HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial

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See Comment page 443

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Summary

Background For maximum effect pre-exposure prophylaxis should be targeted to the subpopulations that account for the largest proportion of infections (population-attributable fraction [PAF]) and for whom the number needed to treat (NNT) to prevent infection is lowest. We aimed to estimate the PAF and NNT of participants in the iPrEx (Pre-Exposure Prophylaxis Initiative) trial.

Methods The iPrEx study was a randomised controlled efficacy trial of pre-exposure prophylaxis with coformulated tenofovir disoproxil fumarate and emtricitabine in 2499 men who have sex with men (MSM) and transgender women. Participants aged 18 years or older who were male at birth were enrolled from 11 trial sites in Brazil, Ecuador, Peru, South Africa, Thailand, and the USA. Participants were randomly assigned (1:1) to receive either a pill with active pre-exposure prophylaxis or placebo, taken daily. We calculated the association between demographic and risk behaviour during screening and subsequent seroconversion among placebo recipients using a Poisson model, and we calculated the PAF and NNT for risk behaviour subgroups. The iPrEx trial is registered with ClinicalTrials.gov, NCT00458393.

Findings Patients were enrolled between July 10, 2007, and Dec 17, 2009, and were followed up until Nov 21, 2010. Of the 2499 MSM and transgender women in the iPrEx trial, 1251 were assigned to pre-exposure prophylaxis and 1248 to placebo. 83 of 1248 patients in the placebo group became infected with HIV during follow-up. Participants reporting receptive anal intercourse without a condom seroconverted significantly more often than those reporting no anal sex without a condom (adjusted hazard ratio [AHR] 5·11, 95% CI 1·55–16·79). The overall PAF for MSM and transgender women reporting receptive anal intercourse without a condom was 64% (prevalence 60%). Most of this risk came from receptive anal intercourse without a condom with partners with unknown serostatus (PAF 53%, prevalence 54%, AHR 4·76, 95% CI 1·44–15·71); by contrast, the PAF for receptive anal intercourse without a condom with an HIV-positive partner was 1% (prevalence 1%, AHR 7·11, 95% CI 0·70–72·75). The overall NNT per year for the cohort was 62 (95% CI 44–147). NNTs were lowest for MSM and transgender women self-reporting receptive anal intercourse without a condom (NNT 36), cocaine use (12), or a sexually transmitted infection (41). Having one partner and insertive anal sex without a condom had the highest NNTs (100 and 77, respectively).

Interpretation Pre-exposure prophylaxis may be most effective at a population level if targeted toward MSM and transgender women who report receptive anal intercourse without a condom, even if they perceive their partners to be HIV negative. Substance use history and testing for STIs should also inform individual decisions to start pre-exposure prophylaxis. Consideration of the PAF and NNT can aid in discussion of the benefits and risks of pre-exposure prophylaxis with MSM and transgender women.

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Introduction

Men who have sex with men (MSM) and transgender women make up the largest proportion of new HIV infections throughout North and South America,[1,2] western Europe,[3] Asia,[2] and Australia.[4] Despite increases in frequency of HIV testing, knowledge of HIV serostatus, and access to antiretroviral therapy, infection rates among MSM and transgender women are stable or rising.[2,5] So far, the only biomedical intervention proven to protect against HIV acquisition in MSM and transgender women in a randomised controlled trial is pre-exposure prophylaxis;[6] postexposure prophylaxis for HIV uninfected and treatment for HIV-positive MSM and transgender women probably also decrease the risk of HIV acquisition and transmission, respectively, although neither has been formally assessed in this population. Condom use is another biomedical intervention, although data on its effectiveness are limited to analyses of observational data.[7] Findings from the iPrEx (Pre-Exposure Prophylaxis Initiative) trial,[6,8] a randomised, placebo-controlled efficacy trial of daily coformulated tenofovir disoproxil fumarate and emtricitabine in HIV uninfected MSM and transgender women, showed a 42% reduction in new infections in participants assigned to the active treatment group when follow-up of the masked phase was complete. Comparison of drug concentrations in the iPrEx trial with findings from studies of directly observed dosing

showed that none of the seroconverters had drug concentrations consistent with daily dosing at the time their infection was detected.[9] In July 2012, the US Food and Drug Administration approved daily tenofovir disoproxil fumarate and emtricitabine for use as pre-exposure prophylaxis against sexually acquired HIV infection in high-risk uninfected adults.

The Centers for Disease Control and Prevention (CDC) interim pre-exposure prophylaxis guidance document recommended pre-exposure prophylaxis for MSM "at substantial, ongoing, high risk for acquiring HIV",[10] and WHO recommended pre-exposure prophylaxis for MSM and transgender women "where HIV transmission occurs...and additional HIV prevention choices for them are needed".[11] However, many health-care providers have difficulty assessing risk,[12] and neither the CDC nor WHO has yet provided specific behavioural criteria for pre-exposure prophylaxis. Some surveys have found that providers prioritise pre-exposure prophylaxis for known serodiscordant couples.[13,14] Findings from cost-effectiveness modelling suggest that the cost per infection averted is lowest if pre-exposure prophylaxis is used by the highest risk populations,[15] with an annual HIV incidence greater than 2 per 100 person-years.[16] However, each set of models uses different behavioural eligibility criteria for MSM and transgender women receiving pre-exposure prophylaxis, and effectiveness is assumed to be uniform across risk groups.[15,17–19]

Two epidemiological constructs, the population-attributable fraction (PAF) and the number needed to treat (NNT), are complementary strategies for identifying populations who may derive the most benefit from pre-exposure prophylaxis. The PAF combines the relative risk of a characteristic with its prevalence in a population to identify the proportion of infections associated with or attributable to that factor. Although the PAF has been estimated for populations of MSM in Australia,[20] estimates in the USA come from studies done 10 years or more ago,[21,22] and none exist for transgender women or MSM and transgender women in other parts of the world. Identification of subgroups of MSM and transgender women who have a high PAF could help to target pre-exposure prophylaxis to have the greatest effect in reducing HIV infections at a population level.

NNT refers to the number of MSM and transgender women who would need to take daily tenofovir disoproxil fumarate and emtricitabine for 1 year to prevent one HIV infection. This measure is based on both the underlying HIV incidence and the effectiveness of pre-exposure prophylaxis within a population. The NNT has not been calculated for subsets of MSM and transgender women, and cost-effectiveness estimates for MSM and transgender women published so far assume a uniform effectiveness across subgroups.[15] Factors associated with a low NNT can be helpful in informing doctors' and patients' decisions regarding pre-exposure prophylaxis.

In this study, we aimed to estimate the PAF and NNT of participants in the iPrEx study to identify subpopulations of people for whom pre-exposure prophylaxis may have the largest effect.

Methods

Study design

We did a secondary analysis of study data from the iPrEx trial, a phase 3 randomised controlled trial of tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis, which is described in detail elsewhere.[6] Briefly, 2499 MSM and transgender women were enrolled from

	Total (n=1248)	Infected (n=83)	Uninfected (n=1165)	Incidence per 100 person-years (95% CI)
Gender				
Male	1086 (87%)	73 (88%)	1013 (87%)	4·0 (3·2–5·0)
Transgender male to female	162 (13%)	10 (12%)	152 (13%)	3·6 (1·9–6·6)
Age (years)				
18–24	661 (53%)	47 (57%)	614 (53%)	4·3 (3·2–5·7)
25–29	242 (19%)	15 (18%)	227 (19%)	3·7 (2·2–6·1)
30–39	224 (18%)	19 (23%)	205 (18%)	4·8 (3·1–7·5)
≥40	121 (10%)	2 (2%)	119 (10%)	1·0 (0·2–4·0)
Education*				
Below secondary	72/1236 (6%)	2/83 (2%)	70/1153 (6%)	4·0 (2·4–6·5)
Secondary	625/1236 (51%)	40/83 (48%)	585/1153 (51%)	3·3 (2·2–4·8)
Beyond secondary	539/1236 (44%)	41/83 (49%)	498/1153 (43%)	4·6 (3·1–5·1)
Country				
Peru	700 (56%)	49 (59%)	651 (56%)	3·5 (2·7–4·6)
Ecuador	150 (12%)	17 (20%)	133 (11%)	6·5 (4·1–10·5)
Brazil	184 (15%)	10 (12%)	174 (15%)	5·0 (2·7–9·2)
USA	114 (9%)	2 (2%)	112 (10%)	1·3 (0·3–5·0)
South Africa	43 (3%)	2 (2%)	41 (4%)	4·7 (1·1–19·1)
Thailand	57 (5%)	3 (4%)	54 (5%)	5·2 (1·7–15·9)
Ethnic origin				
White	209 (17%)	9 (11%)	200 (17%)	4·0 (3·2–5·1)
Black or African-American	97 (8%)	6 (7%)	91 (8%)	3·0 (1·6–5·8)
Mixed or other	874 (70%)	65 (78%)	809 (69%)	4·1 (1·3–12·7)
Asian	68 (5%)	3 (4%)	65 (6%)	3·5 (1·9–6·5)
Alcohol in past month†‡				
None	184/1216 (15%)	10/83 (12%)	174/1133 (15%)	3·5 (1·9–6·5)
1–4 drinks per day	345/1216 (28%)	29/83 (35%)	316/1133 (28%)	5·0 (3·5–7·2)
≥5 drinks per day	687/1216 (56%)	44/83 (53%)	643/1133 (57%)	3·7 (2·8–5·0)
Cocaine use in past month‡				
None	1194 (96%)	76 (92%)	1118 (96%)	3·7 (3·0–4·7)
Any	54 (4%)	7 (8%)	47 (4%)	9·5 (4·6–19·7)
HIV-positive sex partner in past 3 months‡				
None	1139 (91%)	76 (92%)	1063 (91%)	3·9 (3·1–4·9)
Any	109 (9%)	7 (8%)	102 (9%)	4·4 (2·1–9·3)
Sex without a condom§				
None	178 (14%)	3 (4%)	175 (15%)	1·2 (0·4–3·8)
Insertive only	317 (25%)	8 (10%)	309 (27%)	1·5 (0·7–2·9)
Any receptive	753 (60%)	72 (87%)	681 (58%)	5·4 (4·3–6·9)

(Table 1 continues on next page)

	Total (n=1248)	Infected (n=83)	Uninfected (n=1165)	Incidence per 100 person-years (95% CI)
(Continued from previous page)				
Receptive anal intercourse without a condom by partner serostatus§				
None	495 (40%)	11 (13%)	484 (42%)	1·4 (0·8–2·5)
HIV negative only	67 (5%)	9 (11%)	58 (5%)	8·9 (4·7–16·6)
Unknown serostatus	669 (54%)	62 (75%)	607 (52%)	5·2 (4·0–6·6)
Any HIV positive	17 (1%)	1 (1%)	16 (1%)	4·3 (0·6–30·1)
Number of male sex partners§				
1	99 (8%)	5 (6%)	94 (8%)	3·4 (1·4–8·1)
2–5	462 (37%)	26 (31%)	436 (37%)	3·4 (2·3–5·0)
>5	687 (55%)	52 (63%)	635 (55%)	4·3 (3·3–5·7)
Transactional sex¶				
None	738 (59%)	49 (59%)	689 (59%)	4·1 (3·1–5·5)
Any	510 (41%)	34 (41%)	476 (41%)	3·6 (2·6–5·1)
STI by self-report¶				
None	932 (75%)	54 (65%)	878 (75%)	3·6 (2·7–4·6)
Any	316 (25%)	29 (35%)	287 (25%)	4·9 (3·4–7·0)

Data are number (%) or n/N (%), unless otherwise stated. Some percentages do not total 100% because of rounding. STI=sexually transmitted infection. *Data missing for 12 uninfected participants. †Data missing for 32 participants, none of whom became infected. ‡From computer self-administered data collection. §In the previous 3 months according to an interviewer-administered questionnaire. ¶In the previous 6 months according to an interviewer-administered questionnaire.

Table 1: **Baseline demographic and risk variables associated with HIV infection among placebo recipients in iPrEx**

11 trial sites in Brazil, Ecuador, Peru, South Africa, Thailand, and the USA. HIV seronegative individuals aged 18 years or older who were male at birth (irrespective of present gender identity), were without medical contraindications for trial participation, and met behavioural risk criteria in the 6 months before screening were eligible for participation. Behavioural risk factors included anal sex with at least four (or six, depending on the study site) male partners, diagnosis of a sexually transmitted infection (STI), engaging in transactional sex, or anal sex without a condom with an HIV-positive or unknown-serostatus partner. Participants were randomly assigned (1:1) to receive a pill with coformulated tenofovir disoproxil fumarate and emtricitabine or a placebo pill, to be taken on a daily basis. We followed up participants on a monthly basis with HIV antibody testing and medical assessments. All participants were provided with free condoms and lubricant, given regular risk reduction counselling, and provided linkage to appropriate community and medical services.

The study protocol was approved by national government public health authorities in Peru, Ecuador, South Africa, Brazil, Thailand, and the USA, and by the ethics committee at each site. Participants provided written informed consent at screening and enrolment.

Procedures

We collected baseline behavioural risk data at screening by interviewer-administered or computer self-administered data collection, using questions adapted from previous studies in these populations.[23] The total number of male sex partners with whom the participant had had oral or anal sex and the number of male partners with whom they had engaged in specific sexual practices in the previous 3 months were recorded, stratified by perceived HIV serostatus. Questions about exchange of sex for money, drugs, or services and self-reported STIs covered the previous 6 months.

Interviewers asked questions about transactional sex, self-reported STIs, and sexual risk variables. Through computer self-administered data collection, participants answered questions about HIV-positive partners in the past 3 months, and drug and alcohol use in the previous month.

Study staff did monthly HIV antibody testing with point-of-care rapid blood tests. All sites used two rapid HIV antibody tests; all reactive tests were confirmed with western blot or RNA tests.

Statistical analysis

Models for seroconversion were based on HIV infections through the study treatment period ending Nov 21, 2010. Because our goal was to identify subgroups of MSM and transgender women who might benefit most from pre-exposure prophylaxis in the future, analyses used baseline rather than time-dependent measures of sexual risk and drug use. Subgroup effectiveness and hazard ratios (HRs) were estimated from a Poisson model with a log link and offset for follow-up time. Adjusted HRs were adjusted for any of the other significant variables in the model and study site. Variables with a p value of less than 0·20 in univariate analyses were included in the multivariate model.

The PAF for a variable was estimated as follows:

$$P_e \times \frac{RR-1}{1+P_e \times (RR-1)}$$

Where P_e is the prevalence of the exposure and RR is the rate ratio for the factor analyses estimated from a Poisson model for HIV infections estimated from the placebo arm. For a variable with more than two categories, the PAF for the jth category was estimated[24] as follows:

$$p_j(RR_j-1)/\sum_{k=1}^{k} p_k RR_k$$

The NNT was estimated[25] as follows:

$$[\exp\left(-\lambda_{0k}\left(1-\frac{E_k}{100}\right)\right)-\exp(-\lambda_{0k})]^{-1}$$

Where E_k is the percentage modified intention-to-treat efficacy due to study treatment and λ_{0k} is the annual rate of HIV infections on the placebo in the kth stratum.

We calculated efficacy by a Cox model stratified by site with terms for treatment, subgroup, and their interaction. The treatment effects were given by the appropriate linear contrast.

The iPrEx trial is registered with ClinicalTrials.gov, NCT00458393.

Role of the funding source

The sponsors of the study approved the study design, but were not involved in data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	HR (95% CI)	Adjusted HR (95% CI)
Age (years)		
18–24	..	..
25–29	0·88 (0·49–1·58)	..
30–39	1·13 (0·65–1·97)	..
≥40	0·26 (0·06–10·81)	..
Education		
Below secondary	..	..
Secondary	1·92 (0·45–8·17)	..
Beyond secondary	2·54 (0·60–10·81)	..
Ethnic origin		
White	..	..
Black or African-American	1·39 (0·47–4·12)	..
Mixed or other	1·27 (0·57–2·82)	..
Asian	0·00 (0·00–7·69)	..
Alcohol in past month		
None	..	..
1–4 drinks per day	1·69 (0·82–3·52)	..
≥5 drinks per day	1·10 (0·55–2·22)	..
Any cocaine use in past month	2·24 (1·01–4·97)	1·85 (0·81–4·21)
Any HIV-positive sex partner*	1·62 (0·70–3·75)	..
Sex without a condom*		
None	..	..
Insertive only	1·56 (0·40–6·04)	1·68 (0·43–6·57)
Any receptive	5·17 (1·58–16·94)	5·11 (1·55–16·79)
Receptive anal intercourse without a condom by partner serostatus*		
None	..	..
Only HIV negative	6·69 (2·69–16·60)	8·87 (2·29–34·30)
Unknown serostatus	3·56 (1·85–6·84)	4·76 (1·44–15·71)
Any HIV positive	5·21 (0·63–43·21)	7·11 (0·70–72·75)
Number of male sex partners*		
1	..	..
2–5	1·27 (0·48–3·37)	..
>5	1·78 (0·66–4·79)	..
Any transactional sex†	0·96 (0·60–1·55)	..
Any self-reported STI†	1·62 (1·01–2·61)	1·27 (0·76–2·13)
Seropositive for syphilis at baseline	1·58 (0·92–2·71)	1·30 (0·73–2·31)

HR=hazard ratio. STI=sexually transmitted infection. *In the 3 months before screening. †In the 6 months before screening.

Table 2: **Univariate and multivariate risk of HIV seroconversion by baseline demographic and risk behaviours**

Results

Patients were enrolled between July 10, 2007, and Dec 17, 2009, and were followed up until Nov 21, 2010. Of the 2499 MSM and transgender women in the iPrEx trial, 1251 were randomly assigned to receive tenofovir disoproxil fumarate and emtricitabine and 1248 to placebo. Table 1 compares HIV incidence by baseline demographic and behavioural risk characteristics among the placebo group. This cohort was young (median age younger than 25 years) and mostly recruited from the South American countries, where enrolment began. More than half of the participants reported that they had consumed five or more alcoholic drinks per day of drinking in the past month, reported six or more sex partners, or had receptive anal intercourse without a condom with a partner of unknown HIV serostatus in the previous 3 months. Overall HIV incidence was 3·9 per 100 person-years in the placebo group (95% CI 3·17–4·87). Only 1% of participants reported use of amphetamine or poppers (amyl nitrite or related compounds) in the past month.

Participants reporting any receptive anal intercourse without a condom in the previous 3 months were more than five times as likely to acquire HIV as those reporting no sex without a condom (table 2). Among participants reporting receptive anal intercourse without a condom, the hazard was greatest among those reporting this activity with partners believed to be HIV negative, although the risk was also significantly increased for those with partners of unknown serostatus. Only 17 (1%) of 1248 participants reported receptive anal intercourse without a condom with known HIV-positive partners;

	Prevalence	Efficacy	PAF	NNT
Overall	100%	42%	NA	62
Any cocaine use in the past month	4%	87%	6%	12
Any anal sex with an HIV-positive partner*	9%	63%	1%	43
Receptive anal intercourse without a condom by HIV serostatus*				
Only negative	5%	60%	10%	15
Unknown serostatus	54%	49%	53%	41
HIV positive	1%	100%	1%	24
Number of partners*				
1	8%	36%	0%	100
2–5	37%	49%	0%	60
>5	55%	42%	13%	58
Any self-reported STI in the past 6 months	25%	50%	9%	41

NA=not applicable. NNT=number needed to treat. PAF=population-attributable fraction. STI=sexually transmitted infection. *In the 3 months before screening.

Table 3: **Prevalence, efficacy, population-attributable fraction, and number needed to treat for subgroups of iPrEx participants, stratified by baseline risk**

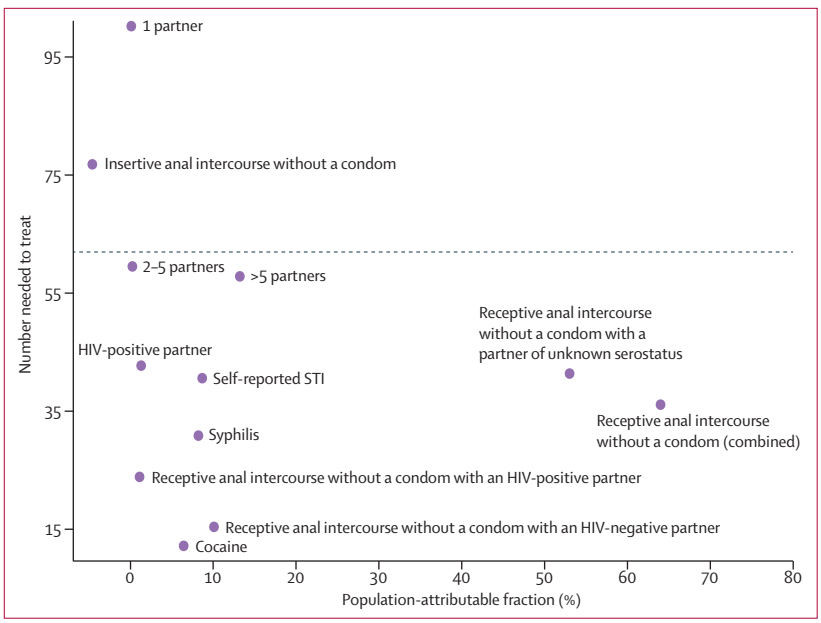

Figure: **Population-attributable fraction by the number needed to treat per year to prevent one infection in iPrEx**

The dashed line shows the mean number needed to treat. The point estimate of the population-attributable fraction for insertive anal sex without a condom is negative because those who report this risk are at slightly lower risk than those who don't report it. STI=sexually transmitted infection.

thus there was limited power to assess their risk of HIV acquisition. 317 (25%) of 1248 participants reported only insertive anal intercourse without a condom, but this risk factor was not associated with increased HIV acquisition in either univariate or multivariate analyses (table 2). Two risk behaviours were significantly associated with HIV acquisition on univariate but not multivariate analysis: cocaine use in the past month and self-reported STI in the past 6 months (table 2).

The PAF combines data on both the prevalence of risk behaviours and the strength of their association with HIV acquisition to apportion new infections to that risk factor. Overall, receptive anal intercourse without a condom accounted for 64% of new infections, with a PAF for receptive anal intercourse without a condom with partners of unknown serostatus of 53% and with HIV-negative partners of 10% (table 3). By contrast, the PAF of receptive anal intercourse without a condom with HIV-positive partners was only 1%.

The overall NNT is lowest when both the prevalence and intervention effectiveness are high for a particular subgroup. The overall NNT was 62 (95% CI 44–147). The figure shows the PAF against the NNT for various subgroups; optimum characteristics would be a high PAF with a low NNT (bottom right corner of the plot), whereas less favourable characteristics would be a low PAF with a high NNT (upper left corner of the plot). Two risk factors stand out as possessing the desirable qualities of a high PAF and low NNT: participants reporting any receptive anal intercourse without a condom and specifically those reporting receptive anal intercourse without a condom with partners of unknown HIV serostatus. Two other factors stand out as having a low PAF and a higher NNT than the mean: participants reporting only one partner and those reporting only insertive anal intercourse without a condom, without receptive anal intercourse without a condom. Having receptive anal intercourse without a condom with an HIV-negative partner, an HIV-positive partner, a self-reported STI, more than one partner, and past substance use had a low PAF but also a low NNT.

Discussion

Based on the results of this analysis, the subgroup of MSM and transgender women most likely to benefit from pre-exposure prophylaxis is those reporting receptive anal intercourse without a condom, irrespective of partner serostatus (panel). The simplest and perhaps most effective strategy for identifying MSM and transgender women who may benefit most from pre-exposure prophylaxis would be to ask them two questions. In the past 3 months, have you had sex with men, women, or both? And in the past 3 months, have you had receptive anal sex without a condom?

In the present study, receptive anal intercourse without a condom accounted for nearly two-thirds of new HIV infections—an estimate similar to that reported in a 2011 study of MSM in Australia (69%).[20] Earlier studies of MSM in the USA also found a substantial PAF of receptive anal intercourse without a condom with partners of unknown serostatus[21,22] and with partners believed to be HIV negative.[22] Findings from several observational studies[23,27] support the notion that sex with HIV seronegative people without a condom (also known as condom serosorting) increases the risk of HIV acquisition compared with consistent condom use. The only exception to the risk associated with receptive anal intercourse without a condom may be for people in monogamous seroconcordant relationships; in this setting, the risk of HIV acquisition is low, even lower than in MSM who report always using condoms but who have several partners.[23]

Conversely, participants who did not report having anal sex without a condom, or who only had insertive anal sex without a condom, had significantly lower rates of HIV acquisition (1·2 and 1·5 per 100 person-years, respectively) than did those who reported having receptive sex without a condom. These infection rates, although not negligible, are substantially lower than the 2 per 100 person-years incidence threshold recommended in some cost-effectiveness modelling exercises.[16] Findings from other studies suggest small-to-moderate PAFs for insertive anal intercourse without a condom (4–20%),[20,28] with a substantially lower per-contact risk from insertive than from receptive anal intercourse without a condom.[29]

Findings from a recent model of HIV transmission dynamics among MSM in Peru and the USA suggest that nearly 40% of new infections among MSM occur within primary relationships, although only two-thirds of these occur in known serodiscordant relationships.[28] By contrast, in our study, having a known HIV-positive partner had a PAF of only 1%. This difference is probably in part a result of the low prevalence of participants with this risk behaviour who entered the study. Another possible explanation is that the previous models were based on older data, when HIV-positive men may have been less likely to receive effective antiretroviral therapy, which may, in turn, reduce their infectiousness.[30] Although no direct data exist on the effectiveness of treatment as prevention for MSM and transgender women in serodiscordant partnerships, providers should prioritise provision of treatment to HIV-positive members of couples, both for the patients' own health and to reduce the risk of transmission to uninfected partners. Pre-exposure prophylaxis can also be offered to the HIV uninfected partner, particularly if the HIV-positive partner is not virally suppressed, has STIs, or if the couple engages in sex without a condom.

Because both cocaine use and self-reporting an STI had a low NNT in the iPrEx study, taking a substance-use history and regular STI screening in at-risk MSM and transgender women will also identify individuals who may benefit from pre-exposure prophylaxis. In other MSM cohort studies, amyl nitrite[21] and amphetamines[22] were independently associated with HIV acquisition, with PAFs of 28% and 16%, respectively. Use of both substances was low in the iPrEx study, precluding our ability to assess these risks. Similarly, we did not ask about alcohol or substance use before sex—another risk factor with a substantial PAF in other cohorts.[22] The imprecision of self-reported versus diagnosed STIs might also reduce the usefulness of the former in identifying people at increased risk of HIV acquisition. Nonetheless, self-reported substance use or STIs should alert the provider to probe more explicitly about sexual risk and to consider pre-exposure prophylaxis as part of a larger screening and risk-reduction strategy.

These examples show the challenges providers face in deciding who should receive pre-exposure prophylaxis. Clinicians must go beyond considerations of public health benefit to weigh the relative risks against potential benefits for their patients in their individual settings. Fortunately, tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis has caused few serious adverse effects in clinical trials,[6,31,32] although longer follow-up of larger cohorts is needed to detect rare serious events. Renal toxicity was uncommon in HIV uninfected people and seemed to be reversible if drugs were stopped during routine monitoring of creatinine.[6,31,32] Tenofovir disoproxil fumarate and emtricitabine seems to cause a small but significant decrease in bone mineral density,[33] but the clinical significance of this decrease is not clear. People with chronic hepatitis B infection might rebound when tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis is stopped and should be monitored, although this rebound has not been reported in trials that enrolled people with chronic hepatitis B infection.[6,34] People with undiagnosed HIV infection who start pre-exposure prophylaxis will probably develop antiretroviral resistance,[6,31,32] which could reduce their treatment options. This factor emphasises the importance of regular HIV testing for patients who receive pre-exposure prophylaxis and the need to counsel patients not to restart pre-exposure prophylaxis without first being tested for HIV.

There is no explicit threshold for PAF or NNT to guide clinicians in choosing to whom they should offer pre-exposure prophylaxis. In addition to consideration of the NNT, clinicians must weigh the benefit of avoiding HIV infection against the dangers of tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for each patient.[35,36] Condoms remain one partially effective

Panel: Research in context

Systematic review

We searched PubMed (from inception to Jan 31, 2014) for studies published in English of population-attributable fraction for HIV infection among and guidance for offering pre-exposure prophylaxis to men who have sex with men (MSM) and transgender women using the following search terms: "HIV", "men who have sex with men", "MSM", "gay", "transgender", "population attributable fraction", "population-attributable risk", "pre-exposure prophylaxis", "preexposure prophylaxis", "eligibility", "guidelines", "guidance", "recommendations", "providers", "physicians", "clinicians", "number needed to treat", and "NNT". We found 168 potentially relevant articles from the search and found additional articles through references from relevant articles and our own files. The studies showed that the major risk factors for HIV acquisition among MSM and transgender women were number of sex partners, receptive anal sex without a condom with partners of any serostatus, insertive anal sex without a condom with an HIV-positive partner, sexually transmitted infections, substance use (primarily amyl nitrate, amphetamines, or substance use with sexual activity), depression, and young age. Black MSM in the USA, Canada, and UK are at disproportionate risk, which is associated with structural factors (low income or education, or incarceration) and partner characteristics (age and race), whereas individual behavioral risk was lower in black MSM than in white MSM in most reports. We found no studies that calculated the number needed to treat for MSM; for heterosexuals, the number needed to treat in one study ranged from 26 to 78,[26] depending on the subgroup.

Interpretation

In this study, we assessed clinical trial data to make recommendations about which MSM and transgender women should be offered pre-exposure prophylaxis. Present Centers for Disease Control and Prevention[10] and WHO[11] guidance is not explicit about risk criteria for pre-exposure prophylaxis for MSM and transgender women. We combined information about the risk behaviours contributing to new HIV infections and the number of patients per year who would have to be given pre-exposure prophylaxis to avert one infection. Receptive anal sex without a condom with partners of unknown serostatus contributed to more than half of all new HIV infections; similar results have been reported in cohorts from the USA.[21,22] We suggest that providers ask a few screening questions of their male and transgender patients and consider offering pre-exposure prophylaxis to patients with sexual or substance use risk, irrespective of knowledge of partner serostatus.

strategy for reducing the risk of HIV acquisition;[7] pre-exposure prophylaxis offers additional protection that is controlled by the receptive partner. The benefits and risks of pre-exposure prophylaxis should be explicitly discussed with potential candidates in the context of other available HIV prevention methods. Potential pre-exposure prophylaxis users might also factor cost into decisions. At a societal level, discussion might also occur about prioritisation of pre-exposure prophylaxis over other health-care needs, including provision of antiretroviral therapy for HIV-infected people.[11] Additional cost-effectiveness analyses will be helpful to prioritise how best to reduce new HIV infections in different target populations.

This analysis has several limitations. Although findings from observational data and models suggest similar risk factors for infection among MSM in Peru and the USA,[28] most participants in iPrEx came from the Andean region of South America, and results might not be generalisable to other regions or people outside of randomised controlled trials. This analysis also does not apply to pre-exposure prophylaxis for heterosexual people, although efficacy has also been shown in this population.[31] The iPrEx trial enrolled few black or African-American MSM in the USA (34 of 227) or transgender women—two populations at particularly high risk of HIV acquisition. The PAFs in this study, although similar in most cases to those from other studies, might have been affected by the behavioural eligibility criteria for iPrEx. Having anal sex without a condom with a known HIV-positive partner, although one of the behavioural inclusion criteria, might be substantially less common in geographical regions in which serostatus is often not discussed. 95% CIs for the PAF and NNT are likely to be large for small subgroups, lending some uncertainty to the estimates. Risk practices are self-reported and might be inaccurate because of social desirability, faulty recall, or desire to meet study eligibility criteria. Effectiveness of pre-exposure prophylaxis in clinical settings, and therefore the NNT, could be reduced if pre-exposure prophylaxis adherence is poor—a common weakness among several pre-exposure prophylaxis trials.[32] Conversely, if high levels of adherence are achieved, such as those reported in the US sites,[37] the NNT will decrease even further. Demonstration projects and studies of innovative, scalable adherence interventions are underway.[38]

Findings from this analysis suggest that MSM and transgender women can be screened for potential eligibility for pre-exposure prophylaxis even in busy clinical practices by focusing on receptive anal intercourse without a condom. By adding a few more questions about number and serostatus of sex partners, sexual practices, substance use, and risk reduction strategies, clinicians can gain a broad understanding of patients' needs and formulate a comprehensive HIV and STI screening and prevention plan. Pre-exposure prophylaxis offers promise for reducing the spread of HIV worldwide, but clinicians will need to screen patients and provide pre-exposure prophylaxis to at-risk MSM and transgender women for it to achieve its promise.

Contributors

All authors contributed to the study design, data analysis, and interpretation. SPB, AYL, JVG, and KHM contributed to the data collection. SPB and DVG did the data analysis. SPB wrote the manuscript and all other authors provided comments leading to revisions.

Declaration of interests

SPB and AYL have led trials in which study drug was donated by Gilead Sciences and have received personal fees from Clinical Care Options. KHM has received unrestricted research and educational grants from Gilead Sciences and an unrestricted research grant from Merck. PG received an unrestricted grant from Gilead Sciences to develop an educational video related to pre-exposure prophylaxis. RMG has led trials in which study drug was donated by Gilead Sciences. Gilead Sciences also provided unrestricted travel grants that partially supported annual iPrEx investigator meetings. RMG has also received personal fees from Siemens Healthcare, University of Pennsylvania, ViiV Healthcare, Clinical Care Options, the Kirby Institute (Sydney), and Medscape Education. DVG, VMM, and JVG declare that they have no competing interests.

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References

1 Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006–2009. *PLoS One* 2011; **6:** e17502.

2 Beyrer C, Baral SD, van Griensven F, et al. Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012; **380:** 367–77.

3 Phillips AN, Cambiano V, Nakagawa F, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. *PLoS One* 2013; **8:** e55312.

4 Feigin A, El-Hayek C, Hellard M, et al. Increases in newly acquired HIV infections in Victoria, Australia: epidemiological evidence of successful prevention? *Sex Health* 2013; **10:** 166–70.

5 Birrell PJ, Gill ON, Delpech VC, et al. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. *Lancet Infect Dis* 2013; **13:** 313–18.

6 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.

7 Smith D, Herbst JH, Zhang X, Rose C. Condom efficacy by consistency of use among MSM. Conference on Retroviruses and Opportunistic Infections; Atlanta, GA, USA; March 3–6, 2013. Abstract 32.

8 Grant R, McMahan V, Liu A, et al. Completed observation of the randomized placebo-controlled phase of iPrEx: daily oral FTC/TDF pre-exposure HIV prophylaxis among men and trans women who have sex with men. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Rome, Italy; July 17–20, 2011. Abstract WELBC04.

9 Anderson PL, Glidden DV, Liu A, et al. Emtricitabine–tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med* 2012; **4:** 151ra125.

10 Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR Morb Mortal Wkly Rep* 2011; **60:** 65–68.

11 WHO. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva: World Health Organization, 2012.

12 Krakower D, Mayer KH. Engaging healthcare providers to implement HIV pre-exposure prophylaxis. *Curr Opin HIV AIDS* 2012; **7:** 593–99.

13 Tellalian D, Maznavi K, Bredeek UF, Hardy WD. Pre-exposure prophylaxis (PrEP) for HIV infection: results of a survey of HIV healthcare providers evaluating their knowledge, attitudes, and prescribing practices. *AIDS Patient Care STDS* 2013; **27:** 553–59.

14 Arnold EA, Hazelton P, Lane T, et al. A qualitative study of provider thoughts on implementing pre-exposure prophylaxis (PrEP) in clinical settings to prevent HIV infection. *PLoS One* 2012; **7:** e40603.

15 Gomez GB, Borquez A, Case KK, Wheelock A, Vassall A, Hankins C. The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies. *PLoS Med* 2013; **10:** e1001401.

16 Schackman BR, Eggman AA. Cost-effectiveness of pre-exposure prophylaxis for HIV: a review. *Curr Opin HIV AIDS* 2012; **7:** 587–92.

17 Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clin Infect Dis* 2009; **48:** 806–15.

18 Desai K, Sansom SL, Ackers ML, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. *AIDS* 2008; **22:** 1829–39.

19 Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012; **156:** 541–50.

20 Guy RJ, Wand H, Wilson DP, et al. Using population attributable risk to choose HIV prevention strategies in men who have sex with men. *BMC Public Health* 2011; **11:** 247.

21 Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2005; **39:** 82–89.

22 Koblin BA, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. *AIDS* 2006; **20:** 731–39.

23 Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88:** 15–19.

24 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319:** 1492–95.

25 Vallabhaneni S, Li X, Vittinghoff E, Donnell D, Pilcher CD, Buchbinder SP. Seroadaptive practices: association with HIV acquisition among HIV-negative men who have sex with men. *PLoS One* 2012; **7:** e45718.

26 Murnane PM, Celum C, Mugo N, et al, for the Partners PrEP Study Team. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. *AIDS* 2013; **27:** 2155–60.

27 Golden MR, Stekler J, Hughes JP, Wood RW. HIV serosorting in men who have sex with men: is it safe? *J Acquir Immune Defic Syndr* 2008; **49:** 212–18.

28 Goodreau SM, Carnegie NB, Vittinghoff E, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PLoS One* 2012; **7:** e50522.

29 Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol* 2010; **39:** 1048–63.

30 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

31 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.

32 Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367:** 411–22.

33 Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. *PLoS One* 2011; **6:** e23688.

34 Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clin Trials* 2007; **2:** e27.

35 Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; **336:** 995–98.

36 Venter F, Allais L, Richter M. Exposure ethics: does HIV pre-exposure prophylaxis raise ethical problems for the health care provider and policy maker? *Bioethics* 2013; published online June 24. DOI:10.1111/bioe.12021.

37 Gilmore HJ, Liu A, Koester KA, et al. Participant experiences and facilitators and barriers to pill use among men who have sex with men in the iPrEx pre-exposure prophylaxis trial in San Francisco. *AIDS Patient Care STDS* 2013; **27:** 560–66.

38 AVAC. Global Advocacy for HIV Prevention. Ongoing PrEP trials. http://data.avac.org/OngoingPrEPTrials.aspx (accessed Jan 31, 2014).