Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study

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Summary

Background The effect of HIV pre-exposure prophylaxis (PrEP) depends on uptake, adherence, and sexual practices. We aimed to assess these factors in a cohort of HIV-negative people at risk of infection.

Methods In our cohort study, men and transgender women who have sex with men previously enrolled in PrEP trials (ATN 082, iPrEx, and US Safety Study) were enrolled in a 72 week open-label extension. We measured drug concentrations in plasma and dried blood spots in seroconverters and a random sample of seronegative participants. We assessed PrEP uptake, adherence, sexual practices, and HIV incidence. Statistical methods included Poisson models, comparison of proportions, and generalised estimating equations.

Findings We enrolled 1603 HIV-negative people, of whom 1225 (76%) received PrEP. Uptake was higher among those reporting condomless receptive anal intercourse (416/519 [81%] *vs* 809/1084 [75%], p=0·003) and having serological evidence of herpes (612/791 [77%] *vs* 613/812 [75%] p=0·03). Of those receiving PrEP, HIV incidence was 1·8 infections per 100 person-years, compared with 2·6 infections per 100 person-years in those who concurrently did not choose PrEP (HR 0·51, 95% CI 0·26–1·01, adjusted for sexual behaviours), and 3·9 infections per 100 person-years in the placebo group of the previous randomised phase (HR 0·49, 95% CI 0·31–0·77). Among those receiving PrEP, HIV incidence was 4·7 infections per 100 person-years if drug was not detected in dried blood spots, 2·3 infections per 100 person-years if drug concentrations suggested use of fewer than two tablets per week, 0·6 per 100 person-years for use of two to three tablets per week, and 0·0 per 100 person-years for use of four or more tablets per week (p<0·0001). PrEP drug concentrations were higher among people of older age, with more schooling, who reported non-condom receptive anal intercourse, who had more sexual partners, and who had a history of syphilis or herpes.

Interpretation PrEP uptake was high when made available free of charge by experienced providers. The effect of PrEP is increased by greater uptake and adherence during periods of higher risk. Drug concentrations in dried blood spots are strongly correlated with protective benefit.

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Introduction

Pre-exposure prophylaxis (PrEP) with oral emtricitabine and tenofovir disoproxil fumarate prevents the acquisition of HIV among men and transgender women who have sex with men,[1] heterosexual couples,[2] and heterosexual men and women.[3] The effectiveness of PrEP depends greatly on both the efficacy of the drugs[4,5] and multiple social interactions and behaviours related to uptake and adherence.

In randomised placebo-controlled trials,[1,2] adherence to PrEP (assessed by detection of drugs in blood) was a strong correlate of efficacy. HIV risk was reduced by 90% or more among people using PrEP who had detectable drug in two trials,[4,5] whereas two trials of African women showed no evidence of efficacy on an intention-to-treat basis; despite high reported adherence, less than a third of participants receiving active drug had detectable concentrations in their blood.[6,7]

The theory of risk compensation predicts that people are more likely to participate in risky sexual practices with the advent of biomedical disease-prevention strategies, including medical circumcision, antiretroviral treatment for HIV infection, and PrEP.[8] By contrast, self-reported sexual practices became safer in trials of PrEP,[2,9,10] including among people who thought that they were receiving the active treatment and that it would be effective.[9] Self-reported increases in safe behaviour were corroborated by decreases in the incidence of syphilis and prevalence of acute HIV infection.[9]

Patterns in PrEP use[11] and sexual practices[12] could differ in clinical practice from those reported in clinical trials. Participants in masked and placebo-controlled efficacy trials are informed that they might be receiving a placebo or a drug with no benefit and that product safety requires further confirmation. Such messages could undermine adherence and limit risk compensation. As information

from trials about PrEP safety and efficacy becomes available, adherence could increase and condom use could decrease. Open-label treatment could also alter uptake of PrEP; as people focus more on their personal goals rather than research goals, intentions to use PrEP might be greater when HIV exposure is greatest or PrEP might be taken up in clinical practice primarily by the so-called worried well, who are already protecting themselves in other ways. The overall effect of PrEP in practice depends on these behaviours.

Our aim was to investigate PrEP uptake, adherence, and sexual practices in a way that more closely resembles clinical practice. Because social desirability can bias self-reported adherence, we use tenofovir diphosphate measured in dried blood spots as a novel biomarker of long-term PrEP use.

Methods

Participants

In this cohort study we sought to identify demographic and behavioural characteristics associated with PrEP uptake and adherence and the effect of PrEP uptake and adherence on HIV incidence and sexual practices. We enrolled participants from three previous randomised controlled trials: ATN 082,[13] iPrEx,[1] and US Safety Study.[14] All participants in the iPrEx open-label extension were designated male at birth, reported having had anal intercourse with men, were older than age 18 years, and had previously participated in a randomised masked placebo-controlled trial of once daily oral PrEP with emtricitabine and tenofovir disoproxil fumarate (iPrEx or ATN 082) or tenofovir disoproxil fumarate only (US Safety Study). Participants who were identified as infected with HIV during the randomised phases of previous trials were followed up, although they were not eligible for PrEP; they are not included in this report.

All participants provided written informed consent. The open-label extension protocol was approved by ethical committees governing each study site and by national regulatory authorities in each country, including registration with the US Food and Drug Administration.

Procedures

Participants were told their randomised assignment before enrolment in the open-label extension. After providing informed consent and before HIV testing, patients answered a computer questionnaire to assess desire to use PrEP, reasons for declining PrEP (selected from a list as all that apply), self-identification as trans (selected a list of identities as all that apply, translated according to local custom), education, alcohol use (in the past 30 days), and controlled substance use (in the past 30 days). At the enrolment visit, all participants were offered daily oral PrEP with emtricitabine and tenofovir disoproxil fumarate if they were HIV-antibody negative and they had no symptoms of acute HIV infection. For those with an acute viral syndrome, PrEP was deferred until HIV RNA testing was negative or HIV antibody testing continued to be negative after resolution of symptoms. All benefits of study participation were provided irrespective of whether participants chose to take PrEP; such benefits varied by study site in accordance with local standards and ethical committee requirements. Visits were done at enrolment and at weeks 4, 8, 12, 24, 36, 48, 60, and 72. Participants could start PrEP on any visit during the first 48 weeks of follow-up, and were followed up at weeks 4, 8, and 12 after starting PrEP then every 12 weeks until completing a total of 72 weeks on study (off or on PrEP). Counselling support included integrated next-step counselling,[15,16] which involved counselling for sexual health for all participants and PrEP adherence assessment and counselling for those receiving PrEP. All participants were informed that the results of PrEP drug testing would be shared with them; results were provided by a medical officer. Results from drug testing done during previous randomised trials were not provided to the study sites or to the study participants.

We assessed drug concentrations in blood plasma for all participants at one of their study visits during the first 12 weeks after receiving PrEP. Drug concentrations in dried blood spots were measured for participants who opted to receive PrEP using a case-cohort design.[17] This design tested all timepoints after PrEP dispensation among those with confirmed HIV infection and a site-stratified sample of seronegative participants. Roughly 27% of seronegative participants were selected with a pseudorandom number list, overseen by the study statistician (DVG). Analyses of drug concentrations were weighted inversely to the probability of selection for testing. Only results from dried blood spots were used in the analysis of correlates of drug detection.

Patients were tested for HIV antibodies at all visits and tested for syphilis, herpes, and urethritis every 24 weeks or if they had symptoms. Two rapid tests were used for HIV testing, with western blot testing to confirm any reactive test result.[1] PrEP was discontinued at the time of any reactive test, and resumed if confirmatory tests were negative. Blood plasma (with EDTA) was drawn and dried blood spots were prepared at enrolment and all 12-week follow-up visits irrespective of receipt of PrEP. Plasma and dried blood spots were also collected 4 weeks and 8 weeks after starting PrEP. Dried blood spots were stored at –20°C within 24 h of collection and shipped on dry ice to the laboratory where 3 mm punches were taken and analysed for tenofovir diphosphate by liquid chromatography and tandem mass-spectroscopy, as previously described.[18,19] We estimated creatinine clearance with the Cockcroft-Gault equation.

We estimated dosing from the tenofovir diphosphate concentration using pharmacokinetic modelling from observations of drug accumulation and decay after 1 month of daily dosing.[18] Tenofovir diphosphate in dried blood spots has a half-life of 17 days, corresponding with a 25-fold accumulation with daily dosing. The lower limit

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