Original article

Prospective cohort study of HIV post-exposure prophylaxis for sexual assault survivors

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Background: There is a lack of standardized programs for HIV counselling and post-exposure prophylaxis (PEP) in the setting of sexual assault.

Methods: We conducted an 18-month prospective cohort study assessing universal HIV counselling for all sexual assault survivors presenting to 18 Ontario Sexual Assault Treatment Centres. HIV PEP was universally offered to those at risk of HIV infection (high risk or unknown risk) presenting ≤72 h after the assault, using Combivir® one pill and Kaletra® three capsules twice a day for 28 days. Those who accepted HIV PEP were monitored via a schedule of frequent follow ups. The primary outcomes were acceptance and completion rates, and their predictors were determined using multivariable logistic regression. Adverse events (AE) were categorized using a standardized toxicity grading system.

Results: Of the 900 evaluable participants eligible for PEP, 798 (69 at high risk and 729 at unknown risk) were offered treatment. Acceptance rates were 66.7% (n=46) and 41.3% (n=301) for participants at high risk and unknown risk, respectively. Participants at high risk were 2.2 times more likely to accept PEP than those at unknown risk (adjusted odds ratio 2.2; 95% confidence interval 1.2–4.0; P=0.01). Overall, 23.9% high-risk (n=11) and 33.2% unknown-risk participants (n=100) completed PEP (P=0.20). Predictors of acceptance and completion included assault by a stranger and participant anxiety. AEs were common, with 77.1% of participants reporting grade 2–4 symptoms.

Conclusion: A province-wide standardized program of universal HIV counselling and offering of PEP to sexual assault survivors with frequent follow up was successfully implemented and feasible.

Introduction

Antiretroviral post-exposure prophylaxis (PEP) to prevent HIV transmission following occupational and certain non-occupational exposures is well established and recommended according to current guidelines [1–3]. However, guidelines for HIV PEP following a sexual assault are limited in availability and inconsistent with respect to recommendations, largely due to a lack of prospective data assessing the completion and adverse event (AE) rates of such a policy in low prevalence countries [4–18]. The lack of research and consensus regarding the provision of PEP in the context of sexual assault are significant barriers to the implementation of local or national programs offering HIV risk counselling and antiretroviral treatment to survivors. Such programs are necessary, as stressed in a recent study published by Carrieri et al. [19]. The reasons for their necessity include not only the right of survivors to information regarding risk, but also because factors pertaining to a sexual assault amplify the risk of HIV transmission, for example, the occurrence of genital trauma, attacks by multiple assailants and the potential presence of concomitant sexually transmitted infections [20–23].

Presently, few jurisdictions have developed standardized guidelines for the provision of HIV PEP for sexual assault [4,6,13–18]. In British Columbia, the only
Canadian province with guidelines for HIV PEP, a ‘high-risk’ approach to prescribing medication has been adapted, such that the cost of antiretrovirals for survivors deemed to have been sexually assaulted by an assailant known to be HIV positive or from a high-risk group (that is, intravenous drug users, men who have sex with men [MSM]) is covered free of charge [4]. In contrast, French guidelines lean towards enhanced free access to HIV PEP in lower risk exposures [19]. In most jurisdictions without standardized guidelines, the decision to offer HIV PEP to a sexual assault survivor is left to the discretion of the individual physician/team and based on the survivor’s ability to pay for treatment.

The purpose of this study was to implement and determine the feasibility of a standardized province-wide program of universal HIV risk counselling for all survivors of sexual assault and offer free access to HIV PEP to all eligible survivors at risk of HIV transmission presenting to hospital-affiliated Sexual Assault Treatment Centres (SATCs) in Ontario, Canada. The universal counselling and free access to PEP are unique features of this program. The study was carried out using a prospective cohort design to determine the demographic characteristics of survivors and assaults, the acceptance and completion rates of HIV PEP and their predictors and the rates of PEP-associated AEs.

Methods

Program description

A reference manual, flow chart, guidelines, counselling tools and participant handouts outlining all facets of HIV counselling and provision of PEP for the study were created in conjunction with an Advisory Committee of nationally recognized experts in the fields of HIV, pharmacology, research methods and sexual assault. Updated versions of these documents are available online [24].

In Ontario, 34 SATCs provide assessment, counselling and treatment to approximately 3,000 sexual assault survivors annually. In total, 24 SATCs participated in this study; 10 SATCs did not participate due to staffing and infrastructural barriers. An additional six SATCs were excluded during the study due to collection of non-consecutive data. Program training was delivered regionally in six in-person train-the-trainer sessions by the study team. Approval from all SATCs’ hospital Medical Advisory Committees, Pharmacy and Therapeutic Committees, and Ethics Review Boards was obtained prior to the commencement of the study.

Counselling regarding the risk of HIV acquisition following sexual assault, the provision of HIV PEP for those at risk and follow up was provided to all participants. The SATC staff assessed each participant as being at ‘high’, ‘unknown’ or ‘no risk’ of HIV acquisition (Figure 1). All participants assessed as being either at high risk or unknown risk and presenting ≤72 h post-assault were offered HIV PEP, whereas participants at no risk were counselled regarding the zero chance of transmission and were not offered PEP.

The drug regimen used was a combination of Combivir® (zidovudine and lamivudine), one tablet orally twice a day, and Kaletra® (lopinavir/ritonavir), three capsules orally twice a day, for 28 days. A five-day starter kit of medication was provided to participants who agreed to take PEP, and counselling regarding dosing, the importance of adherence and AEs was provided. HIV PEP medications were dispensed through the hospital-based pharmacies and costs were reimbursed through the study. Prior to the start of PEP, blood was drawn for tests including complete blood count, renal function tests, glucose, liver enzymes, creatine kinase, β-hCG (human chorionic gonadotropin) and an HIV antibody test.

A five-visit follow-up schedule at days 2–4 and weeks 1 (by phone or in person), 2, 3 and 4 was designed to provide additional counselling and to review treatment adherence and tolerance in participants accepting the medications. PEP was dispensed in quantities sufficient to last until the next visit to promote follow up and reduce the potential for medication waste. Bloodwork was repeated at the 2-week visit to monitor drug toxicity. Participants were advised to have repeat HIV antibody testing at weeks 4–6, and months 3, 6 and 12 post-assault.

Each SATC was linked with a local HIV/infectious diseases expert to assist with issues related to risk assessment, serious drug interactions, severe AEs or any other complicated clinical matter. AEs were graded 1–4 using the National Institute of Allergy and Infectious Diseases (NIAID) standardized toxicity grading system [25]. Grade 1–3 AEs could be managed by the SATC team, whereas grade 4 events required consultation with the HIV expert. In cases of severe AEs or serious drug interactions, the HIV expert could recommend the use of Combivir® alone or discontinuation of the medications.

Data collection

Prospective baseline data were collected for all consecutive participants, regardless of risk category. The baseline data included demographics, risk status, details of the assault and assailant(s), health care provider (HCP) evaluation of participant anxiety, strength of HCP recommendation to take PEP, reasons for not offering PEP, PEP acceptance and reasons for refusing PEP. If the participant accepted PEP, the baseline bloodwork was documented.

Follow-up data were collected from all participants offered PEP who returned for visits including information
on medication adherence, AEs and their management, and reasons for stopping treatment if PEP was discontinued. The week 2 bloodwork was recorded.

**Statistical analysis**

The primary outcomes were the proportion of sexual assault survivors who accepted HIV PEP and the proportion that completed the 28-day course, with the primary predictor being high risk versus unknown risk of HIV acquisition. The proportion of participants with grade 2 or higher AEs was a secondary outcome.

The Fisher’s exact test was used to compare the proportions of PEP acceptance and completion in the high risk versus unknown risk groups; results were described as an absolute risk difference and a relative risk with 95% confidence intervals (CIs). Multivariable logistic regression was used to examine predictors associated with HIV PEP acceptance and completion; results were described as odds ratios (OR) with 95% CIs. All variables with a P-value <0.05 in univariate logistic regression models were considered for inclusion in the multivariable logistic regression models. The multivariable models were finalized using stepwise logistic regression. AEs and reasons for discontinuing HIV PEP were summarized as proportions and correlated to one another using Fisher’s exact test. All statistical analyses were performed using SAS v9.1 statistical software (SAS Institute Inc., Cary, NC, USA). All reported P-values are two-sided and no interim analyses were conducted.

**Results**

**Participant and assault characteristics**

There were 1,103 consecutive participants presenting at 18 sites from 10 September 2003 to 31 January 2005. Characteristics of participants, assailants and assaults are summarized in Table 1. Most participants were female (97.1%) with a median age of 21 years (range 4–80). Three assailants were known to be HIV positive; 31 assailants were drug users and 79 had a history of sexual assault.

Penetration means suspected, partial or completed penetration or ejaculation in mouth, vagina or anus. Oral penetration means victim/survivor forced to perform fellatio on assailant. PEP, post-exposure prophylaxis; Combivir® (AZT/3TC), combination of zidovudine and lamivudine in one pill; IVDU, intravenous drug user; Kaletra®, combination of lopinavir and ritonavir in one capsule; MSM, men who have sex with men.

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**Figure 1. HIV PEP risk assessment**

<table>
<thead>
<tr>
<th>High risk</th>
<th>Unknown risk</th>
<th>No risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk exposure</strong></td>
<td><strong>Unknown-risk assailant</strong></td>
<td><strong>Any assailant</strong></td>
</tr>
<tr>
<td>Anal penetration</td>
<td>Unknown assailant</td>
<td>HIV-positive, high-risk or unknown HIV status</td>
</tr>
<tr>
<td>Vaginal penetration</td>
<td>or known assailant with unknown HIV status</td>
<td>+</td>
</tr>
<tr>
<td>Oral penetration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(with or without condom)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown exposure</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>(for example, drug-facilitated sexual assault)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines**

- **Strongly recommend**
  - HIV PEP
  - Combivir® (AZT/3TC) and Kaletra®
  - Provide counselling and education about high risk of HIV acquisition and side effects of drug regimen

- **Recommend**
  - HIV PEP
  - Combivir® (AZT/3TC) and Kaletra®
  - Provide counselling and education about possible risk of HIV acquisition and side effects of drug regimen

- **Do not offer or recommend**
  - HIV PEP
  - Provide counselling and education about the zero risk of HIV acquisition
positive; an additional 66 were considered at high risk of being HIV positive.

Of the 1,103 participants, 900 fulfilled the eligibility criteria for receipt of HIV PEP (Figure 1). Reasons for PEP ineligibility included being assessed as being at no risk of HIV infection (n=81), presenting for assessment ≥72 h post-assault (n=121) and being HIV-positive at baseline (n=1). Of the eligible participants, 829 (92.1%) and 71 (7.9%) were classified as being at unknown risk and high risk of HIV infection, respectively.

PEP offering

PEP was offered to 69 of the 71 high-risk participants and 729 of the 829 unknown-risk participants (97.2% versus 87.9%; P=0.02) (Figure 2). Reasons for not offering PEP included HCP-perceived low risk of transmission (40.2%), unstable participant living situation (28.4%), lack of participant concern about HIV (23.5%) and medical concerns such as illness, contraindicated medication use and fear of AEs.
Relative to participants to whom PEP was not offered, those offered PEP were more likely to be accompanied by an adult (28.4% versus 16.8%; \(P=0.004\)), younger (20.6% versus 1.0%; \(P<0.0001\)), unemployed (40.5% versus 26.2%; \(P=0.03\)), and needing an interpreter (4.9% versus 1.6%; \(P=0.027\)).

In documenting their recommendations to participants regarding PEP, 25.9% \((n=207)\) of HCPs reported encouraging or strongly encouraging participants to take PEP, 70.9% reported that they neither discouraged nor encouraged and 3.1% reported they discouraged or strongly discouraged participants from taking PEP.

## PEP acceptance

PEP was accepted by 66.7% of participants at high risk and 41.3% of participants at unknown risk \((P<0.0001)\) (Figure 3). High- and unknown-risk participants declined PEP for similar reasons, including a lack of concern about HIV (63.0%), anxiety about AEs (44.6%) and an inability or unwillingness to follow the regimen or return for follow-up (16.4%).

Factors predictive of PEP acceptance are summarized in Table 2. Participants at high-risk were 2.2 times more likely to accept PEP than those at unknown risk \((P=0.01)\). Other predictors of HIV PEP acceptance included younger age, HCP encouragement to start PEP, HCP-perceived moderate or high participant anxiety, assaults involving a stranger, multiple sexual acts or multiple physical injuries.

### PEP completion

PEP completion rates by risk group are presented in Figure 3. The 28-day course was completed by 23.9% of participants at high risk and 33.2% of participants at unknown risk \((P=0.20)\). Predictors of completion are summarized in Table 3 and include HCP-perceived moderate or high participant anxiety at initial visit, assault by a stranger or an assailant known to the participant for <24 h, and an absence of concomitant physical assault. Participant risk status was not associated with completion of PEP in the multivariable analysis.
A total of 236 participants accepted PEP but did not complete the full course of treatment. Reasons for PEP discontinuation were documented in 96 cases. AEs (81.2%), interference with usual routine (42.0%), inability to take time away from work, school or other commitments (21.7%) and reassessment of HIV risk (18.8%) were the most frequently cited reasons for premature discontinuation.

Adverse events
Of the 275 participants who initiated HIV PEP and attended one or more follow-up visits, 265 (96.4%) reported at least one AE of any grade and 212 (77.1%) reported at least one AE (median 3, range 1–8) of grade 2–4 severity. Three grade 4 AE's resulting in drug discontinuation were reported. The presence or severity of AEs did not appear to influence PEP completion, as grade 2–4 symptoms were reported by 77.5% of PEP completers and 76.8% of participants who discontinued PEP. The most common AEs were fatigue (58.5%), nausea (49.5%), diarrhoea (22.5%), headache (20.7%), mood changes (20.4%) and vomiting (16.4%). Participants who experienced vomiting were less likely to complete PEP than those who did not (OR 0.27; 95% CI 0.12–0.6; $P=0.0007$). No significant blood dyscrasias were observed.

Discussion
Our study represents an important contribution to the state of knowledge regarding the delivery of HIV PEP in the context of sexual assault for several reasons. Most notably, it is the first large prospective study undertaken in a low prevalence country to collect systematic data on all sexual assault survivors and assaults treated through hospital-based treatment centres. Although other studies addressing this topic have been published, these trials have been limited by their small sample sizes and/or retrospective designs ([4–18]). In addition, detailed statistics describing rates...
and predictors of HIV PEP acceptance and completion have been provided, and common AEs summarized. Furthermore, the provision of universal HIV counselling to all sexual assault survivors and the offering of HIV PEP to all participants assessed as being at-risk of HIV acquisition provided a framework for the integration of health education and treatment in a structured, consistent manner. Finally, the frequent follow-up schedule targeting the participants’ emotional well being and practical issues related to PEP is unique to this program and probably promoted higher rates of completion than previously reported.

Whilst providing PEP in populations with established high rates of HIV (for example, in endemic countries and MSM communities in low prevalence countries) is seen as both necessary and cost effective, there is no consensus with regards to exposure in which it is unlikely that the source is HIV-positive [26]. The specific context of sexual assault provides a complicating factor to any PEP policy given that both the HIV status and risk factors of the assailant are usually unknown. However, the coercive nature of sexual assault provides an additional vulnerability to contracting HIV should the source be positive. These factors argue in favour of a universal model of counselling and access to HIV PEP for sexual assault survivors, where access to treatment is determined primarily by the nature of the exposure, and the decision to accept and complete PEP is left to the survivor, to be made in consultation with their HCP [3].

The regimen of Combivir® and Kaletra® was selected based on data and guidelines available at the outset of the study [3,19,27]. As better-tolerated agents become available, local guidelines regarding the provision of PEP in sexual assault must be continuously reassessed.

Frequent follow up and thorough staff training were significant components of our study design, and may have contributed to the increased completion rates seen in our study as compared with others. However, given the high number of participants lost to follow up in this and other studies of HIV PEP for sexual assault, further research is needed to determine how best to engage participants to return for ongoing monitoring and support. Furthermore, ongoing evaluation of strategies aimed at increasing PEP completion rates is clearly necessary. Although a respectable proportion of survivors in our study completed PEP, rates for participants in both the high and unknown risk groups were well below 50%. Potentially useful strategies for augmenting PEP completion rates could include the provision of home support through community home care programs, peer counselling and support provided by sexual assault survivors who have previously taken PEP, and multi-disciplinary

### Table 2. Adjusted OR for acceptance of PEP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown risk*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>2.2 (1.2, 3.9)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–17*</td>
<td>0.5 (0.3, 0.7)†</td>
<td></td>
</tr>
<tr>
<td>18–21</td>
<td>0.8 (0.5, 1.3)</td>
<td></td>
</tr>
<tr>
<td>22–29</td>
<td>0.6 (0.4, 1.0)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Physical trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal and/or genital injury plus other physical injury*</td>
<td>0.5 (0.3, 0.9)†</td>
<td></td>
</tr>
<tr>
<td>Anal and/or genital injury</td>
<td>0.5 (0.3, 0.9)†</td>
<td></td>
</tr>
<tr>
<td>Other physical injury (no anogenital)</td>
<td>0.5 (0.3, 0.8)†</td>
<td>0.01</td>
</tr>
<tr>
<td>None/unknown</td>
<td>0.5 (0.3, 0.8)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of sexual acts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or unknown number*</td>
<td>1.8 (1.2, 2.8)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Two or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Client-assailant relationship</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stranger*</td>
<td>0.3 (0.2, 0.6)†</td>
<td></td>
</tr>
<tr>
<td>Partner or ex-partner</td>
<td>0.9 (0.6, 1.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other</td>
<td>1.3 (0.7, 2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.7 (0.7, 3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Client’s overall anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low*</td>
<td>3.1 (2.2, 4.4)</td>
<td></td>
</tr>
<tr>
<td>Moderate or high</td>
<td>1.7 (0.7, 3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9 (0.5, 1.8)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Reference group (all other categories compared with the reference group).  †Statistically significant. CI, confidence interval; HCP, health care provider; OR, odds ratio; PEP, post-exposure prophylaxis.

### Table 3. Adjusted OR for completion of PEP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client’s overall anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/unknown*</td>
<td>2.4 (1.2, 4.5)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>2.3 (1.4, 3.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1.2 (0.5, 3.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of time client knew assailant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 24 h*</td>
<td>3.6 (2.5, 5.3)</td>
<td></td>
</tr>
<tr>
<td>Not at all/less than 24 h</td>
<td>0.3 (0.1, 1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical assault</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes*</td>
<td>2.0 (1.2, 3.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.9 (0.5, 1.8)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Reference group (all other categories compared with the reference group). †Statistically significant. CI, confidence interval; OR, odds ratio; PEP, post-exposure prophylaxis.
involvement of other allied health personnel with specific training in counselling and treatment of sexual assault survivors (for example, social workers, nurse practitioners, pharmacists).

Our findings are subject to several limitations, including the inability to ascertain the effectiveness of PEP in preventing new HIV infections. However, given the low risk of HIV transmission per exposure, a randomized trial recruiting several thousands of participants would be necessary to adequately address this question. Furthermore, our findings were limited by the number of participants (72 out of 347) who did not return for the day 2–4 follow-up visit. It is possible that these participants reconsidered their decision and chose not to continue PEP, which may have contributed to an overestimation of acceptance and underestimation of completion rates. Additionally, the low rate of follow up of participants discontinuing PEP limits our ability to generalize about reasons for discontinuing PEP. Finally, the effect of trauma related to the assault in the experience of AEs and adherence difficulties was not captured in our study. This knowledge could affect the nature of the counselling necessary to optimally support sexual assault patients taking PEP.

We have described the implementation and feasibility of a province-wide program designed to provide HIV counselling to all sexual assault survivors and HIV PEP free of charge to all those deemed to be at high-risk and unknown risk of HIV infection who choose to accept the medication. Although many questions regarding the efficacy of HIV PEP in this setting remain, the findings of our prospective observational cohort study have addressed important issues concerning the feasibility of such a program and the acceptance, completion and tolerability of HIV PEP for sexual assault survivors.

Acknowledgements
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Disclosure statement
The authors declare no competing interests.

References
4. Wiebe ER, Comay SE, McGregor M, Ducechesi S. Offering HIV prophylaxis to people who have been sexually assaulted: 16 months’ experience in a sexual assault service. CMAJ 2006; 162:641–645.

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