

Pre-exposure prophylaxis for people who inject drugs: *A systematic review*

Authors: **Caitlin Kennedy** and **Virginia Fonner** (*Johns Hopkins Bloomberg School of Public Health, Department of International Health, Social and Behavioral Interventions program, USA*)

Date: 2014-03-04

✉ *Caitlin Kennedy* (caitlinkennedy@jhu.edu)

Table of Contents

Systematic review write up	3
Background	3
Methods	4
PICO question	4
Inclusion criteria	4
Search strategy	4
Search terms	5
Screening abstracts	5
Data extraction and management	5
Data analysis	6
Results	6
HIV infection	7

Any adverse event.....	8
Any stage 3 or 4 adverse event	8
Condom use	8
Number of sexual partners	8
Injection frequency	8
Needle/syringe sharing.....	9
Values and preferences literature review	13
Summary of findings.....	13
Annexes	14
Annex 1. GRADE table	14
Annex 2. Annotated bibliography.....	16
References.....	23
References for the systematic review write up	23
References for the values and preferences review of the literature.....	24

Systematic review write up

Background

An estimated 35.3 million people globally are living with HIV (UNAIDS, 2013). A number of prevention methods are available, from condoms to male circumcision, prevention of mother-to-child transmission to clean needles, but to date these have not been sufficient to stop the epidemic. In 2012 alone, an estimated 2.3 million people became newly infected (UNAIDS, 2013). Additional safe and effective approaches to HIV prevention are urgently needed.

People who inject drugs (PWID) have a disproportionate burden of HIV. Existing methods of HIV prevention for PWID include approaches used across populations to reduce sexual transmission as well as approaches specific to PWID to reduce HIV transmission through sharing unclean needles and other injection equipment. However, political and structural barriers prevent access to needle and syringe programs and opioid substitution therapy in many settings, and additional prevention modalities would be helpful for these populations.

PrEP is the use of an antiretroviral drug to block the acquisition of HIV infection by uninfected people. Proof of concept has long been established in the laboratory by animal studies and in real world application by the prevention of mother-to-child transmission and post-exposure prophylaxis. The safety of the drugs being considered for PrEP, tenofovir and emtricitabine, has been established through their use for treatment and in safety trials in uninfected people (Peterson et al., 2007). Five trials of effectiveness (Phase IIb and Phase III) of oral PrEP have been conducted in the last decade. These have examined the effectiveness of PrEP among PWID, serodiscordant couples, heterosexual women and high risk men who have sex with men (MSM).

Of the five effectiveness trials, only one trial examined efficacy among PWID: the Bangkok Tenofovir Study (Choopanya et al., 2013). This Phase III clinical trial tested whether daily tenofovir disoproxil fumarate (TDF) could safely and effectively prevent HIV infection among PWID in Bangkok, Thailand. Over 2400 PWID were enrolled in the study and randomly assigned to daily TDF or placebo. Participants were also provided regular HIV testing and risk reduction counseling. The primary outcome of the trial was HIV incidence, which was 0.35 per 100 person-years (py) in the TDF group (17 infections) and 0.68 per 100 py in the placebo group (33 infections), indicating a 48.9% reduction in HIV incidence related to PrEP (95% CI: 9.6, 72.2; $p=0.01$). Serious adverse events were not statistically significantly different between the two groups ($p=0.35$). Trial findings led the U.S. Centers for Disease Control and Prevention (CDC) to recommend PrEP be considered “as one of several prevention options for persons at very high risk for HIV acquisition through the injection of illicit drugs” (CDC, 2013).

This systematic review examined evidence to answer the following PICO question: Should oral PrEP (containing tenofovir (TDF)) be used for HIV prevention among people who inject drugs (PWID)? In addition, we reviewed the values and preferences about PrEP among people who use drugs and considered studies of cost and feasibility for the GRADE process.

Methods

PICO question

PICO 1: Should oral PrEP (containing tenofovir (TDF)) be used for HIV prevention among people who inject drugs (PWID)?

P: People who inject drugs

I: Oral PrEP (containing tenofovir (TDF))

C: Placebo

O: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) condom use, (5) number of sexual partners, (6) injection frequency, (7) needle/syringe sharing

Inclusion criteria

To be included in the review, an article had to meet the following criteria:

- 1) Randomized controlled trial evaluating the use of oral PrEP (containing tenofovir (TDF)) to prevent HIV infection among PWID.
- 2) Measured one or more of the following key outcomes: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) condom use, (5) number of sexual partners, (6) injection frequency, (7) needle/syringe sharing
- 3) Published in a peer-reviewed journal, or presented as an abstract at a scientific conference, between January 1, 1990 and January 1, 2014.

Only studies among people who *inject* drugs were included; studies among people who *use*, but do not inject, drugs were excluded, as HIV risk and transmission modalities differ between these groups. However, both terms were used in the search.

No restrictions were placed based on location of the intervention. No language restrictions were used on the search. Articles in languages other than English were translated where necessary.

Following the GRADE approach, if direct evidence from PWID populations was limited for one or more of the key outcomes, indirect evidence from other populations (men who have sex with men, or heterosexual men or women) would be used instead, but downgraded for indirectness. If evidence from other populations was limited, evidence from non-randomized but controlled studies would be used instead, but also downgraded for directness.

Search strategy

The following electronic databases were searched using the date ranges January 1, 1990 to January 1, 2014: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and EMBASE. Secondary reference searching was conducted on all studies included in the review. Further, selected

experts in the field were contacted to identify additional articles not identified through other search methods.

Abstracts from the following conferences were searched from January 1, 1990 to January 1, 2014: International AIDS Conference (IAC) and IAS Conference on HIV Pathogenesis, Treatment, and Prevention (IAS). We had planned to search the Conference on Retroviruses and Opportunistic Infections (CROI) as well, but abstracts from this conference were no longer available online to the public at the time the search was conducted.

Search terms

The following terms were entered into all computer databases:

(“people who use drugs” or PWUD or “people who inject drugs” or PWID or “drug users” or IDU or IDUs) AND (“pre-exposure prophylaxis” or PrEP or tenofovir or TDF) AND (HIV OR AIDS)

These search terms were used both for the main systematic review (PICO question) and for the values and preferences review.

The search for abstracts was more difficult given the search engines available on conference websites. For each conference, a search was first conducted for all abstracts including the word “PrEP”. These search results were then further searched for keywords regarding PWID.

Screening abstracts

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by two reviewers. Full text articles were obtained for all selected abstracts and both reviewers independently assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus.

Articles not meeting the inclusion criteria for the review, but presenting potentially interesting background information relevant to PrEP among PWID, including review articles, qualitative studies, cost or cost-effectiveness analyses, or descriptions of interventions without an evaluation component, were included in an annotated bibliography of additional articles.

Data extraction and management

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior team member from WHO when necessary. Study authors were contacted when additional information or data were needed.

The following information was gathered from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; description of the intervention; study design; sample size; follow-up periods and loss to follow-up

- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Handbook, chapter 8.5 – Higgins & Green, 2011). This tool assesses random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias) incomplete outcome data (attrition bias), and selective reporting (reporting bias). Methodological components of the studies were assessed and classified as high, low, or uncertain risk of bias.

Data analysis

Data were analyzed according to coding categories and outcomes. If multiple studies reported the same outcome, meta-analysis would have been conducted using random-effects models to combine effect sizes with the program Comprehensive Meta-Analysis (CMA). Data were summarized in GRADE tables, summary of finding tables, and risk/benefit tables.

Results

Our initial database search yielded 183 citations and 243 conference abstracts; no additional studies were identified through other means (Figure 1). Once duplicates were removed, 392 records were reviewed and 131 article citations and 236 abstracts were excluded for being unrelated to the study topic. After review of the remaining 17 articles and 7 abstracts by two independent screeners, 16 articles were excluded for not meeting the study design criteria and were coded as background or values and preferences, while 6 abstracts were excluded for providing additional information on the included trial, but without reporting key outcomes. The remaining study (with data for PICO outcomes reported in one article and one conference abstract) was deemed eligible for inclusion in our review.

The one study that met all inclusion criteria was the Bangkok Tenofovir Study (Choopanya et al., 2013; Vanichseni et al., 2013). This study was a randomized controlled trial to assess whether daily oral use of tenofovir disoproxil fumarate (tenofovir) can reduce HIV transmission in injecting drug users. The trial was conducted in Bangkok, Thailand, where 2413 total participants were recruited from 17 drug treatment clinics. Participants' ages ranged from 20 to 59 years (mean=32.4), 80% were male, and 63% reported injecting drugs in the past 12 weeks.

Using the Cochrane Risk of Bias tool, the study was judged to have low risk of bias across all of the following categories: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and selective reporting (reporting bias). For selective reporting (reporting bias), the study was initially judged to have uncertain risk of bias. The study protocol was available, and all of the study's pre-specified primary outcomes of interest were reported in the pre-specified way. However, for two secondary outcomes, condom use and number of sexual partners, outcomes that were predefined in the protocol were not available, or not available in the pre-specified way, in published reports. After contacting the study authors for additional information, data on these outcomes were shared with the review team that have not yet been published given the recent conclusion of the trial. Therefore, the judgment on selective reporting was changed to low risk. For incomplete outcome data (attrition bias), we

noted that loss to follow-up was high relative to the number of events. Loss to follow-up was 14.9% in the PrEP group and 14.6% in the placebo group; additional participants from both groups withdrew from the study, died, or otherwise stopped follow-up. Although there were no differences in follow-up time, withdrawal, or loss to follow-up between treatment groups, GRADE guidance notes that "large loss to follow-up in relation to the number of events always... raises the issue of a serious threat of bias" (Guyatt et al., 2011). Further, GRADE generally urges caution classifying a single RCT in a single location as an overall high quality of evidence (Guyatt et al., 2011). For these reasons, we made a judgment of high risk for this measure and downgraded the quality of evidence for potential risk of bias across all study outcomes (as most outcomes had relatively high loss to follow-up relative to the number of events, and the single trial was the only evidence across all outcomes). Finally, we calculated relative risks and 95% confidence intervals for outcomes where effect size estimates were not presented. Based on this analysis, in GRADE, we downgraded three outcomes – condom use, number of sexual partners and needle/syringe sharing – for imprecision because the 95% CI includes appreciable benefit or harm according to the GRADE general guideline of a relative risk of under 0.75 or over 1.25.

The study measured all seven key outcomes for this review: (1) HIV infection, (2) any adverse event, (3) any stage 3 or 4 adverse event, (4) condom use, (5) number of sexual partners, (6) injection frequency, and (7) needle/syringe sharing. Results for each outcome are presented below.

HIV infection

Incident HIV infection was significantly reduced among participants in the tenofovir study arm as compared to the control arm using both an intention-to-treat analysis and a modified intention-to-treat. In the intention-to-treat analysis, there were 17 incident cases of HIV infection out of 1204 participants in the tenofovir study arm and 35 incident HIV infections out of 1209 participants in the control group, resulting in a 51.8% reduction in HIV incidence (95% confidence interval (CI): 15.3-73.7, $p=0.01$). In the modified intention-to-treat analysis (excluding 2 control participants who were HIV-positive at enrolment), there were 17 incident cases of HIV in the tenofovir group out of 4843 person-years (py) for an incidence of 0.35 per 100 py and 33 incident cases of HIV in the control group out of 4823 py for an incidence of 0.68 per 100 py. Thus, in the modified intention-to-treat analysis, there was a 48.9% reduction in HIV incidence (95% CI: 9.6–72.2, $p=0.01$).

In age-stratified analyses, PrEP was effective in those age 40 and older, while there was no significant difference between PrEP and placebo in the age groups 20-29 or 30-39 (although results trended in a positive direction). For participants age 40 and older, the number of incident infections overall was small, with 1 incident infection out of 1066 py in the tenofovir group for an incidence of 0.09 per 100 py (95% CI: 0.002-0.52) and 9 incident infections out of 1052 py in the control group for an incidence of 88.9 per 100 py (95% CI: 41.1-99.4); this difference was statistically significant ($p=0.01$). For participants age 20-29, there were 11 incident infections out of 1976 py in the tenofovir group for an incidence of 0.56 per 100 py (95% CI: 0.28-1.00), versus 17 incident infections out of 1993 py in the control group for an incidence of 0.85 per 100 py (95% CI: 0.50-1.37); this difference was not statistically significant ($p=0.30$). For participants age 30-39, there were 5 incident infections out of 1801 py in the tenofovir group for an incidence of 0.28 per 100 py (95% CI: 0.09-0.65), versus 7 incident infections out of 1778 py in the

control group for an incidence of 0.39 per 100 py (95% CI: 0.16-0.81); this difference was not statistically significant (p=0.55).

Any adverse event

There was no statistically significant difference in reported adverse events between the two study arms. In the tenofovir arm, 91% of participants (1098/1204) had an adverse event (10965 events total). In the placebo arm, 90% of participants (1083/1209) had an adverse event (11550 events total). This difference between arms was not statistically significant (p=0.46).

Any stage 3 or 4 adverse event

Both study arms also reported similar rates of stage 3 and 4 adverse events. In the tenofovir arm, 13% of participants (156/1204) had a stage 3 or 4 adverse event (414 events total). In the placebo arm, 13% of participants (160/1209) had a stage 3 or 4 adverse event (389 events total). This difference between arms was not statistically significant (p=0.89).

Condom use

Condom use data were not reported in any published articles or abstracts at the time of the search, but the Bangkok Tenofovir Study authors were contacted and provided additional unpublished data for condom use outcomes. Participants who self-reported sex with a live-in or casual partner were then asked questions about condom use. A skip pattern error in the initial years of the study made data on condom use with casual partners unreliable. Therefore, we present data on condom use with live-in partners. At baseline, 6.5% (34/526) of tenofovir study arm participants with live-in partners reported always using condoms with those partners (vs. less than always condom use), compared with 8.5% (44/518) of placebo arm participants. At 12-month follow-up, these changed to 11.1% (41/369) in the tenofovir group and 11.3% (44/388) in the placebo group. At 12-month follow-up, this translates to a relative risk (RR) of 0.979 (95% CI: 0.656 to 1.463).

Number of sexual partners

Self-report of sex with more than one partner in the previous 3 months was 22% at enrollment across both study arms and dropped to 11% at the 12-month follow-up and 6% at the 72-month follow-up. Additional unpublished data were also shared by the study investigators. At the 12 month follow-up, reported number of sexual partners in the previous 3 months was not statistically significant between the tenofovir and placebo arms (p=0.181). At the 12 month follow-up, 44.9% (413/919) of tenofovir arm participants and 41% (394/960) of placebo arm participants reported no sexual partners in the past 3 months, 45% (414/919) and 47% (451/960) respectively reported 1 partner, 6.4% (59/919) and 7.5% (72/960) respectively reported 2 partners, 1.5% (14/919) and 2.1% (20/960) respectively reported 3 partners, and 2.1% (19/919) and 2.4% (23/960) respectively reported 4 or more partners. In regression analyses there were no interactions between time and treatment group for this outcome.

Injection frequency

Self-report of injecting drugs in the previous 3 months was 63% at enrollment across both study arms and dropped to 23% at the 12-month follow-up and 18% at the 72-month follow-up. Additional unpublished data were also shared by the study investigators. At the 12 month follow-up, reported injecting drugs in the previous 3 months was 22.1% (203/919) for the tenofovir arm and 23.3% (224/960) for the placebo

arm; this difference was not statistically significant ($p=0.520$). In regression analyses there were no interactions between time and treatment group for this outcome.

Needle/syringe sharing

Self-report of needle sharing in the previous 3 months was 18% at enrollment across both study arms and dropped to 2% at the 12-month follow-up and 1% at the 72-month follow-up. Additional unpublished data were also shared by the study investigators. At the 12 month follow-up, reported needle sharing in the previous 3 months was 2.3% (21/919) for the tenofovir arm and 2.4% (23/960) for the placebo arm; this difference was not statistically significant ($p=0.874$). In regression analyses there were no interactions between time and treatment group for this outcome.

Figure 1: Disposition of citations during the search and screening process

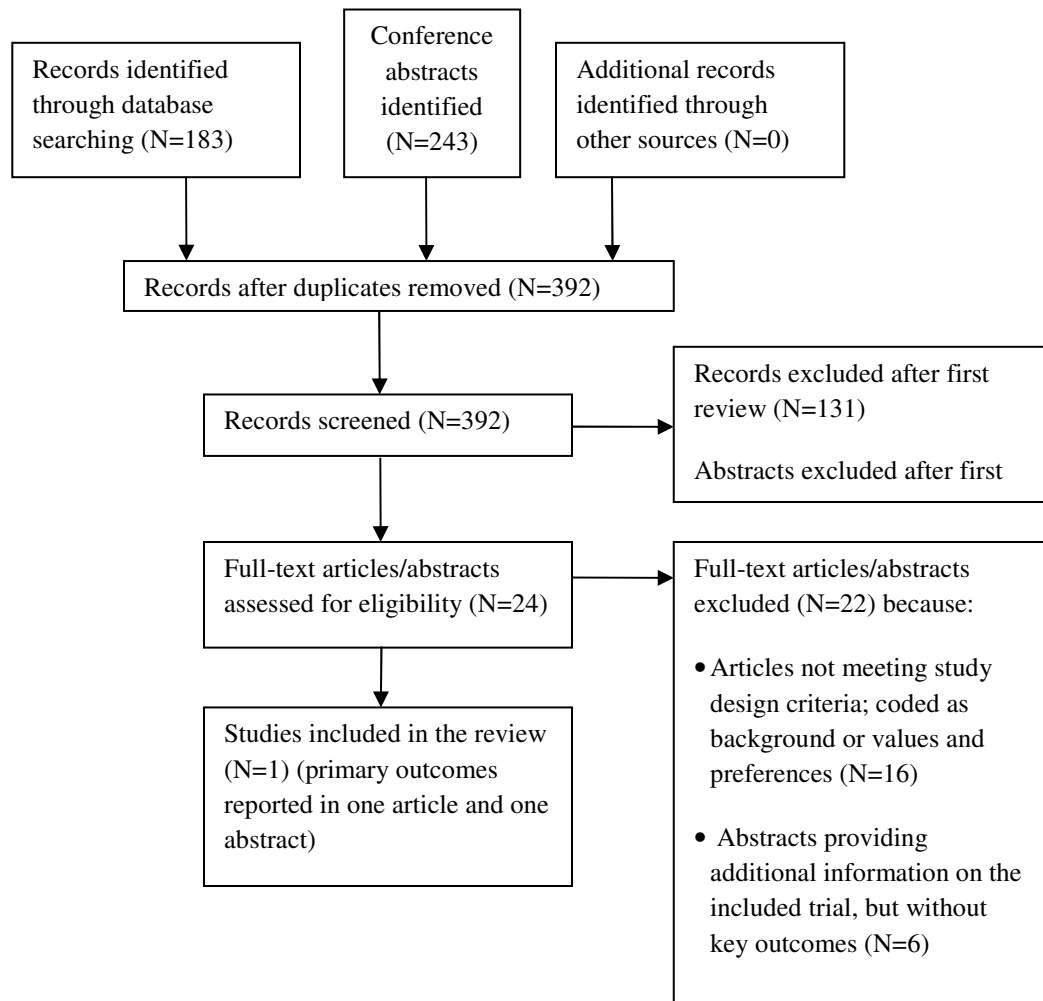


Table 1: Risk-benefit table

Factor	Explanation / Evidence
Quality of Evidence	One RCT from a single country with some limitations.
Balance of Benefits vs. Harms	<p>HIV infection Oral PrEP was associated with reduced risk of HIV in both intention-to-treat analysis (HR: 0.53, 95% CI 0.36-0.78, p=0.001) and modified intention-to-treat analysis (HR: 0.56, 95% CI 0.37-0.85, p=0.005).</p> <p>Adverse events There were no significant differences in reported adverse events between the TDF and placebo arms for either any adverse event (91% vs. 90%, p=0.46) or grade 3 and 4 adverse events (13% vs. 13%, p=0.89).</p> <p>Condom use Both the TDF and placebo arms reported increased condom use with live-in partners over the course of the study. At 12-month follow-up, intervention and control group rates were 11.1% and 11.3%, respectively.</p> <p>Number of sexual partners Both the TDF and control study arms reported reduced number of sexual partners over the course of the study; however, there was no significant difference between study arms over time or at 12-month follow-up (p=0.181).</p> <p>Injection frequency and needle/syringe sharing Both the TDF and control study arms reported reduced injection behavior and injecting with used needles over the course of the study. However, there were no significant differences between study arms over time or at 12 month follow-up (p=0.520 for injection frequency and p=0.874 for needle/syringe sharing).</p>
Values and Preferences	<p>A systematic review (see page 11) identified one published study examining acceptability of PrEP and factors likely to influence uptake. This quantitative study was conducted among 128 PWID in Ukraine. Most PWID said they would definitely (53%) or probably (32%) use PrEP if it became available. These results were generally maintained when participants were prompted on potential side effects, the need to combine condom use with PrEP, and the need for regular HIV testing. Route of administration was considered the most important attribute influencing PrEP uptake, with injections preferred over pills.</p> <p>A WHO consultation qualitatively interviewed 21 PWID and experts, service providers and activists from all geographic regions. Qualified support for PrEP was based on its potential usefulness for some PWID in countries where other harm reduction options or not available and with good ART access. Resistance was based on perceptions that cheap, proven harm reduction interventions are already available for PWID; PrEP is not proven for PWID; unethical to give PrEP when not all PLHIV can get treatment; medicalizes the HIV response; investment should be made in other interventions (e.g.,</p>

Factor	Explanation / Evidence
	<p>Hep C); and concern about hidden agendas. Ambivalent feelings expressed were based on concerns that PrEP was too new and unproven; unnecessary and impractical for many PWID; skepticism about adherence; not a priority; and concern about undermining established harm reduction programs. The consultation concluded: “A recommendation for the use of PrEP as a harm reduction intervention for people who inject drugs is not supported by the community at this time.”</p>
Resource Use	<p>One conference abstract (Alistar 2011) examined cost-effectiveness of PrEP for PWID. The dynamic compartmental model used data from Ukraine and added oral PrEP for PWID (25% access) to a package of services including methadone maintenance therapy and antiretroviral treatment. In this scenario, adding oral PrEP for PWID was cost-effective at \$12,240 per QALY gained. Oral PrEP alone became cost-effective for annual PrEP costs comparable to annual HIV care costs.</p>
Feasibility	<p>Concerns have been raised about the ethics of the Bangkok Tenofovir Study. Issues of criminalization, stigma and discrimination, and violence should be considered during implementation, especially where injection drug use is illegal. Issues of feasibility are for further discussion in the consensus conference.</p>

Values and preferences literature review

Summary of findings

The comprehensive search of the literature identified one study reporting on values and preferences of people who inject drugs (PWID) about pre-exposure prophylaxis (PrEP) for HIV prevention. This study by Eisingerich, Wheelock et al. (2012) was a multi-country study of the acceptability of PrEP among various user groups and factors likely to influence uptake. This study included one population of 128 PWID from Ukraine (specifically, Donetsk, Kharkiv, Mykolayiv, and Vinnitsa). Data were collected between October 2010 and May 2011, prior to the release of any results from the PrEP trials. PWID were non-randomly sampled from needle-exchange points and NGOs.

Among the 128 PWID participants from Ukraine, a strong majority said that based on what they had heard, they would definitely (53%) or probably (32%) use PrEP if it became available. Of these, most (59%) said they would definitely take it as soon as it becomes available. These numbers decreased only slightly when researchers mentioned potential side effects of PrEP; when asked if they would take PrEP if it caused mild temporary side effects such as tiredness, headaches and gassiness, 28% said “yes, definitely” and 46% said “yes, probably”. A slightly smaller proportion (63%) said they would definitely or probably take PrEP if they had to pay for it. The majority (78%) said they would definitely or probably take PrEP even if they had to also use condoms, and 88% said they would take PrEP even if they had to be regularly tested for HIV.

Only a small percent (6%) said the thought of taking PrEP made them feel very or fairly anxious. Conversely, many thought that PrEP gave them a lot of hope (32%) or some hope (44%) for new possibilities in life. Many (43%) also said they would definitely or probably want their partner(s) to know if they were taking PrEP, although 25% said they would definitely or probably *not* want their partner(s) to know if they were taking PrEP. In terms of sharing and selling PrEP, 41% said that if PrEP were free of charge, they would definitely or probably share it with other people in need, while 9% said they would definitely or probably sell PrEP to others.

In terms of factors likely to influence PrEP uptake, route of administration was considered the most important attribute, with injections in the arm or buttocks preferred over daily or coitally-dependent pills. HIV testing frequency was the second most important attribute, while time spent obtaining PrEP and frequency of pickup were less important.

In summary, many PWID perceived PrEP as giving them hope and would consider using it as soon as it becomes available. These results were generally maintained when participants were prompted on potential side effects, the need to combine condom use with PrEP, and the need for regular HIV testing. Route of administration was considered the most important attribute of the presented alternatives.

Annexes

Annex 1. GRADE table

Author (s): Caitlin Kennedy and Virginia Fonner

Date: 2014-03-11

Question: Should oral PrEP (including tenofovir (TDF)) be used in people who inject drugs (PWID)?

Bibliography: Choopanya, K., et al. (2013). 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*, 381, (9883): 2083-90. doi: 10.1016/S0140-6736(13)61127-7. Vanichseni, S., et al. (2013). HIV-associated risk behaviour among injecting drug users participating in an HIV pre-exposure prophylaxis trial in Bangkok, Thailand. IAS 2013 poster: MOLBPE27.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral PrEP (including tenofovir (TDF))	Control	Relative (95% CI)	Absolute		
HIV infection (follow-up mean 4.0 years; assessed with: intention to treat analysis)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/1204 (1.4%)	35/1209 (2.9%)	HR .482 (0.263 to 0.847)	15 fewer per 1000 (from 4 fewer to 21 fewer)	□□□□ MODERATE	CRITICAL
HIV infection (follow-up mean 4.0 years; assessed with: modified intention to treat analysis)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/4843 (0.35%)	33/4823 (0.68%)	HR .511 (0.278 to 0.904)	3 fewer per 1000 (from 1 fewer to 5 fewer)	□□□□ MODERATE	CRITICAL
Any adverse event (follow-up mean 4.0 years)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	1098/1204 (91.2%)	1083/1209 (89.6%)	RR 1.018 (0.992 to 1.045)	16 more per 1000 (from 7 fewer to 40 more)	□□□□ MODERATE	IMPORTANT
Any grade 3 or 4 adverse event (follow-up mean 4.0 years)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/1204 (13%)	160/1209 (13.2%)	RR 0.979 (0.797 to 1.202)	3 fewer per 1000 (from 27 fewer to 27 more)	□□□□ MODERATE	IMPORTANT
Condom use (follow-up mean 12 months; assessed with: always condom use with live-in partners (among participants with live-in partners))												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	41/369 (11.1%)	44/388 (11.3%)	RR 0.979 (0.656 to 1.463)	2 fewer per 1000 (from 39 fewer to 53 more)	□□□□ LOW	IMPORTANT
Number of sexual partners (follow-up mean 12 months; assessed with: self-report of more than one partner in the past 3 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	92/919 (10%)	115/960 (12%)	RR 0.836 (0.645 to 1.083)	20 fewer per 1000 (from 43 fewer to 10 more)	□□□□ LOW	IMPORTANT
Injection frequency (follow-up mean 12 months; assessed with: self-report of injecting drugs in the past 3 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	203/919 (22.1%)	224/960 (23.3%)	RR 0.947 (0.801 to 1.119)	12 fewer per 1000 (from 46 fewer to 28 more)	□□□□ MODERATE	CRITICAL
Needle/syringe sharing (follow-up mean 12 months; assessed with: self-report of injecting with needles someone else had used in the past 3 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	21/919 (2.3%)	23/960 (2.4%)	RR 0.954 (0.532 to 1.711)	1 fewer per 1000 (from 11 fewer to 17 more)	□□□□ LOW	CRITICAL

¹ Loss to follow-up was high relative to the number of events. Although there were no differences in follow-up time, withdrawal, or loss to follow-up between treatment groups GRADE guidance notes that "large loss to follow-up in relation to the number of events always... raises the issue of a serious threat of bias" (Guyatt et al., 2011). Further, GRADE generally urges caution classifying a single RCT in a single location as an overall high quality of evidence (Guyatt et al., 2011). For these reasons, we have therefore downgraded the quality of evidence for potential risk of bias.

² The 95% CI includes appreciable benefit or harm according to the GRADE general guideline of a RR of under 0.75 or over 1.25.

Annex 2. Annotated bibliography

Choopanya, K., M. Martin, et al. (2013). "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* 381(9883): 2083-2090.

BACKGROUND: Antiretroviral pre-exposure prophylaxis reduces sexual transmission of HIV. We assessed whether daily oral use of tenofovir disoproxil fumarate (tenofovir), an antiretroviral, can reduce HIV transmission in injecting drug users. **METHODS:** In this randomised, double-blind, placebo-controlled trial, we enrolled volunteers from 17 drug-treatment clinics in Bangkok, Thailand. Participants were eligible if they were aged 20-60 years, were HIV-negative, and reported injecting drugs during the previous year. We randomly assigned participants (1:1; blocks of four) to either tenofovir or placebo using a computer-generated randomisation sequence. Participants chose either daily directly observed treatment or monthly visits and could switch at monthly visits. Participants received monthly HIV testing and individualised risk-reduction and adherence counselling, blood safety assessments every 3 months, and were offered condoms and methadone treatment. The primary efficacy endpoint was HIV infection, analysed by modified intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00119106. **FINDINGS:** Between June 9, 2005, and July 22, 2010, we enrolled 2413 participants, assigning 1204 to tenofovir and 1209 to placebo. Two participants had HIV at enrolment and 50 became infected during follow-up: 17 in the tenofovir group (an incidence of 0.35 per 100 person-years) and 33 in the placebo group (0.68 per 100 person-years), indicating a 48.9% reduction in HIV incidence (95% CI 9.6-72.2; $p=0.01$). The occurrence of serious adverse events was much the same between the two groups ($p=0.35$). Nausea was more common in participants in the tenofovir group than in the placebo group ($p=0.002$). **INTERPRETATION:** In this study, daily oral tenofovir reduced the risk of HIV infection in people who inject drugs. Pre-exposure prophylaxis with tenofovir can now be considered for use as part of an HIV prevention package for people who inject drugs. **FUNDING:** US Centers for Disease Control and Prevention and the Bangkok Metropolitan Administration.

Values and Preferences

Eisingerich, A. B., A. Wheelock, et al. (2012). "Attitudes and acceptance of oral and parenteral HIV preexposure prophylaxis among potential user groups: a multinational study." *PLoS One* 7(1): e28238.

BACKGROUND: The use of antiviral medications by HIV negative people to prevent acquisition of HIV or pre-exposure prophylaxis (PrEP) has shown promising results in recent trials. To understand the potential impact of PrEP for HIV prevention, in addition to efficacy data, we need to understand both the acceptability of PrEP among members of potential user groups and the factors likely to determine uptake. **METHODS AND FINDINGS:** Surveys of willingness to use PrEP products were conducted with 1,790 members of potential user groups (FSWs, MSM, IDUs,

SDCs and young women) in seven countries: Peru, Ukraine, India, Kenya, Botswana, Uganda and South Africa. Analyses of variance were used to assess levels of acceptance across different user groups and countries. Conjoint analysis was used to examine the attitudes and preferences towards hypothetical and known attributes of PrEP programs and medications. Overall, members of potential user groups were willing to consider taking PrEP (61% reported that they would definitely use PrEP). Current results demonstrate that key user groups in different countries perceived PrEP as giving them new possibilities in their lives and would consider using it as soon as it becomes available. These results were maintained when subjects were reminded of potential side effects, the need to combine condom use with PrEP, and for regular HIV testing. Across populations, route of administration was considered the most important attribute of the presented alternatives. CONCLUSIONS: Despite multiple conceivable barriers, there was a general willingness to adopt PrEP in key populations, which suggests that if efficacious and affordable, it could be a useful tool in HIV prevention. There would be a willingness to experience inconvenience and expense at the levels included in the survey. The results suggest that delivery in a long lasting injection would be a good target in drug development.

Background studies

(2013). "Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for injecting drug users." MMWR Morb Mortal Wkly Rep 62(23): 463-465.

On June 12, 2013, the Thailand Ministry of Health and CDC published results from a randomized controlled trial of a daily oral dose of 300 mg of tenofovir disoproxil fumarate (TDF) that showed efficacy in reducing the acquisition of human immunodeficiency virus (HIV) infection among injecting drug users (IDUs) (1). Based on these findings, CDC recommends that preexposure prophylaxis (PrEP) be considered as one of several prevention options for persons at very high risk for HIV acquisition through the injection of illicit drugs.

Abdool Karim, S. S. (2013). "HIV pre-exposure prophylaxis in injecting drug users." The Lancet 381(9883): 2060-2062.

Baral, S. D., S. Stromdahl, et al. (2012). "The potential uses of preexposure prophylaxis for HIV prevention among people who inject drugs." Curr Opin HIV AIDS 7(6): 563-568.

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.

Bruce, R. D. (2013). "Is it time for treatment as prevention among people who inject drugs?" Journal of Acquired Immune Deficiency Syndromes 63(5): 545-547.

Choopanya, K., M. Martin, et al. (2013). "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 381(9883): 2083-2090.

BACKGROUND: Antiretroviral pre-exposure prophylaxis reduces sexual transmission of HIV. We assessed whether daily oral use of tenofovir disoproxil fumarate (tenofovir), an antiretroviral, can reduce HIV transmission in injecting drug users. METHODS: In this randomised, double-blind, placebo-controlled trial, we enrolled volunteers from 17 drug-treatment clinics in Bangkok, Thailand. Participants were eligible if they were aged 20-60 years, were HIV-negative, and reported injecting drugs during the previous year. We randomly assigned participants (1:1; blocks of four) to either tenofovir or placebo using a computer-generated randomisation sequence. Participants chose either daily directly observed treatment or monthly visits and could switch at monthly visits. Participants received monthly HIV testing and individualised risk-reduction and adherence counselling, blood safety assessments every 3 months, and were offered condoms and methadone treatment. The primary efficacy endpoint was HIV infection, analysed by modified intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00119106. FINDINGS: Between June 9, 2005, and July 22, 2010, we enrolled 2413 participants, assigning 1204 to tenofovir and 1209 to placebo. Two participants had HIV at enrolment and 50 became infected during follow-up: 17 in the tenofovir group (an incidence of 0.35 per 100 person-years) and 33 in the placebo group (0.68 per 100 person-years), indicating a 48.9% reduction in HIV incidence (95% CI 9.6-72.2; $p=0.01$). The occurrence of serious adverse events was much the same between the two groups ($p=0.35$). Nausea was more common in participants in the tenofovir group than in the placebo group ($p=0.002$). INTERPRETATION: In this study, daily oral tenofovir reduced the risk of HIV infection in people who inject drugs. Pre-exposure prophylaxis with tenofovir can now be considered for use as part of an HIV prevention package for people who inject drugs. FUNDING: US Centers for Disease Control and Prevention and the Bangkok Metropolitan Administration.

Craig, A. P., R. Gray, et al. (2013). "HIV antiretroviral prophylaxis for injecting drug users [4]." The Lancet 382(9895): 854-855.

Eisingerich, A. B., A. Wheelock, et al. (2012). "Attitudes and acceptance of oral and parenteral HIV preexposure prophylaxis among potential user groups: a multinational study." PLoS One 7(1): e28238.

BACKGROUND: The use of antiviral medications by HIV negative people to prevent acquisition of HIV or pre-exposure prophylaxis (PrEP) has shown promising results in recent trials. To understand the potential impact of PrEP for HIV prevention, in addition to efficacy data, we need to understand both the acceptability of PrEP among members of potential user groups and the factors likely to determine uptake. **METHODS AND FINDINGS:** Surveys of willingness to use PrEP products were conducted with 1,790 members of potential user groups (FSWs, MSM, IDUs, SDCs and young women) in seven countries: Peru, Ukraine, India, Kenya, Botswana, Uganda and South Africa. Analyses of variance were used to assess levels of acceptance across different user groups and countries. Conjoint analysis was used to examine the attitudes and preferences towards hypothetical and known attributes of PrEP programs and medications. Overall, members of potential user groups were willing to consider taking PrEP (61% reported that they would definitely use PrEP). Current results demonstrate that key user groups in different countries perceived PrEP as giving them new possibilities in their lives and would consider using it as soon as it becomes available. These results were maintained when subjects were reminded of potential side effects, the need to combine condom use with PrEP, and for regular HIV testing. Across populations, route of administration was considered the most important attribute of the presented alternatives. **CONCLUSIONS:** Despite multiple conceivable barriers, there was a general willingness to adopt PrEP in key populations, which suggests that if efficacious and affordable, it could be a useful tool in HIV prevention. There would be a willingness to experience inconvenience and expense at the levels included in the survey. The results suggest that delivery in a long lasting injection would be a good target in drug development.

Gomez, G. B., A. Borquez, et al. (2013). "The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies." PLoS Med 10(3): e1001401.

BACKGROUND: Cost-effectiveness studies inform resource allocation, strategy, and policy development. However, due to their complexity, dependence on assumptions made, and inherent uncertainty, synthesising, and generalising the results can be difficult. We assess cost-effectiveness models evaluating expected health gains and costs of HIV pre-exposure prophylaxis (PrEP) interventions. **METHODS AND FINDINGS:** We conducted a systematic review comparing epidemiological and economic assumptions of cost-effectiveness studies using various modelling approaches. The following databases were searched (until January 2013): PubMed/Medline, ISI Web of Knowledge, Centre for Reviews and Dissemination databases, EconLIT, and region-specific databases. We included modelling studies reporting both cost and expected impact of a PrEP roll-out. We explored five issues: prioritisation strategies, adherence, behaviour change, toxicity, and resistance. Of 961 studies retrieved, 13 were included. Studies modelled populations (heterosexual couples, men who have sex with men, people who inject drugs) in generalised and concentrated epidemics from Southern Africa (including South Africa),

Ukraine, USA, and Peru. PrEP was found to have the potential to be a cost-effective addition to HIV prevention programmes in specific settings. The extent of the impact of PrEP depended upon assumptions made concerning cost, epidemic context, programme coverage, prioritisation strategies, and individual-level adherence. Delivery of PrEP to key populations at highest risk of HIV exposure appears the most cost-effective strategy. Limitations of this review include the partial geographical coverage, our inability to perform a meta-analysis, and the paucity of information available exploring trade-offs between early treatment and PrEP. **CONCLUSIONS:** Our review identifies the main considerations to address in assessing cost-effectiveness analyses of a PrEP intervention--cost, epidemic context, individual adherence level, PrEP programme coverage, and prioritisation strategy. Cost-effectiveness studies indicating where resources can be applied for greatest impact are essential to guide resource allocation decisions; however, the results of such analyses must be considered within the context of the underlying assumptions made. Please see later in the article for the Editors' Summary.

Hu, Z. and Y. Yang (2013). "HIV antiretroviral prophylaxis for injecting drug users [3]." The Lancet 382(9895): 853-854.

Hudgens, M. G. and S. R. Cole (2013). "HIV antiretroviral prophylaxis for injecting drug users [1]." The Lancet 382(9895): 853.

Jintarkanon, S., S. Nakapiew, et al. (2005). "Unethical clinical trials in Thailand: A community response [2] (multiple letters)." Lancet 365(9471): 1617-1619.

Koblin, B. A., G. Mansergh, et al. (2011). "Condom-use decision making in the context of hypothetical pre-exposure prophylaxis efficacy among substance-using men who have sex with men: Project MIX." J Acquir Immune Defic Syndr 58(3): 319-327.

OBJECTIVE: To examine condom-use decision making in the context of hypothetical pre-exposure prophylaxis (PrEP) efficacy among men who have sex with men who use alcohol and other substances during sex. **METHODS:** Substance-using men who have sex with men were recruited in 4 US cities for a behavioral intervention trial. Three groups were defined as follows: men who indicated that to not use a condom for receptive/insertive unprotected anal intercourse (UAI) while using PrEP, PrEP would need to be: (1) "almost always or always" effective (high efficacy); (2) effective "at least half the time or more but not almost always or always" (mid-range efficacy corresponding to recent PrEP trial results); (3) effective "less than half the time" (low efficacy). The mid-range efficacy group was compared with the low-efficacy group (as the reference) and to the-high efficacy group (as the reference). **RESULTS:** Among 630 men who never used PrEP, 15.2% were in the mid-range efficacy group for receptive UAI and 34.1% in the mid-range efficacy group for insertive UAI. Scores on difficulty communicating about safer sex while high were significantly higher in the mid-range efficacy group compared with each of the other groups for both receptive and insertive UAI. Men who seemed to be differentiating PrEP use by anal sex role also scored higher on communication difficulties, although scoring lower on condom intentions. **CONCLUSIONS:** Communication about safer sex while under the influence

of alcohol or other substances and condom intentions are important factors to consider for HIV prevention interventions for PrEP users.

Martin, M., S. Vanichseni, et al. (2011). "Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand." PLoS One 6(9): e25127.

BACKGROUND: The Bangkok Tenofovir Study was launched in 2005 to determine if pre-exposure prophylaxis with tenofovir will reduce the risk of HIV infection among injecting drug users (IDUs). We describe recruitment, screening, enrollment, and baseline characteristics of study participants and contrast risk behavior of Tenofovir Study participants with participants in the 1999-2003 AIDSVAX B/E Vaccine Trial. **METHODS:** The Bangkok Tenofovir Study is an ongoing, phase-3, randomized, double-blind, placebo-controlled, HIV pre-exposure prophylaxis trial of daily oral tenofovir. The Tenofovir Study and the Vaccine Trial were conducted among IDUs at 17 drug-treatment clinics in Bangkok. Tenofovir Study sample size was based on HIV incidence in the Vaccine Trial. Standardized questionnaires were used to collect demographic, risk behavior, and incarceration data. The Tenofovir Study is registered with ClinicalTrials.gov, number--NCT00119106. **RESULTS:** From June 2005 through July 2010, 4094 IDUs were screened and 2413 enrolled in the Bangkok Tenofovir Study. The median age of enrolled participants was 31 years (range, 20-59), 80% were male, and 63% reported they injected drugs during the 3 months before enrollment. Among those who injected, 53% injected methamphetamine, 37% midazolam, and 35% heroin. Tenofovir Study participants were less likely to inject drugs, inject daily, or share needles (all, $p < 0.001$) than Vaccine Trial participants. **DISCUSSION:** The Bangkok Tenofovir Study has been successfully launched and is fully enrolled. Study participants are significantly less likely to report injecting drugs and sharing needles than participants in the 1999-2003 AIDSVAX B/E Vaccine Trial suggesting HIV incidence will be lower than expected. In response, the Bangkok Tenofovir Study enrollment was increased from 1600 to 2400 and the study design was changed from a defined 1-year follow-up period to an endpoint-driven design. Trial results demonstrating whether or not daily oral tenofovir reduces the risk of HIV infection among IDUs are expected in 2012.

Miller, W. C., I. F. Hoffman, et al. (2013). "HIV antiretroviral prophylaxis for injecting drug users [2]." The Lancet 382(9895): 853.

Williams, B. G., V. Lima, et al. (2011). "Modelling the impact of antiretroviral therapy on the epidemic of HIV." Current HIV Research 9(6): 367-382.

Thirty years after HIV first appeared it has killed close to 30 million people but transmission continues unchecked. In 2009, an estimated 1.8 million lives were lost and 2.6 million more people were infected with HIV [1]. To cut transmission, many social, behavioural and biomedical interventions have been developed, tested and tried but have had little impact on the epidemic in most countries. One substantial success has been the development of combination antiretroviral therapy (ART) that reduces viral load and restores immune function. This raises the possibility of using ART not only to treat people but also to prevent new HIV infections. Here we consider the impact of ART on the transmission of HIV and show how it could help to control the epidemic.

Much needs to be known and understood concerning the impact of early treatment with ART on the prognosis for individual patients and on transmission. We review the current literature on factors associated with modelling treatment for prevention and illustrate the potential impact using existing models. We focus on generalized epidemics in subSaharan Africa, with an emphasis on South Africa, where transmission is mainly heterosexual and which account for an estimated 17% of all people living with HIV. We also make reference to epidemics among men who have sex with men and injection drug users where appropriate. We discuss ways in which using treatment as prevention can be taken forward knowing that this can only be the beginning of what must become an inclusive dialogue among all of those concerned to stop acquired immune deficiency syndrome (AIDS). (copyright) 2011 Bentham Science Publishers.

Zhong, X., X. N. Zhong, et al. (2012). "Attitude on pre-exposure prophylaxis (PrEP) among drug users from high-risk population of aids in western China." Academic Journal of Second Military Medical University 33(4): 374-379.

Objective To investigate the attitude on pre-exposure prophylaxis (PrEP) among drug users from high-risk population of AIDS in western China and its influencing factors. Methods A total of 190 drug users were recruited by snowball sampling from high-risk population of AIDS including those involved in men having sex with men (MSM), female sex workers (FSW) and the spouse or sex partner (PAR) of HIV carrier in Chongqing, Sichuan, Guangxi and Xinjiang. Self-administered questionnaire survey was conducted with the assistance of investigators. Univariate and multivariate logistic regression was employed for statistical analysis. Results MSM, FSW and PAR accounted for 34.74% (66/190), 48.42% (92/190) and 16.84% (32/190) among the 190 drug users, respectively. The positive attitude rate for PrEP among drug users reached 70% in the premise of drug safety and effectiveness, which increased with favorable condition provided. The results of multivariate logistic regression analysis indicated that the factors significantly associated with the positive attitude for PrEP included awareness of AIDS seriousness (OR= 2.66, 95% CI: 1.14-6.25, P = 0.024 2), attitudes towards HIV patients (OR= 4.41, 95% CI: 1.68-11.58, P = 0.002 6, OR= 2.99, 95% CI: 1.05-8.54, P = 0.040 3) and virus detection of AIDS (OR= 1.94, 95% CI: 0.98-3.87, P = 0.058 1). Conclusion The attitude for PrEP among drug users from AIDS high-risk population is mainly related to the attitude for AIDS, AIDS-related knowledge and behavior, and preventive measures for AIDS, indicating that PrEP should be implemented and promoted with a sound social background, and education on HIV/AIDS prevention should be reinforced. Positive attitude towards AIDS prevention need to be developed among drug users by various behavioral therapies, so as to improve the attitude for PrEP among drug users with high HIV risks.

References

References for the systematic review write up

- Alistar, S.S. (2011). TR2-2: Effectiveness and cost-effectiveness of oral pre-exposure prophylaxis for injection drug users in mixed HIV epidemics. Available from: <http://smdm.confex.com/smdm/2011ch/webprogram/Paper6553.html>. 33rd Annual Meeting of the Society for Medical Decision Making, Hillsborough, USA. Accessed 2 March 2014.
- Centers for Disease Control and Prevention (CDC). (2013). Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for injecting drug users. *MMWR Morb Mortal Wkly Rep*, 62, (23): 463-5.
- Choopanya, K., Martin, M., Suntharasamai, P., Sangkum, U., Mock, P.A., Leethochawalit, M., Chiamwongpaet, S., Kitisin, P., Natrujirote, P., Kittimunkong, S., Chuachoowong, R., Gvetadze, R.J., McNicholl, J.M., Paxton, L.A., Curlin, M.E., Hendrix, C.W., Vanichseni, S.; Bangkok Tenofovir Study Group. (2013). 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*, 381, (9883): 2083-90. doi: 10.1016/S0140-6736(13)61127-7.
- Guyatt, G.H., Oxman, A.D., Vist, G., Kunz, R., Brozek, J. Alonso-Coello, P., Montori, V., Akl, E.A., Djulbegovic, B., yngve, F-Y., Norris, S.L., Williams, J.W. Jr., Atkins, D., Meerpohl, J., Schunemann H. (2011). GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). *Journal of Clinical Epidemiology*, 64, 407e415.
- Higgins, J.P.T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Available from: <http://www.cochrane-handbook.org/>. Accessed on: June 10, 2011.
- Peterson, L., Taylor, D., Roddy, R., Belai, G., Phillips, P., Nanda, K., Grant, R., Kekawo Clarke, E. E., Sama Doh, A., Ridzon, R., Jaffe, H. S., & Cates, W. (2007). Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clinical Trials*, 2, (5): e27.
- Vanichseni, S., Martin, M., Suntharasamai, P., Sangkum, U., Mock, P., Leethochawalit, M., Chiamwongpaet, S., Kittimunkong, S., Paxton, L., Curlin, M., Choopanya, K., & Bangkok Tenofovir Study Group. (2013). HIV-associated risk behaviour among injecting drug users participating in an HIV pre-exposure prophylaxis trial in Bangkok, Thailand. *IAS 2013 poster: MOLBPE27*.
- UNAIDS. (2013). Global report: UNAIDS report on the global AIDS epidemic 2013. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf. Accessed 2 March 2014.

References for the values and preferences review of the literature

Eisingerich AB, Wheelock A, Gomez GB, Garnett GP, Dybul MR, Piot P. (2012) Attitudes and Acceptance of Oral and Parenteral HIV Preexposure Prophylaxis among Potential User Groups: A Multinational Study. PLoS ONE 7(1): e28238. doi:10.1371/journal.pone.0028238