This may be of particular importance in the acute postrelease phase, in which both sexual and substance use exposures may be marked.

CONSIDERATIONS FOR THE EFFECTIVE IMPLEMENTATION OF PREEXPOSURE PROPHYLAXIS FOR PEOPLE WHO INJECT DRUGS

To realize effective implementation of PrEP for IDU, there is a need to exploit the existing platforms of recommended services including needle and syringe exchange programs (NSEP), MAT, targeted HIV counseling and testing services, prevention and treatment of sexually transmitted infections, and vaccination and treatment of blood-borne pathogens to provide PrEP [56,57]. In settings such as Manipur, Northeast India, where the epidemic is driven by IDUs, NSEP have shown significant benefit in decreasing sharing of needles (OR 0.35, $P < 0.05$) highlighting the possibility of implementing PrEP in this context [58[■]]. Separately, in Tallinn, Estonia, NSEP distribution for approximately 10 000 IDUs increased from 230 000 syringes in 2005 to 770 000 in 2009 [59[■]]. During the same time frame, HIV incidence among new injectors halved from 18 per 100 person-years in 2005 to nine per 100 person-years in 2009 with HIV prevalence stabilizing at about 50% [60]. For people who inject cocaine or other stimulants or people who are actively injecting, NSEP could especially represent an important opportunity for the provision of PrEP given that MAT will be of limited uptake for these populations. These trends were highlighted among IDUs in Bangkok where the proportion injecting heroin has decreased and the proportion injecting methamphetamines has increased and this is now a strong predictor of HIV seroconversion [61]. Moreover, in Bangkok, among IDUs, similar to the experience in Tallinn, enrollment characteristics of participants in the ongoing Bangkok PrEP Tenofovir Study in 2005 demonstrated less sharing of needles than participants enrolled in 1999 in the AIDS VAX B/E HIV vaccine study prompting investigators to increase the sample size from 1600 to 2400 because of presumably lower HIV incidence [4[■]].

Strathdee *et al.* [56] posited that addictophobia, apathy, and inattention have all played a role in limiting HIV prevention research for IDUs and these same factors would likely limit coverage of services even if found to be efficacious in trial settings. However, where studies have been done, accrual and study retention have been good including 2456 IDU accrued in approximately 1 year in

Bangkok for the AIDS VAX B/E HIV vaccine study, several studies evaluating hepatitis C virus treatment, and other studies evaluating vaccine immunogenicity or efficacy [62,63–66]. However, increasingly punitive policies in countries where IDUs carry the highest burden of HIV will limit PrEP research where it would otherwise be most feasible given sustained and high HIV incidence [8,67].

A further important consideration with the implementation of PrEP among IDUs is that both tenofovir and emtricitabine are primarily renally excreted. IDU have several risk factors for both acute and chronic renal failure including chronic opiate exposure, hepatitis C virus infection, and codependency on other nephrotoxic drugs [68,69]. This highlights the importance of closely monitoring renal function among IDUs that would receive PrEP including FTC/TDF or alternatively exploring PrEP drug regimens that are metabolized by the liver.

CONCLUSION

Existing and interim guidelines for PrEP do not describe usage among IDUs, and decisions about the use of PrEP for IDUs and their sexual partners will likely be informed by the findings of the Thai phase III trial [70[■],71–73]. For drug users in some settings, such as the USA, who meet risk recommendation criteria for PrEP based on sexual risks (gay men who also inject drugs might be an example) PrEP may already be a reality. Every effort should be made to capture the data on these persons as PrEP is implemented in the USA and other settings, as such operational data may be critical to further decision making for providers and patients seeking to reduce HIV acquisition risks. There is a clear need for an implementation science agenda in this area. Studies of the sexual partners of IDU are of particular urgency because in most settings the majority of IDU are men of reproductive age, and their wives, spouses, and sex partners are markedly understudied and underserved populations. Recent work suggests, for example, that a significant proportion of HIV infections among women in Pakistan may be due to their husband's IDU risks, yet accessing these women has proven to be extremely difficult [74–77].

Adapting PrEP, should it prove efficacious, will also require provision of quality HIV testing, counseling, prevention, and care services. Like all other HIV status-dependent interventions, PrEP mandates regular HIV testing in settings in which clients are willing to have regular testing, trust the confidentiality of services, and are willing to work with providers to maintain high adherence as long as they are on drug [45]. For far too many IDUs, the

basic platforms to support PrEP now do not exist, and so a 'first things first' approach will likely be required for PrEP to benefit this currently least served of all populations in the HIV response.

Acknowledgements

None.

Conflicts of interest

None declared for S.B., S.S., and C.B. C.B. receives salary support from the Johns Hopkins Center for AIDS Research (NIAID, 1P30AI094189-01A1).

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