Medication adherence, condom use and sexually transmitted infections in Australian PrEP users: interim results from the Victorian PrEP Demonstration Project.

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ABSTRACT

Objective: HIV Pre-exposure prophylaxis (PrEP) decreases risk of HIV acquisition however its efficacy is closely dependent on adherence. There is also concern that the preventive effect of PrEP may be offset by risk compensation, notably an increase in condomless anal sex.

Design: Multi-site, open-label demonstration study that recruited people at current or recent risk of HIV infection in Melbourne, Australia.

Methods: Participants were recruited from three general practice clinics and one sexual health clinic in Melbourne and consented to take daily tenofovir/emtricitabine for 30 months. Sexual practice data, HIV and sexually transmitted infection (STI) test results were collected at baseline and 3-monthly during follow up. PrEP adherence was evaluated by self-report at clinical visits, online surveys, refill-based assessments and dried blood spot (DBS) testing. We present a 12-month interim analysis.

Results: 114 people were recruited. We observed a significant decline in condom use which occurred concomitantly with a significant increase in STIs over the first 12 months of PrEP. Incidence (per 100PY) of any STI was 43.2 and 119.8 at m0-3 and M3-12, respectively (IRR 2.77 (1.52, 5.56)). Adherence to PrEP medication was high by all measures, including six month TDF-FTC levels in DBS.
Conclusions: We found significant reduction in condom use and an increase STIs over the first 12 months of follow-up. High medication adherence rates coupled with a decline in condom use and a rise in STIs, suggests that prevention, early detection and treatment of STIs is a chief research priority in the current era of HIV PrEP.

Keywords: adherence; HIV; preexposure prophylaxis; sexually-transmitted infections; tenofovir/emtricitabine
Background

Since the late 1990s, Australia has witnessed a steady increase in the number of HIV diagnoses, which have stabilised at approximately 1,000 cases annually. In the past decade, 84% of new HIV infections have occurred in gay men [1]. In June 2014, Australia’s first HIV pre-exposure prophylaxis (PrEP) demonstration study opened in Melbourne, Victoria. Participants were offered up to 30 months of once daily tenofovir/emtricitabine for PrEP, with a prescription for 90 days medication given at quarterly study visits. Here we report on PrEP adherence, sexual practices and sexually transmitted infections (STI) in study participants over the first 12 months of PrEP.

Methods

Participants and recruitment

During June 2014 to August 2015, 114 individuals commenced PrEP. The study was conducted at three high-caseload general practices and one sexual health clinic. Participants were included if they were at current, or recent risk of HIV infection through at least one of: (i) condomless receptive or insertive intercourse (anal and/or vaginal) with an HIV seropositive person; (ii) receptive condomless anal intercourse with casual partners of unknown HIV status; (iii) uncircumcised, condomless insertive anal intercourse with casual partners of unknown HIV status; or (iv) condomless penile-vaginal sex with an HIV seropositive partner while seeking to conceive. Inclusion criteria were compatible with extant Australian PrEP guidelines. Safer sex practices, including condom use, were recommended at each study visit. Participants were asked to pay for PrEP at the equivalent Australian Pharmaceutical Benefits Scheme co-payment rate of $AUS 6.20 - $AUS 28.30 to emulate
‘real world’ conditions. Outstanding payments of pharmacy invoices did not prevent study participation. Written informed consent was obtained from all participants and the study was approved by the Alfred Hospital’s Human Research Ethics Committee.

Data abstraction and collection

Clinical and laboratory data were collected at baseline and quarterly follow-up visits, including HIV antibody/antigen ELISA results, STI results (syphilis, gonorrhoea and chlamydia), serum creatinine and Cockcroft-Gault glomerular filtration rate. Sites tested for gonorrhoea were anal and pharyngeal, while anal and urethral (urine) were tested for chlamydia. At baseline, syphilis results were classified as prior/treated or current/untreated, based on syphilis test results and treatment history. PrEP adherence over follow-up was evaluated by: (i) self-report at 3-monthly study visits where participants indicated whether they had taken < 50%, 50%–90%, or > 90% of daily doses; (ii) quarterly online self-report where participants indicated number of doses missed; (iii) refill-based assessments where the percentage of days PrEP was available between study visits was calculated; and (iv) dried blood spot (DBS) testing (month 6 sample only) where red blood cell (RBC) levels of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) were assayed.

Online surveys

Based on three-month recall, participants were asked about type (regular and/or casual) and number of sexual partners, occasions of anal intercourse and proportion of occasions during which condoms were used. Likert-type items with 5-point response options were used to assess condom use with sexual partners (never, some of the time, half of the time, most of the time, always).
Dried blood spot (DBS) testing

DBS samples were analysed using reverse-phase liquid chromatography mass-spectrometry to detect TFV-DP and FTC-TP in red blood cells (RBCs) [2]. TFV-DP has a half-life of 17 days in RBCs, and provides cumulative dosing information over the preceding 1-2 months. FTC is phosphorylated to FTC-TP in RBCs with a half-life of approximately 33 hours (22-53), hence it provides information on dosing in the past 48 hours.

Statistical analysis

Statistical analyses were undertaken to assess the impact of PrEP on sexual practices, STI infections and to assess adherence to PrEP in the first 12 months of individuals receiving PrEP. Analyses included generalized estimating equations to model categorical and linear slopes for each outcome measure over time. Binomial distribution with a logit link function to model dichotomous outcomes, negative binomial distribution with a logit link function to model count outcomes, and normal distribution with an identity link function were used to model Likert-type outcomes. Age, a potential confounder, was included as a covariate in all models. Variances were estimated using the robust sandwich technique. We reported exponentiated coefficients for dichotomous and count models and raw coefficient for Likert-type models with corresponding 95% confidence intervals to evaluate statistical significance and precision. Incidence per 100 person-years (PY) were calculated for STIs and incidence rate ratios were calculated which compared baseline-month three to month three-month twelve. Baseline could not be used as a comparator timepoint for STI incidence as there was no direct measure of incidence, or STI testing history at study entry. Proportion of participants with ≥1STI at baseline-month 3 was compared to month three-month twelve using the Chi square test.
Results

Study participants

The median age of participants was 34.0 years (interquartile range (IQR) 30.8-45.0).
Reported ethnicity was 93.9% Caucasian, 4.4% Asian, 0.9% Aboriginal/Torres Strait Islander
and one participant declined to state their ethnicity. Detailed demographic data were available
at baseline for 106 of the 114 participants. Of the 106 participants, 64.1% had completed an
undergraduate or higher degree, 90.6% identified as gay, 4.7% as bisexual and 4.7% as
“other”. There was one transgender participant, all other were male. At baseline 44.3%
reported having a regular partner, with 7.5% of the cohort reporting a monogamous
relationship. At study entry 91.5% participants reported sex with casual partners in the
preceding three months.

The cohort met the following inclusion criteria: 35.1% identified condomless receptive or
insertive intercourse with an HIV seropositive person, 67.5% identified condomless anal
intercourse with casual partners of unknown HIV status and 9.7% identified uncircumcised,
condomless insertive anal intercourse with casual partners of unknown HIV status.
Participants could identify multiple risk factors. No heterosexual couples seeking to conceive
were recruited. Uncircumcised, condomless insertive anal intercourse was identified as sole
inclusion criterion by only 2.6% of the cohort. The month three, six, nine and twelve month
study visits were completed by 97% (n=111), 92% (n=105), 94% (n=107) and 92% (n=105)
of participants, respectively.

HIV infection
There were two HIV seroconversions. One participant seroconverted to HIV four weeks after study entry, but prior to commencing PrEP. Another participant, who had an undisclosed HIV exposure two days prior to testing HIV negative at study entry, delayed starting PrEP for two weeks. This participant had seroconverted when tested 4 weeks after PrEP commencement. HIV genotyping revealed the M184I/M/V mutation, which is associated with resistance to emtricitabine.

**Sexual practices**

**Regular partners**

There was no significant change in the proportion of participants with regular partners, or in the frequency of sexual intercourse with regular partners, over 12 months follow-up. There was, however, a significant decrease in condom use \((p=0.001)\) and withdrawal before ejaculation \((p=0.001)\) with regular partners (Table 1).

**Casual partners**

The proportion of participants who reported sex with casual partners remained stable over 12 months follow-up and there was no significant change in the number of sexual acts with casual partners (Table 1). The baseline proportion of any condomless anal sex with casual partners was 76.4%. Condom use \((p<0.001)\), HIV serosorting \((p=0.019)\) and withdrawal before ejaculation \((p<0.001)\) with casual partners all decreased significantly over 12 months follow-up (Table 1).

**STI rates**
STI data were available for 114 participants at baseline; then 111, 105, 107, and 105 at months 3, 6, 9 and 12, respectively. At all timepoints >97% of participants were tested for anal gonorrhoea and anal chlamydia, >96% were tested for pharyngeal gonorrhoea, ≥92% tested for urine chlamydia and ≥99% for syphilis. Asymptomatic urethral gonorrhoea was not tested and pharyngeal chlamydia results were not available for this analysis. There was a significant increase in the proportion of participants with STIs at months three-twelve compared to baseline-month three (Table 1). Incidence rate ratios (months three-twelve compared to baseline-month three), by site and infection type showed significant increases in anal site STIs, total gonorrhoea and total chlamydia (Table 1, Figure 1 and supplementary table, http://links.lww.com/QAD/B97).

Adherence to PrEP

Adherence to PrEP was high across all measures (Table 1). DBS test results at six months showed that 90% of samples had TFV-DP levels equivalent to participants taking on average at least four doses per week. Only one DBS sample was below the lower limit of quantification for both recent and cumulative drug levels (Table 1).

Discussion

We observed a significant decline in condom use occurring concomitantly with a significant increase in STIs in individuals receiving PrEP. PrEP adherence was high as assessed by self-report, refill-based measures and DBS assays of drug levels. While the adherence outcomes are salutary, an increase in condomless sex was evident and may explain the significant increase in the rate of STI infections.
As the baseline rate of any condomless anal sex in VicPrEP (76%) was similar to reports from other studies (60-70%) [3-5], VicPrEP participants had similar relative opportunity to reduce condom use. Our study participants’ high medication adherence rates may reflect confidence in the efficacy of PrEP, which may have afforded study participants a greater sense of confidence to have condomless sex.

Our findings are similar to one other study reporting that during the first 12 months of PrEP in the Kasier Permanete Cohort Study a significant increase in STI rates occurred [6]. However this study did not report on changes in sexual practices that may have accounted for their report of a rise in STI rates [6].

No HIV seroconversion was observed in participants who had commenced PrEP before HIV exposure. This supports the efficacy of PrEP, as in an Australian population at risk of acquiring HIV, an HIV incidence of 2% or more would be expected [7]. Two participants did seroconvert, either prior to commencing PrEP or with an HIV exposure just prior to screening. This emphasises the need for expeditious evaluation of people seeking PrEP and facilitation of access to PrEP for those who are eligible.

This study’s strengths include that we emulated ‘real world’ conditions, undertook a rigorous evaluation of behaviour, adherence and STI rates from baseline through follow-up for all study participants, obtained detailed behavioural data and evaluated adherence using a number of measures. Our study’s limitations include that this is a sample of self-selected volunteers, we have provided 12 month follow-up data only and we did not collect participants’ STI rates prior to study entry. We are likely to have underestimated the
incidence of STIs because we did not screen for asymptomatic urethral gonorrhoea, and pharyngeal chlamydia results were not available. Finally we did not measure group sex as a variable wherein a potential increase in group sex may have contributed to the rise in STI rates.

We report high medication adherence rates coupled with a decline in condom use and a rise in STIs, suggesting that prevention, early detection and treatment of STIs is a chief research priority in the current era of HIV PrEP. These results support the need for PrEP providers to provide quarterly screening for bacterial STIs to those receiving PrEP.

Acknowledgments

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References


Table 1: VicPrEP Interim results to 12 months—sexually transmitted infections, sexual practice and adherence data
<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>0-m3</th>
<th>3-m6</th>
<th>6-m9</th>
<th>9-m12</th>
<th>m3-m12 (cumulative)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEXUAL PRACTICES (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regular partner (n)</strong></td>
<td>54</td>
<td>48</td>
<td>46</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-0.38 (-1.62, 0.85)</td>
</tr>
<tr>
<td>Anal sex acts (n) in past 3 months, mean (SD)</td>
<td>21.7 (21.0)</td>
<td>16.9 (13.1)</td>
<td>26.7 (32.1)</td>
<td>19.3 (17.8)</td>
<td>18.8 (16.3)</td>
<td>-</td>
<td>LG, 95% CI</td>
</tr>
<tr>
<td>Condom use in the past 3 months mean Likert score (SD)</td>
<td>2.0 (1.5)</td>
<td>1.9 (1.4)</td>
<td>1.6 (1.3)</td>
<td>1.4 (1.0)</td>
<td>1.5 (1.0)</td>
<td>-</td>
<td>LG, 95% CI</td>
</tr>
<tr>
<td>Withdrawal before ejaculation in the past 3 months, mean Likert score (SD)</td>
<td>2.3 (1.7)</td>
<td>2.2 (1.5)</td>
<td>2.3 (1.5)</td>
<td>1.6 (1.2)</td>
<td>1.7 (1.3)</td>
<td>-</td>
<td>LG, 95% CI</td>
</tr>
<tr>
<td>HIV serosorting in the past 3 months, mean Likert score (SD)</td>
<td>2.7 (1.8)</td>
<td>2.8 (1.9)</td>
<td>2.6 (1.9)</td>
<td>3.1 (1.9)</td>
<td>2.8 (2.0)</td>
<td>-</td>
<td>0.03 (-0.08, 0.14)</td>
</tr>
<tr>
<td><strong>Casual partner (n)</strong></td>
<td>97</td>
<td>79</td>
<td>72</td>
<td>78</td>
<td>78</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anal sex acts (n) in past 3 months, mean (SD)</td>
<td>19.2 (18.8)</td>
<td>16.4 (14.7)</td>
<td>20.2 (14.8)</td>
<td>16.4 (14.7)</td>
<td>20.3 (21.1)</td>
<td>-</td>
<td>-0.01 (-0.05, 0.05)</td>
</tr>
<tr>
<td>Condom use in the past 3 months, mean Likert score (SD)</td>
<td>3.1 (1.3)</td>
<td>2.5 (1.4)</td>
<td>2.5 (1.2)</td>
<td>2.3 (1.2)</td>
<td>2.4 (1.3)</td>
<td>-</td>
<td>-0.17, (-0.24, -0.09)</td>
</tr>
<tr>
<td>Withdrawal before ejaculation in the past 3 months, mean Likert score (SD)</td>
<td>2.6 (1.6)</td>
<td>2.3 (1.5)</td>
<td>2.3 (1.5)</td>
<td>1.8 (1.3)</td>
<td>1.8 (1.3)</td>
<td>-</td>
<td>-0.20 (-0.30, -0.11)</td>
</tr>
<tr>
<td>HIV serosorting in the past 3 months, mean Likert score (SD)</td>
<td>3.3 (1.4)</td>
<td>3.3 (1.5)</td>
<td>3.2 (1.4)</td>
<td>2.9 (1.5)</td>
<td>3.0 (1.4)</td>
<td>-</td>
<td>-0.09 (-0.17, -0.02)</td>
</tr>
<tr>
<td><strong>STI DIAGNOSES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incidence Rate Ratio (m3-m12:0-m3), 95%CI</td>
<td></td>
</tr>
<tr>
<td>Participants (n) evaluable</td>
<td>114</td>
<td>111</td>
<td>105</td>
<td>107</td>
<td>105</td>
<td>317</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Person years of follow up</th>
<th>27.8</th>
<th>26.3</th>
<th>26.8</th>
<th>26.3</th>
<th>79.3</th>
</tr>
</thead>
</table>
| Participants with at least 1 new STI diagnosis, n (%) | 14 (12.3) | 12 (10.8) | 26 (24.8) | 38 (35.5) | 95 (30.2) | p<0.001
| Participants (n) with >1 STI | 1 | 2 | 4 | 7 | 6 | 17 | 2.83 (1.55, 5.67) |

**Incidence per 100 person years for STIs by site or type**

<table>
<thead>
<tr>
<th>Any STI positive diagnosis</th>
<th>N/A</th>
<th>43.2</th>
<th>98.9</th>
<th>141.8</th>
<th>117.9</th>
<th>119.8</th>
<th>2.77 (1.52, 5.56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis (new, untreated infections)</td>
<td>N/A</td>
<td>10.8</td>
<td>19.0</td>
<td>14.9</td>
<td>7.6</td>
<td>13.9</td>
<td>1.29 (0.34, 7.80)</td>
</tr>
<tr>
<td>Gonorrhoea - Throat</td>
<td>N/A</td>
<td>0</td>
<td>11.4</td>
<td>11.2</td>
<td>19.0</td>
<td>13.9</td>
<td>-</td>
</tr>
<tr>
<td>Gonorrhoea - Anal</td>
<td>N/A</td>
<td>7.2</td>
<td>34.2</td>
<td>44.8</td>
<td>34.2</td>
<td>37.8</td>
<td>5.26 (1.33, 45.41)</td>
</tr>
<tr>
<td>Chlamydia - Urethra</td>
<td>N/A</td>
<td>3.6</td>
<td>3.8</td>
<td>18.7</td>
<td>7.6</td>
<td>10.1</td>
<td>2.81 (0.38, 124.44)</td>
</tr>
<tr>
<td>Chlamydia - Anal</td>
<td>N/A</td>
<td>21.6</td>
<td>38.0</td>
<td>52.2</td>
<td>49.4</td>
<td>46.7</td>
<td>2.16 (0.90, 6.27)</td>
</tr>
<tr>
<td>Any anal site diagnoses (gonorrhoea/chlamydia)</td>
<td>N/A</td>
<td>28.8</td>
<td>72.2</td>
<td>97</td>
<td>83.7</td>
<td>84.5</td>
<td>2.94 (1.41, 7.08)</td>
</tr>
<tr>
<td>Gonorrhoea any site</td>
<td>N/A</td>
<td>7.2</td>
<td>45.6</td>
<td>56.0</td>
<td>53.2</td>
<td>51.7</td>
<td>7.19 (1.87, 61.33)</td>
</tr>
<tr>
<td>Chlamydia any site</td>
<td>N/A</td>
<td>25.5</td>
<td>41.8</td>
<td>70.9</td>
<td>57.0</td>
<td>56.7</td>
<td>2.25 (1.01, 5.92)</td>
</tr>
</tbody>
</table>

**PrEP ADHERENCE**

<table>
<thead>
<tr>
<th>Self-report at clinic visit</th>
<th>&lt;50% of daily doses taken, (%) n</th>
<th>0</th>
<th>0</th>
<th>1.9 (2)</th>
<th>0</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-90% of daily doses taken, (%) n</td>
<td>-</td>
<td>5.5 (6)</td>
<td>1.9 (2)</td>
<td>3.8 (4)</td>
<td>5.7 (6)</td>
<td>-</td>
</tr>
<tr>
<td>90% of daily doses taken, (%) n</td>
<td>-</td>
<td>94.5 (103)</td>
<td>98.1 (103)</td>
<td>94.2 (98)</td>
<td>94.3 (99)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Refill-based assessment**
Comparing 0-m3 and m3-m12, Chi square test

Likert scale: 1 - never, 2 - some of the time, 3 - half of the time, 4 - most of the time, 5 - always

3: % days drug available calculated as the number of pills dispensed / days between study visits x 100
4: participants who reported no missed doses not included

N/A – not applicable; LG – Linear-Gaussian; CI – confidence interval; IQR – interquartile range; STI – sexually transmitted infection; SD – standard deviation; n – number; FTC-TP - emtricitabine-triphosphate; TFV-DP - tenofovir-diphosphate.
**Figure 1**: STI incidence per 100 person-years over follow-up

PY - person years; CT – chlamydia trachomatis; NG – Neisseria gonorrhoea