High acceptability, adherence and tolerability of HIV pre-exposure prophylaxis in a pilot demonstration project among Toronto gay and bisexual men

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In the past 2 years, DHST's institution has received research support for investigator-initiated research studies from Gilead and Viiv Healthcare, and DHST has been a Site Principal Investigator for clinical trials sponsored by Glaxo Smith Kline. JR is a co-investigator on several projects with in-kind contributions or research support from Merck and Gilead Sciences. All other authors declare no competing interests.

ABSTRACT

Background: PrEP is highly efficacious at preventing HIV, but concerns persist about adherence and sexual transmitted infections (STIs). We assessed PrEP acceptability, adherence, and clinical outcomes in a pilot demonstration project among Toronto gay, bisexual and other men who have sex with men (gbMSM).

Methods: HIV-uninfected adult gbMSM scoring ≥10 on a validated HIV risk score (HIRI-MSM) and reporting condomless receptive anal sex were sequentially enrolled into a one-year, open-label clinical trial of daily oral tenofovir disoproxil fumarate/emtricitabine. Visits included adherence assessments (four-day recall, pill count, dried blood spot analysis), questionnaires about PrEP acceptability, and laboratory testing for HIV, STIs and creatinine.

Results: Of 86 men screened, 52 were enrolled. Participants were mostly White (73.1%), young (median age 33, IQR=28,37), gay (94.2%) men. PrEP acceptability was high, with all participants reporting their experience as "good" or "very good". Median adherence was high at 100% (95%, 100%) by self-report and 96.9% (93.4%, 98.4%) by pill count. Dried blood spots suggested doses were taken on 4-7 days/week at 88.7% of visits. No HIV seroconversions occurred, but 48% of participants experienced ≥1 bacterial STI, with incidences per 100 person-years of 32.8, 32.8, 8.2 and 8.2 for chlamydia, gonorrhea, syphilis and lymphogranuloma venereum respectively. Estimated glomerular filtration rate declined by 0.22 ml/min/month.

Interpretation: PrEP was associated with high adherence and acceptability, and no HIV infections in this demonstration project. Frequent STIs and subclinical effects on renal function reinforce the need for ongoing vigilance.

Trial registration: NCT 02149888

KEYWORDS

HIV; pre-exposure prophylaxis; demonstration project; men who have sex with men; adherence; sexually transmitted infections

BACKGROUND

Despite decades of traditional prevention efforts, Canada continues to see large numbers of new HIV diagnoses every year. A disproportionate burden occurs among gay, bisexual and other men who have sex with men (gbMSM), who make up 49.7% of prevalent infections and have a 131-fold higher risk of incident HIV than other Canadian men.[1] Pre-exposure prophylaxis (PrEP) with daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is a biomedical HIV prevention approach that has been shown to be safe and efficacious in reducing HIV acquisition in randomized trials.[2-5] As the results of these studies became available, interest increasingly turned to evaluating PrEP rollout through 'demonstration projects', or clinical trials addressing implementation outcomes such as adherence and real-world effectiveness.[6-8] However, in surveys we conducted among men undergoing HIV testing,[9, 10] physicians,[11] staff from AIDS service organizations,[12] and pharmacists[13] across Canada, respondents expressed concerns that suboptimal PrEP adherence could drive the emergence of drug-resistant HIV, that PrEP could be associated with more sexually transmitted infections (STIs), and that healthy individuals could be unnecessarily exposed to drug toxicities, despite overall optimism about the potential to prevent new infections. Further, there was uncertainty about the acceptability of PrEP for at-risk populations, fuelled in part by reports that uptake in settings with greater PrEP availability was slower than expected.[14, 15]

To address these concerns and to inform the broader rollout of PrEP in Canada, we conducted a pilot PrEP demonstration project among gbMSM in Toronto. Our primary objective was to assess the acceptability of PrEP at the community and individual levels, by quantifying both the volume of referrals to the study and participants' satisfaction with their experience on PrEP.

Secondary objectives included estimating PrEP adherence, and quantifying key clinical outcomes including HIV seroconversion, bacterial STIs, and adverse events. We conceived the trial as a pilot study because we planned to use the findings to inform the design and sample size calculations for larger PrEP implementation studies in the future.

METHODS

Study design

PREPARATORY-5 was a one-arm, open-label pilot demonstration project of daily PrEP among Toronto gbMSM at high risk of sexually acquired HIV infection (NCT 02149888). Study staff dispensed tenofovir disoproxil fumarate/emtricitabine 300/200 mg, one tablet orally once daily over one year, during quarterly follow-up visits at a tertiary academic hospital in downtown Toronto.

Participants

We recruited participants through self-referrals and provider-referrals between October 16, 2014 and December 30, 2014, as previously described.[16] English-speaking gbMSM aged ≥18 years were eligible if they tested non-reactive on a 4th generation HIV test (ARCHITECT HIV antigen/antibody Combo Assay, Abbott Laboratories, Abbott Park, IL), had a creatinine clearance ≥60 mL/min by the Modified Diet in Renal Disease (MDRD) formula, reported at least one condomless receptive anal sex act over the preceding six months, and scored ≥10 on the HIV Incidence Risk Index for MSM (HIRI-MSM),[17] a recommended cut-off for identifying gbMSM PrEP candidates.[17]

Exclusion criteria included symptoms or signs of HIV seroconversion, use of pre- or post-exposure prophylaxis within the preceding three months, concomitant nephrotoxic or immunomodulatory drugs, hepatitis B surface antigen positivity, high risk of osteoporosis, enrollment in any other HIV prevention trial, or perceived inability to adhere with the study protocol.

Study procedures

Eligible men attended a baseline visit within two weeks, and follow-up visits at months 1, 3, 6, 9 and 12 thereafter. Each visit included assessment for adverse events, INSTI® HIV-1/HIV-2 rapid antibody testing (bioLytical® Laboratories, Richmond, BC),[18] 4th generation HIV testing, complete blood count, creatinine, phosphate, syphilis serology, pill count, dried blood spot (DBS) collection for measurement of intra-erythrocytic tenofovir disphosphate (TFV-DP) levels[19] and drug dispensing. At all visits except month 1, participants also underwent a urinalysis and screening for gonorrhea and chlamydia infections, using urine nucleic acid amplification testing as well as pharyngeal and rectal swabs for culture. Data on incident STIs diagnosed at other facilities were collected through clinical history-taking. Every visit included personalized counseling on PrEP adherence and STI risk reduction. Electronic questionnaires at each visit included assessments of PrEP acceptability and adherence (AIDS Clinical Trials Group Adherence Questionnaire[20]). Participants received $25 CAD per visit as compensation for time. Each participant was also asked to attend a single adherence support session with an experienced counsellor housed at a partner community-based organization, where one-on-one counseling was provided based on a published PrEP adherence support intervention.[21]

Outcome Measures and Analysis

We summarized demographic and clinical characteristics of enrolled participants using descriptive statistics. To assess community-level interest in PrEP, we quantified the number of individual referrals received per unit time. To assess individual-level PrEP acceptability, we calculated each participant's response to the question, "Overall, how would you rate your experience on PrEP?", averaged over all available study visits, on a Likert Scale ranging from 1="very bad" to 5="very good". The proportion of participants reporting 'good' overall PrEP acceptability was defined as the proportion with average scores of 4 or higher.

We PrEP adherence using self-report, pill count and intra-erythocytic TFV-DP levels on DBS analysis.[22] We used self-report data to calculate the proportion of doses taken over the preceding four days, and pill count data to estimate the total number of doses taken between successive study visits. We used DBS data to classify results into four categories of PrEP adherence: dosing 7 days/week, 4-6 days/week, 2-3 days/week or <2 days/week, corresponding to HIV risk reductions of 100%, 100% (95%CI=86, 100%), 84% (95%CI=-24, 99%) and 44% (95%CI=-31, 77%) respectively.[23]

We tabulated incident HIV infections and STIs, converted into incidence rates per 100 person-years of follow-up (PYFU). We classified clinical adverse events according to the Division of AIDS Grading system[24] and tabulated these according to severity and investigator-assessed probability of association with study drug. We calculated creatinine clearance at each visit using the MDRD equation, and modelled the effect of time on eGFR using a linear mixed model with a random intercept and a fixed effect of continuous time.

All analyses were by intention-to-treat. Analyses were conducted using SAS version 9.4 (Cary, NC) and R version 3.4.1 (R Development Core Team, Vienna, Austria).

Sample size considerations

The target sample size was 50 participants, based primarily on feasibility considerations. This sample size permitted estimation of the proportion of participants reporting high PrEP acceptability, anticipated at 80-90%, with reasonable precision (±10%).

Ethical approval

Ethics approval was provided by the Research Ethics Boards of St. Michael's Hospital, Ryerson University, University Health Network and the University of Toronto. All participants provided written informed consent prior to any study activities.

RESULTS

During the 75-day recruitment period, community-based organizations referred 115 individuals to the study, and our electronic advertisements generated 1518 click-throughs. These referrals generated 165 unique inquiries about trial participation (2.2/day), suggesting substantial PrEP interest in the local gbMSM community.

Of 86 men screened for participation, 52 were eligible and enrolled into the study (Figure 1). Of these, 43 (83%) were retained for the full one-year period, while one, two and six participants left the study early at months 3, 6 and 9 respectively, producing 48.75 person-years of follow-up

overall. Baseline characteristics were similar for the 43 retained participants and the nine who left early (data not shown). Study visits were conducted between November 10, 2014 and June 28, 2016

Enrolled participants were mostly gay-identified (94%), White (73%) men with an undergraduate degree or higher (73%), and median (interquartile range, IQR) age was 33 (28, 37) years (Table 1). The median number of prescription medications taken was zero (0, 1), but the median number of supplements taken was 1 (0, 3). Most (69%) had a prior history of ≥1 bacterial STI. Over the preceding six months, the median number of sexual partners was 18 (12, 30.5), and the median number of condomless receptive or insertive anal sex acts was 5 (2, 15) and 5 (2, 12.5) respectively.

Individual-level PrEP acceptability was high. After averaging data for each participant over all follow-up visits for which responses were available (five, four or three visits for 81%, 12% and 8% of participants, respectively), 100% of participants rated their experience on PrEP as '4' ("good") or '5' ("very good"), and the median overall response was 4.8 (4.4, 5.0).

Overall PrEP adherence was high, whether assessed by self-report, pill count or DBS analysis (Table 2). Median adherence was 100% (95%, 100%) by self-report, and 96.9% (93.4%, 98.4%) by pill count. Quantification of intra-erythrocytic TFV-DP levels was consistent with PrEP dosing on 7 days, 4-6 days, 2-3 days and <2 days per week at 50.6%, 36.8%, 9.7% and 2.8% of all study visits, respectively. After removing month 1 data, since TFV-DP may not have reached

steady state inside red blood cells at this early time point,[22] these figures increased to 58.5%, 30.3%, 8.7% and 2.6% respectively.

There were no HIV seroconversions. However, the burden of bacterial STIs was high, with 40 confirmed infections occurring in 25 (48%) study participants. Most (60%) of these 25 individuals had a prior history of bacterial STI. Incident STIs included 16 chlamydia (32.8/100 PYFU, 95%CI=19.4-52.2/100 PYFU), 16 gonorrhea (32.8/100 PYFU, 95%CI=19.4-52.2/100 PYFU), 4 early syphilis (8.2/100 PYFU, 95%CI=2.6-19.8/100 PYFU) and 4 lymphogranuloma venereum (8.2/100 PYFU, 95%CI=2.6-19.8/100 PYFU) infections. In addition, there were six episodes of non-specific urethritis treated empirically with ceftriaxone and azithromycin at other facilities, for which gonorrhea and chlamydia testing were reportedly negative.

Of 185 adverse events overall (Table 3), 37 (20%) were at least possibly related to study drug, but all were either mild (81%), or moderate (19%) in severity, and none led to PrEP discontinuation. The most common adverse events at least possibly related to study drug were nausea, diarrhea and headache, occurring in 21%, 12% and 12% of study participants respectively. The only serious adverse event was a hospitalization for severe but self-limited colitis; the two other adverse events graded as severe included one episode each of lymphogranuloma venereum and stress. All three severe events were deemed unrelated to study drug.

We observed one grade 2 and three grade 1 creatinine elevations, all of which resolved spontaneously without interrupting PrEP use. Creatinine clearance appeared to change by -0.22

(95%CI=-0.45, 0.01) ml/min per month of follow-up in a generalized linear mixed model but this change was of borderline statistical significance (p=0.06).

DISCUSSION

In this pilot demonstration project of daily oral TDF/FTC in Toronto gbMSM at elevated HIV risk, we observed high PrEP interest at the community level, high acceptability at the individual level, excellent study drug adherence, a favourable adverse event profile, and no HIV seroconversions over 48.75 person-years of follow-up. The high PrEP adherence in this study is important because adherence is the key predictor of PrEP effectiveness.[2, 23, 25] However, bacterial STIs were common, as seen in other reports,[26, 27] and creatinine clearance appeared to decline by 0.22 ml/min per month. Taken together, these findings confirm the feasibility of using PrEP to decrease HIV infections in this population, while highlighting the need for ongoing attention to STIs and subclinical drug toxicities.

Because our study lacked a comparison group, it is not possible to determine to what extent PrEP was causally related to the high burden of STIs observed. Existing studies have had mixed findings on this topic. A meta-analysis summarizing rates of STIs among cohorts of gbMSM using versus not using PrEP found incidence rate ratios of 25.3, 11.2 and 44.6 for infection with gonorrhea, chlamydia and syphilis respectively.[28] However, since bacterial STIs are also an important marker of HIV risk, these results are heavily confounded by indication, and the high STI incidence could alternatively signify that programs have been successful at linking PrEP to those in greatest need. That 69% of our study participants had a prior bacterial STI at study entry may further support this notion. High STI rates could also be partly attributable to

increased STI screening in PrEP users. The PROUD study found that after adjustment for the frequency of testing, the odds of any bacterial STI was similar to those not using PrEP (odds ratio=1.07, 90%CI=0.78, 1.46).[27] In the context of continually increasing gonorrhea, chlamydia and syphilis epidemics in Canada,[29] additional STI control strategies are urgently needed.

Although concern about side effects has been reported as the most common reason for not wanting to use PrEP in acceptability studies,[30, 31] adverse events in our cohort were minimal, and generally restricted to mild gastrointestinal symptoms that resolved spontaneously. These findings are consistent with a systematic review of PrEP clinical trials, in which the risk of adverse events was similar to placebo (relative risk=1.01, 95%CI=0.99, 1.03).[32] However, we did observe subclinical declines in renal function, at -0.22 ml/min per month, or -2.64 ml/min per year. This is greater than the age-related decline in eGFR observed in cohorts of healthy adults, estimated at roughly 0.75 to 0.97 ml/min/year.[33, 34] Our findings are consistent with those from randomized trials, in which PrEP has been associated with decreases in eGFR that were roughly 1 ml/min/year greater than placebo.[35-39] Importantly, findings from a cohort of 3924 individuals in East Africa have shown that PrEP-related changes in renal function are generally reversible, with eGFR levels among PrEP users becoming comparable to placebo participants by four weeks after drug discontinuation, and returning to >75% of baseline levels in over 96% of PrEP users by eight weeks.[40] PrEP has also been associated with reversible decreases in BMD.[36] Results from a bone substudy of this trial will be reported elsewhere.

Our study has several limitations that warrant consideration. First, our single-arm design precluded the ability to compare results to non-PrEP using individuals, and our sample size in this pilot study was modest. However, our purpose was to conduct descriptive analyses only, to inform the design of future studies. Second, several factors may have contributed to our favourable adherence results. Most participants were already taking ≥1 health supplement at study entry, suggesting considerable experience with regular pill-taking and high health-seeking behaviour within the cohort, and our adherence support intervention may have further bolstered adherence. However, the one-time nature of that counseling session makes it unlikely that it impacted adherence overall. Finally, because we recruited participants in a context where PrEP was not widely available, our participants could be considered PrEP "early adopters" according to classical diffusion theory,[41] and thus may not represent the broader population of at-risk gbMSM in Canada. Health Canada only granted regulatory approval for use of TDF/FTC as PrEP in February 2016, and public reimbursement only became available in Ontario in September 2017.

In conclusion, daily oral TDF/FTC as PrEP was associated with high adherence and acceptability, and no HIV infections in this study. As Canada's first demonstration project of this emerging HIV prevention intervention, our findings support the broader rollout of PrEP for at-risk gbMSM in this country and similar industrialized settings. However, changes in sexual behaviour, frequent STIs and subclinical effects on renal function reinforce the need for ongoing vigilance. It will be important to continually monitor these outcomes as public drug coverage and community uptake increase, and as PrEP clinical practice guidelines[42] lead to greater prescribing.

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Table 1. Participant characteristics

Characteristic	Value[a]
Age (years)	33 (28, 37)
Race	
White	38 (73.1)
Asian	4 (7.7)
Latino	3 (5.8)
Middle Eastern	3 (5.8)
Other[b]	4 (7.7)
Sexual orientation	
Gay	49 (94.2)
Bisexual[c]	3 (5.8)
Education	
High school or Some postsecondary	14 (26.9)
Undergraduate	23 (44.2)
Graduate	15 (28.9)
Annual income ($CAD)	
≤$20K	9 (17.3)
$20-40K	11 (21.2)
$40-60K	14 (26.9)
$60-80K	7 (13.5)
$80-100K	5 (9.6)
>$100K	6 (11.5)
Number of prescription medications	0 (0, 1)
Number of supplements	1 (0, 3)
Current smoking	13 (25)
Previously STI diagnoses	
Gonorrhea	21 (40.4)
Chlamydia	24 (46.2)
Syphilis	10 (19.2)
Any bacterial STI	36 (69.2)
Baseline HIRI-MSM score	29 (22.5, 33)
Baseline sexual behaviours, past 6 months	
Number of partners	18 (12, 30.5)
Number of HIV-positive partners	1 (0, 3)
Condomless receptive anal sex (# times)	5 (2, 15)
Condomless receptive anal sex with HIV+ partners (# times)	0 (0, 0)
Condomless insertive anal sex (# times)	5 (2, 12.5)
Condomless insertive anal sex with HIV+ partners (# times)	0 (0, 3)

[a] Values are frequencies (proportions) and median (interquartile range).
[b] Includes individuals who identified as mixed (n=2), Black (n=1) and First Nations (n=1)
[c] Includes one individual who identified as 'pansexual'

Table 2. PrEP adherence by study visit and measurement technique

Month	N	Self-reported 4-day recall	Pill count	TFV-DP levels [a]			
					Number (Proportion) of participants in each adherence category		
		Median (IQR) % doses taken	Median (IQR) % doses taken	Median (IQR) TFV-DP level (fmol/punch)	≤349 fmol/punch (≤2 days/wk)	350-699 fmol/punch (2-3 days/wk)	700-1249 fmol/punch (4-6 days/wk)	≥1250 fmol/punch (7 days/wk)
1	52	100% (100%, 100%)	100% (96.4%, 100%)	930 (746.5, 1199)	2 (3.9)	7 (13.5)	32 (61.5)	11 (21.2)
3	52	100% (100%, 100%)	98.7% (93.7%, 100%)	1341 (1062, 1555.5)	0 (0)	4 (7.7)	18 (34.6)	30 (57.7)
6	51	100% (100%, 100%)	98.9% (92.9%, 100%)	1432 (1068, 1847)	0 (0)	4 (7.8)	15 (29.4)	32 (62.8)
9	48	100% (100%, 100%)	98.9% (95.0%, 100%)	1392.5 (1141, 1662.5)	1 (2.1)	3 (6.3)	11 (22.9)	33 (68.8)
12	42	100% (95.0%, 100%)	98.0% (90.1%, 100%)	1191.5 (777, 1527)	2 (4.8)	6 (14.3)	15 (35.7)	19 (45.2)

[a] TFV-DP levels of ≤349, 350-699, 700-1249 and ≥1250 fmol/punch correspond to PrEP dosing on ≤2, 2-3, 4-6 and 7 days per week, respectively.[23]

Table 3. Adverse events

	Number of participants (%)	Number of events (% of total)
Any adverse event	47 (90)	185
Grade 1	34 (65)	144 (78)
Grade 2	10 (19)	38 (21)
Grade 3	3 (6)	3 (2)
Any serious adverse event	1 (2)	1 (0.5)
Adverse events by relationship to study drug		
Possibly	14 (27)	26 (14)
Probably	9 (17)	11 (6)
Adverse events at least possibly related to study drug, by type		
Nausea	11 (21)	12 (7)
Diarrhea	6 (12)	6 (3)
Headache	6 (12)	6 (3)
Fatigue	5 (10)	5 (3)
Bloating	2 (4)	2 (1)
Vivid Dreams	2 (4)	2 (1)
Anorexia	1 (2)	1 (0.5)
Difficulty sleeping	1 (2)	1 (0.5)
Flatulence	1 (2)	1 (0.5)
Itching	1 (2)	1 (0.5)

FIGURE TITLES

Figure 1. Participant flow diagram

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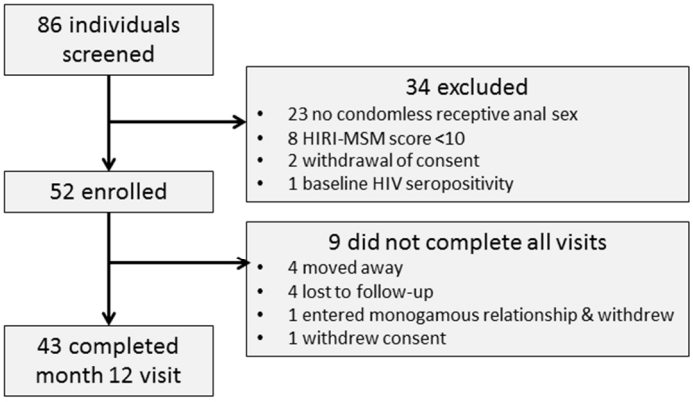

Participant flow diagram

254x190mm (96 x 96 DPI)