

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Emtricitabine/Tenofovir for Post-Exposure Prophylaxis Against HIV: A Review of Clinical Effectiveness and Cost-Effectiveness

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Context and Policy Issues

HIV post-exposure prophylaxis (PEP) refers to the provision of anti-retroviral (ARV) medication following an exposure to potentially infected blood or body fluids, in order to minimize the risk of acquiring HIV infection.¹ HIV PEP is recommended for both occupational and non-occupational exposures.²⁻⁴

The use of ARVs for PEP is based on assumptions regarding efficacy extrapolated from animal data, mother to child transmission, occupational exposure and prospective studies with limited sample sizes of PEP regimens in HIV-negative men.⁴ Factors to consider when selecting a PEP regimen include efficacy, convenient administration in terms of pill burden, and frequency of dosing, minimal drug interactions, tolerability, side effects, toxicity, and safety in pregnancy and lactation.² People receiving PEP should complete a full 4-week ARV regimen to maximize efficacy. The tolerability and side effects of the selected PEP regimen, therefore, are extremely important to ensure regimen completion and adherence.² Newer ARV agents are better tolerated and have preferable toxicity profiles as compared with their predecessors.²

Current PEP guidelines from Canada³ and the United States² both recommend a preferred three-drug regimen consisting of a nucleoside reverse-transcriptase inhibitor (NRTI) backbone of tenofovir (TDF) plus emtricitabine (FTC), along with a third drug, either an integrase strand transfer inhibitor, raltegravir (RAL),^{2,3} or a boosted protease inhibitor, darunavir/ritonavir (DRV/r).³ TDF plus FTC may be dispensed as Truvada (TVD), a fixed-dose combination tablet.² Suggested alternative backbone regimens include zidovudine (ZDV) plus FTC, ZDV plus lamivudine (3TC), or TDF plus 3TC, combined with various protease inhibitors (with or without ritonavir) or integrase strand inhibitors.^{2,3} ZDV plus 3TC are also available as a fixed dose combination tablet called Combivir (CBV).²

A 2012 CADTH Rapid Response⁵ provided limited evidence that suggested TDF-based regimens in non-occupational exposures were associated with generally mild adverse events, including nausea or vomiting, diarrhea, headache, and fatigue, and that they were generally better tolerated as compared with historical controls using ZDV-based regimens. Improved tolerance is thought to enhance patient adherence and regimen completion.⁵

The objective of this Rapid Response report is to evaluate the clinical and cost-effectiveness of TDF plus FTC, with or without integrase strand transfer inhibitors, as compared with other NRTI regimens with or without protease inhibitors boosted with ritonavir.

Research Question

1. What is the clinical effectiveness of emtricitabine/tenofovir, with or without integrase strand transfer inhibitors, compared with alternative antiretroviral drug regimens for post-exposure prophylaxis against HIV?
2. What is the cost-effectiveness of emtricitabine/tenofovir, with or without integrase strand transfer inhibitors, compared with alternative antiretroviral drug regimens for post-exposure prophylaxis against HIV?

Key Findings

Limited low-quality evidence suggested that patients prescribed a tenofovir-based two or three-drug regimen were more likely to adhere to post-exposure prophylaxis (PEP), or complete the prescribed PEP regimen, than those prescribed a zidovudine-based two or three drug-regimen. Very limited low-quality evidence suggested that a tenofovir based on two or three-drug regimen was associated with lower discontinuation rates of PEP due to adverse events as compared with zidovudine-based regimens. HIV seroconversion was rare in the PEP population, and an association with PEP regimen was not determined. Cost-effectiveness studies in the PEP population were not identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and February 15, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults requiring post-exposure prophylaxis for the prevention of HIV infection (from both occupational and non-occupational exposure)
Intervention	Emtricitabine/tenofovir combination (e.g., fixed dose combination Truvada), with or without integrase strand transfer inhibitors (e.g., raltegravir [Isentress], elvitegravir, dolutegravir)
Comparator	Fixed dose combination lamivudine/zidovudine (Combivir), or other nucleoside reverse transcriptase inhibitors, with or without protease inhibitors boosted with ritonavir (e.g., fixed dose combination lopinavir/ritonavir [Kaletra], darunavir plus ritonavir)

Outcomes	<p>Q1: Clinical benefits and harms (e.g., tolerability, adherence rates or completion of treatment regimen, HIV infection or seroconversion rates, adverse events [including types, frequency, and severity])</p> <p>Q2: Fixed dose combination lamivudine/zidovudine (Combivir), or other nucleoside reverse transcriptase inhibitors, with or without protease inhibitors boosted with ritonavir (e.g., fixed dose combination lopinavir/ritonavir [Kaletra], darunavir plus ritonavir)</p> <p>Cost-effectiveness outcomes (e.g., cost per health benefit or QALY)</p>
Study Designs	Health Technology Assessments (HTAs), Systematic Reviews (SRs), Meta-Analyses, Randomized Controlled Trials (RCTs), Non-Randomized Studies, Economic Evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Studies were also excluded if they evaluated drugs which are no longer commonly used in developed countries (i.e., stavudine, indinavir), and studies in which the comparison was predominantly between two different protease inhibitors or integrase strand inhibitors with the same NRTI backbone.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised using AMSTAR,⁶ and individual clinical studies were critically appraised using the Downs and Black checklist.⁷ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 514 citations were identified in the literature search. Following screening of titles and abstracts, 505 citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, seven publications were excluded for various reasons, while one SR and one prospective cohort study met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Detailed study characteristics are presented by study type in Appendix 2.

Study Design

Systematic Reviews

One SR⁸ was identified that evaluated the effectiveness of different PEP regimens in terms of PEP completion and discontinuation. This SR included two RCTs of adherence support, two RCTs of drug regimens, and 20 prospective cohort studies. The SR was published in 2015, with a literature search from database inception through December 2013, with a June 2014 update in one of the databases searched.

Non-Randomized Studies

One prospective cohort study⁹ evaluated adherence to PEP and incidence of HIV seroconversion following sexual exposures, between October 2000 and July 2014 .

Country of Origin

Systematic Reviews

The SR⁸ was conducted by a lead author from Sweden.

Individual Clinical Studies

The included study⁹ was conducted by authors in Canada.

Patient Population

Systematic Reviews

The SR⁸ included studies in which the reason for PEP was described as sexual assault, non-occupational, occupational, or a mix of both occupational and non-occupational exposures. There were seven primary studies in which the exposure was described as sexual assault, with a total of 1,651 participants, with sample sizes ranging from 33 to 457. Eight primary studies described the exposure as non-occupational, with 1,494 participants, and sample sizes ranged from 35 to 395. Three primary studies described the exposure as occupational, with 740 participants, and sample sizes ranged from 68 to 380 participants. Six primary studies described the exposure as a mix of occupational and non-occupational with sample sizes ranging from 46 to 306 participants. The included studies were conducted across a wide range of countries, with two in Canada, eight in the United States, two in Brazil, three in South Africa, one in Kenya, two in Australia, one in Spain, three in France, one in Germany, and one in the Netherlands.

Non-Randomized Studies

The prospective cohort study⁹ reported on a total of 3,547 PEP consults at a community clinic specializing in HIV. Patients included in the study were predominantly male (92%), men having sex with men (MSM) (83%), and university educated (49%), with a mean age of 34.6 years (standard deviation, 10.2 years). It was the first PEP consultation for 70% of patients, while 25% had between two to four previous PEP consults. The consultation delay was less than 24 hours in 48% of patients, between 25 to 48 hours in 34%, between 49 to 72 hours in 16%, and greater than 72 hours in 1%. The risk of exposure was considered low in 18% of cases and moderate to high in 81% of cases. The source was known to the patient in 33% of cases, and that source was confirmed as HIV positive in 64% of cases.

Of the total 3,547 PEP consults, 2,772 (78%) of participants received a PEP prescription, as treatment was not indicated for those presenting more than 72 hours after exposure, for those with a negligible risk, or where the participant tested HIV positive at baseline. Of these, 2,731 participants were treated, as 41 stopped PEP prematurely because the source tested HIV negative. Therefore, the actual number of participants receiving treatment was 2,731.

*Interventions and Comparators***Systematic Reviews**

The SR⁸ included 13 primary studies of ZDV-based two-drug regimens, and three primary studies of TDF-based two-drug regimens. The SR also included six studies of ZDV-based three-drug regimens and seven studies of TDF-based three-drug regimens.

Non-Randomized Studies

The included prospective cohort study⁹ included three treatment regimens: TVD plus lopinavir/ritonavir (LPV/r), n = 2,062 (74%); TVD plus RAL, n = 275 (10%), and CBV plus LPV/r, n = 275 (10%). In 7% of cases (n = 206) other combinations were used (details not provided), and in less than 1% of cases (n = 12), no data on treatment regimen were available.

*Outcomes***Systematic Reviews**

The primary outcome for the SR⁸ was discontinuation due to adverse events, and the secondary outcomes were PEP completion rates, defined as completing a full 28-day course of PEP, severe adverse events, PEP failure, and mortality due to adverse events

Non-Randomized Studies

The primary outcomes for the included prospective cohort study⁹ included treatment adherence, defined as not missing more than five doses during the month-long treatment, factors associated with adherence, and the incidence of HIV seroconversion due to PEP failure.

*Follow-up***Systematic Reviews**

The included SR⁸ did not provide follow-up periods for the included studies.

Non-Randomized Studies

In the included prospective cohort study,⁹ follow-up occurred at week four, and either week 12, 16, or 24, depending on the year of the PEP consult (due to PEP protocol changes over the years during which the study was conducted)

Summary of Critical Appraisal

A detailed summary of the critical appraisal is presented in Appendix 3.

Systematic Reviews

The included SR⁸ did not provide detailed population characteristics and follow-up periods for the included studies. Detailed information was provided for completion rates across the different regimens, but limited detail was provided on discontinuation rates due to adverse events, even though that was described as the primary outcome as interest. The nature of the adverse events was not reported. PEP failure as determined by HIV seroconversion was described as rare but was not quantified. The SR authors stated that PEP failure across different regimens could not be compared due to a paucity of events and different protocols for longer term post-PEP monitoring. Statistical details, such as heterogeneity and probability, were not

provided. The data were pooled even though they included both evidence from prospective cohort studies that may not have had comparators, and RCTs. Some of the included studies were designed to answer different research questions other than drug regimen evaluation. The confidence intervals for some drug regimens did not overlap across the included studies suggesting significant heterogeneity, and that factors other than prescribed drug regimen were influencing the observed outcomes. There was very limited evidence for some of the included drug regimens. There seemed to be some discrepancy in the SR between what was reported in the text and what was reported in the tables in terms of the number of studies evaluating a particular regimen. In these cases, the information in the tables was included in this Rapid Response report.

Non-Randomized Studies

The included prospective cohort study⁹ described the objective of the study, the main outcomes measured, patient characteristics, and the interventions of interest. It was not clear whether there were differences in confounders between the treatment groups. Risk factors for the observed outcomes were evaluated, but it was uncertain if other factors not identified were distributed across the different treatment groups, or if the potential for confounding was considered in the analysis. The main findings of the study were described, and confidence intervals were reported. While the rate of adverse events was provided, the actual adverse events were not reported. The characteristics of the patients lost to follow-up were not described, and it is not clear whether those lost to follow-up were considered in the analysis. Actual probability values were reported.

Patients included in the study were not representative of the entire population from which they were recruited as only patients requiring PEP for sexual exposures were included. The proportion of those asked that agreed to participate was provided. The staff, places, and facilities where the patients were treated appeared to be representative of the treatment that the majority of people requiring PEP would receive, although geared toward those with non-occupational HIV exposure. It was not reported whether study subjects were blinded to the prescribed intervention, but it is unlikely given that participants requiring PEP were given a prescription. It was not reported whether those measuring the main outcomes were blinded to the intervention or whether there was allocation concealment. There were no unplanned subgroup analyses. There were differences in follow-up time due to changes in protocol over the years that the study was in progress, and it does not appear that the analysis made any adjustment for the different lengths of follow-up. However, this is likely not a major factor since PEP is considered to be an effective preventive measure to avoid HIV infection within a 28-day window.⁹ The statistical tests used to assess the main outcomes appeared to be appropriate. Noncompliance with allocated treatment was reported for 6% of participants. Regimen completion data was missing for 8% of the included study population, but intention to treat analysis was conducted to compensate for the missing data. The main outcome measures used appeared to be accurate. The patients in the different treatment groups appeared to be selected from the same population, although it was not stated why different treatment regimens were prescribed in some patients and not others. It was uncertain whether the participants in the different treatment groups were recruited over the same period of time, and randomization to treatment was not performed. A power calculation was not provided.

Summary of Findings

A detailed summary of study findings is presented in Appendix 4.

What is the clinical effectiveness of emtricitabine/tenofovir, with or without integrase strand transfer inhibitors, compared with alternative antiretroviral drug regimens for post-exposure prophylaxis against HIV?

PEP Completion, Adherence and Discontinuation due to Adverse Events

The included SR⁸ reported that for three-drug regimens, pooled PEP completion rates (i.e., completion of the month-long regimen) were lowest for ZDV plus 3TC plus LPV/r (59.1%) and highest (93.9%) for TDF plus FTC plus DVR/r. Pooled completion rates for other TDF regimens ranged from 71.1% to 74.7%. Completion rates for other ZDV-based regimens ranged from 78.3% to 78.8%. Statistical significance was not reported, and the quality of evidence was rated as very low.

Two-drug regimens included in the SR⁸ reported pooled completion rates of 58.8% for ZDV-based regimens, and 78.4% for TDF based regimens. Statistical significance was not reported and the quality of the evidence was rated as very low.

Three-drug discontinuation rates due to adverse events reported in the SR⁸ were lowest for TDF plus FTC plus RAL at 1.9% and highest for ZDV plus 3TC plus ritonavir-boosted atazanavir (ATV/r) at 18.7%. Discontinuation rates were not reported for other three-drug regimens. Two-drug regimen discontinuation rates were reported as lower among people taking TDF-based regimen (0.3%) versus a ZDV-based regimen (3.2%). Statistical significance was not reported. The overall quality of the evidence was rated as very low.⁸

The prospective cohort study⁹ reported that of the 2,731 treated patients, 69% completed the entire treatment, while 2% missed more than five doses, 4% discontinued prophylaxis, and 1% switched to a different regimen (included in the total completing treatment). Side effects were responsible for regimen switching in 90% of patients that changed regimens, and for discontinuation of treatment in 70% of those discontinuing treatment.⁹

Patients taking TVD-based regimens were significantly more adherent (72% adherent) as compared with CBV-based regimens (60% adherent), or other regimens (not described) at 59% adherence.⁹ Compared to patients who received TVD plus LPV/r, patients taking CBV plus LPV/r were less likely to adhere to treatment while patients taking TVD plus RAL were as likely as those taking TVD plus LPV/r to be adherent to treatment.⁹ Patients that are male, older, and first-time PEP consults, tended to be more adherent.⁹

Mortality

No studies reported any cases of mortality due to adverse events in the SR.⁸ Mortality was not reported in the included study.⁹

PEP Failure/Seroconversion

The SR⁸ reported that PEP failure as measured by seroconversion was rare and could not be compared across regimens because of the paucity of events and different protocols for longer-term monitoring after PEP provision.

The included clinical study⁹ reported that 11 participants seroconverted during the post-PEP follow-up period. One participant was not treated as the source was presumed to be HIV negative, suggesting that 10 (0.37%) could be considered treatment failures. However, nine of these treated cases continued to engage in high risk behavior following treatment. Therefore, 1 case was attributed purely to treatment failure.

What is the cost-effectiveness of emtricitabine/tenofovir, with or without integrase strand transfer inhibitors, compared with alternative antiretroviral drug regimens for post-exposure prophylaxis against HIV?

No studies were identified that evaluated cost-effectiveness for PEP.

Limitations

One primary study⁹ and one SR⁸ met the inclusion criteria for this Rapid Response report, and both were of low quality. The SR⁸ included studies that were of very-low quality, with concerns relating to both imprecision and inconsistency.⁸ The SR also pooled completion and discontinuation rates from some studies that were not designed to compare different PEP regimens, and, therefore, reported outcomes cannot be attributed solely to PEP regimen.

The included SR⁸ reported limited details of the included study populations, beyond potential HIV exposure (i.e., sexual assault, non-occupational, occupational) and country. Hence, it is uncertain whether the outcomes reported in the included studies are generalizable to other populations. The prospective cohort study⁹ excluded exposures that were non-sexual in nature, meaning that the results of the study may not be generalizable to other populations. In addition, the study population was predominantly MSM, and hence the observed outcomes may not be generalizable to women and heterosexual populations.

Conclusions and Implications for Decision or Policy Making

There is limited low-quality evidence from one prospective cohort study⁹ and from one SR⁸ to suggest that PEP regimen is associated with treatment adherence, regimen completion, and discontinuation due to adverse events. Patients prescribed a TDF-based two or three-drug regimen were more likely to be adherent to treatment and to complete the prescribed regimen than patients prescribed a ZDV-based two or three-drug regimen. Limited low-quality evidence from the included SR⁸ suggested that discontinuation rates of PEP due to adverse events are lower for TDF plus FTC plus RAL than for ZDV plus 3TC plus ATV/r; however, it is important to note that discontinuation rates were not reported for other three-drug combinations. Limited low-quality evidence from one primary study⁹ suggests that first time PEP consults, older, and male patients were more likely to be adherent. The outcomes in this study, however, were observed in a predominantly male, MSM population, and may not be generalizable to other populations. The included SR⁸ did not report sufficient details

about the populations of the included studies to assess generalizability. Additionally, outcomes observed in the studies included in the SR may have been due to other interventions, such as telephone support or adherence counselling.

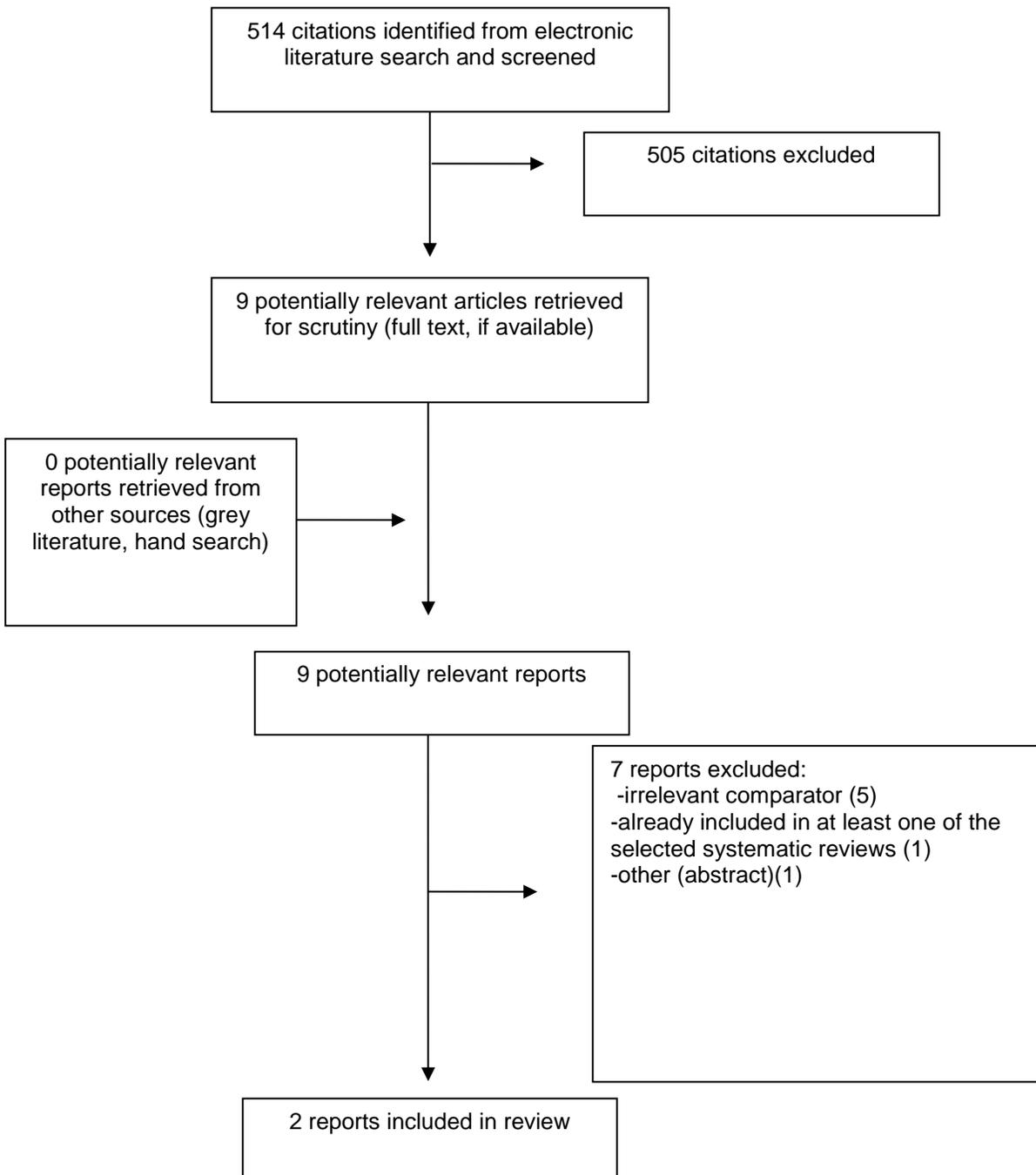
HIV seroconversion was reported as rare in the included studies, and, hence, comparisons of efficacy across drug regimens were not possible. Efficacy was impacted when patients continued to exhibit high-risk sexual behaviours during the PEP period.⁹ Therefore, a combination of risk-reducing behavioural interventions in addition to PEP was recommended.⁹

Relevant cost-effectiveness studies in the PEP population were not identified.

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country; Search Dates and Databases	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
<p>Ford⁸, 2015, Switzerland;</p> <p>Search dates: Inception through December 2013 with MEDLINE update in June 2014</p> <p>MEDLINE, Embase, Cochrane, LILACS</p>	<p>N = 24 studies (n = 2 RCTs of adherence support, n = 2 RCTs of drug regimens, n = 20 prospective cohorts)</p>	<p>N = 5,061 participants</p> <p>PEP due to: Sexual assault (n = 7 studies, 1,651 participants, range 33 to 457)</p> <p>Non-occupational (n = 8 studies, 1,494 participants, range 35 to 395)</p> <p>Occupational (n = 3 studies, 740 participants, range 68 to 380)</p> <p>Occupational and Non-Occupational (n = 6 studies, 1,176 participants, range 46 to 306)</p>	<p>1830 initiations for two-drug regimens:</p> <p>ZDV+3TC (n = 13 studies, 11 prospective cohorts and 2 RCTs)</p> <p>TDF+FTC (n = 3 prospective cohort)</p> <p>1,755 initiations for three-drug regimens:</p> <p>ZDV+3TC+ATV (n = 1 prospective cohort, n = 1 RCT)</p> <p>ZDV+3TC+ATV/r (n = 1 prospective cohort)</p> <p>ZDV+3TC+LPV/r (n = 3 prospective cohort and n = 1 RCT)</p> <p>TDF+FTC+LPV/r (n = 2 prospective cohorts, n = 1 RCT)</p> <p>TDF+FTC+RAL (n = 2 prospective cohort studies)</p> <p>TDF+FTC+DRV/r (n = 1 RCT)</p>	<p>Comparators reported for only 5 studies</p> <p>TDF+FTC (n = 1 prospective cohort)</p> <p>TDF+FTC+RAL (n = 1 prospective cohort)</p> <p>ZDV+3TC+LPV/r (n = 1 RCT)</p> <p>ZDV+3TC+LPV/r (n = 1 prospective cohort)</p> <p>TDF+FTC+LPV/r (n = 1 RCT)</p>	<p>Completion rates, discontinuation due to adverse events</p> <p>Mortality</p> <p>PEP failure as determined by seroconversion</p> <p>Follow-up not provided</p>

3TC = lamivudine; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; DRV/r = ritonavir-boosted darunavir; FTC = emtricitabine; LPV/r = ritonavir-boosted lopinavir; PEP = post-exposure prophylaxis; RAL = raltegravir; RCT = randomized controlled trial; TDF = tenofovir; ZDV = zidovudine.

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Thomas, ⁹ 2015, Canada	Prospective Cohort	<p>N = 3,547 (n = 3,245 male, 92%) following sexual exposures.</p> <p>Of the 3547 patients, 2,772 were prescribed treatment (78%) and 41 stopped their treatment entirely as the source tested HIV negative.</p> <p>N receiving treatment = 2,731 28-day ARV regimen</p> <p>Mean age: 34.6 years, range 18 to 76 MSM = 2933 (83%)</p> <p>Education Level High school or less, n = 535 (15%); College, n = 776 (22%) University, n = 1,730 (49%) Missing data, n = 507 (14%)</p> <p>Consultation Delay <24 hours, n = 1,719 patients (48%) 25 to 48 hours: 1,189 patients (34%) 49 to 72 hours: 558 patients (16%) >72 hours, n = 51 patients (1%) Missing data, n = 30 patients (1%)</p> <p>Number of PEP Episodes: First episode: 2,497 patients (70%) 2 to 4 episodes: 881% (25%) >= 5 episodes: n = 107 patients (3%) Missing data, n = 62 patients (2%)</p> <p>Intoxicated during intercourse, n = 1,530 (43%)</p> <p>Risk of Exposure Low, n = 647 (18%) Moderate to High, n = 2,883 (81%) Missing data, n = 17 (1%)</p> <p>Source known to patient, n = 1,184 (33%)</p> <p>HIV+ source (confirmed), n = 753 (64% of known sources)</p> <p>Serodiscordant couple, n = 132 (4%)</p>	<p>TVD+LPV/r: n = 2,062 (74%)</p> <p>28-day ARV regimen</p>	<p>CBV+LPV/r: n = 275 (10%)</p> <p>TVD+ RAL: n = 217 (8%)</p> <p>Other combinations: n = 206 (7%)</p> <p>Missing data: n = 12 (<1%)</p>	<p>PEP adherence (Patients considered adherent if they did not miss more than 5 doses)</p> <p>HIV Seroconversion</p> <p>Side effects</p> <p>Ongoing at risk sexual behavioural</p> <p>Scheduled follow-up at 4 weeks, and then at 12, 16, or 24 weeks after the initial PEP consultations (protocol changes over study period)</p>

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Violence/agression, n = 101 (3%)			

AOR = adjusted odds ratio; CBV = Combivir (zidovudine-lamivudine); CI = confidence interval; LPV/r = lopinavir/ritonavir; NNRTI = Non-nucleoside reverse-transcriptase inhibitors; PEP = post-exposure prophylaxis; RAL = raltegravir; TVD = Truvada (tenofovir-emtricitabine).

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR⁶

Strengths	Limitations
Ford8	
<ul style="list-style-type: none"> • Two investigators independently reviewed titles and abstracts, with a consensus procedure in place. • The authors stated that no language or geographical limits were applied to the search. • Four databases were searched, and abstracts for related conferences were searched. It appears that the authors searched for reports regardless of their publication type. • Data extraction was performed independently. • A list of included studies was provided. • A predefined protocol was referenced. A research question was provided, and limited inclusion criteria were provided. • Outcomes were provided in the methods section. • The overall quality of the evidence was assessed using GRADE, and the scientific quality of the included studies was used appropriately in formulating conclusions. • Conflict of interest and sources of support were addressed for the SR authors. 	<ul style="list-style-type: none"> • Publication bias was mentioned but not assessed. • No list of excluded studies was provided. • Key words and the search strategy were not provided. • Conflict of interest for included studies was not provided. • The scientific quality of the included studies was not used appropriately in formulating conclusions. • While a random effects model was used due to heterogeneity, the combination of studies and pooling of results without comparators and with different research questions was probably not appropriate. • Limited characteristics of included studies were provided.

Table A4: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist⁷

Strengths	Limitations
Thomas ⁹	
<ul style="list-style-type: none"> • The objective of the study was clearly described. • The main outcomes to be measured were reported in the introduction and methods. • Patient characteristics were clearly described. • Interventions of interest were clearly described (although some drug interventions were described as ‘Other’ without further detail provided, and for a small number of study participants, regimen information was not available). • The main findings of the study were clearly described. • Confidence intervals were reported, as were actual probability values. • The proportion of those asked who agreed to participate was provided. • The staff, places and facilities where the patients were treated appeared to representative of the treatment that the majority of people requiring PEP would receive, although geared toward those with non-occupational HIV exposure. • No unplanned subgroup analyses were reported. • The statistical tests used to assess the main outcomes seemed appropriate. • The main outcome measures used appeared to be accurate. • The patients in the different treatment groups appeared to be selected from the same population, although it was not stated why different treatment regimens were prescribed in some patients and not others. 	<ul style="list-style-type: none"> • It was not clear whether there were differences in confounders between the treatment groups. Risk factors for the observed outcomes were evaluated, but it is not clear if other factors not identified were distributed across groups, or if the potential for confounding was considered in the analysis. • Adverse event rate was reported, but details of the adverse events were not reported. • The characteristics of the patients lost to follow-up (16%) were not described). • Patients in the study were not representative of the entire population from which they were recruited as only patients requiring PEP for sexual exposures were included. • Blinding of study subjects and those measuring the intervention was not reported. • It does not appear that adjustment was made for different lengths of follow-up that occurred due to changes in the centre’s protocol (though this would be unlikely to affect the outcomes observed) • Noncompliance with allocated treatment was reported for 6% of participants (with another 16% unknown due to loss to follow-up and 8% with missing information, and 1% that switched treatment regimen). • It was not clear whether the participants in the different treatment groups were recruited over the same period of time, and randomization to treatment was not performed. • Concealed allocation was not reported. • There was an intention-to-treat analysis that was applied to missing data, but it is not clear if it was also applied to the number lost to follow-up (16%). • A power calculation was not provided.

Appendix 4: Main Study Findings and Author’s Conclusions

Table A5: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Author’s Conclusion
Ford, 2015 ^b	
<p>2-Drug Regimen</p> <p><u>Pooled PEP Completion Rates</u></p> <p>TDF+FTC 78.4%; 95% CI, 66.1% to 90.7%</p> <p>ZDV+3TC 58.8%; 95% CI, 47.2% to 70.4%</p> <p><u>Pooled PEP Discontinuation Rate due to Adverse Event(s)</u></p> <p>TDF-based regimen 0.3%; 95% CI, 0% to 1.1%</p> <p>ZDV-based regimen 3.2%; 95% CI, 1.5% to 4.9%</p> <p>3-Drug Regimen</p> <p><u>Pooled PEP Completion Rates</u></p> <p>TDF+FTC+LPV/r 71.1%; 95% CI, 43.6%–98.6%;</p> <p>TDF+FTC+RAL 74.7%; 95% CI, 41.4% to 100%;</p> <p>TDF+FTC+DRV/r 93.9%; 95% CI, 90.2% to 97.7%;</p> <p>ZDV+3TC+LPV/r 59.1%; 95% CI, 36.2% to 82.0%;</p> <p>ZDV+3TC+ATV 78.3%; 95% CI, 51.2% to 100%;</p> <p>ZDV+3TC+ATV/r 78.8%; 95% CI, 71.0 % to 86.5%;</p> <p><u>Pooled Discontinuations Due to Adverse Drug Reactions</u></p> <p>TDF+FTC+RAL 1.9%; 95% CI, 0% to 3.8%</p> <p>ZDV+3TC+ATV/r 21.2%; 95% CI, 13.5% to 30.0%</p> <p><u>Mortality</u> Zero studies reported mortality due to adverse drug events</p>	<p><i>“...the findings of this review provide evidence supporting TDF combined with 3TC or FTC as preferred backbone drugs for PEP. Choice of third drug will depend on setting; for resource-limited settings, LPV/r is a reasonable choice, pending the improved availability of better-tolerated drugs, with less potential for drug–drug interactions.” (p. S175)</i></p>

Table A5: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusion
PEP failure Rare and could not be compared across regimens due to paucity of events.	

3TC = lamivudine; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; CI = confidence interval; DRV/r = ritonavir-boosted darunavir; FTC = emtricitabine; LPV/r = ritonavir-boosted lopinavir; PEP = post-exposure prophylaxis; RAL = raltegravir; RCT = randomized controlled trial; TDF = tenofovir; ZDV = zidovudine.

Table A6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Thomas, 2015 ⁹	
<p><u>Completion Rate</u> N = 2731 treated patients, 69% completed the entire treatment 2% missed more than five doses 4% discontinued prophylaxis, 1% switched to a different regimen (included in the total completing treatment).</p> <p>Side effects were responsible for: regimen switching in 90% discontinuation of treatment in 70%.</p> <p><u>Adherence</u> Overall adherent: 1902 (70%)</p> <p>CBV-based regimens (CBV in combination with combination with LPV/r, nelfinavir, NNRTIs or other protease and integrase inhibitors):</p> <p>Adherent: n = 233 (60%); Nonadherent: 158 (40%), $P < .001$</p> <p>TVD-based regimens (TVD in combination with LPV/r, RAL, NNRTIs or other protease and integrase inhibitors):</p> <p>Adherent: n = 1650 (72%); Nonadherent: n = 654 (28%)</p> <p>Other regimens:</p> <p>Adherent: n = 17 (59%); Nonadherent: 12 (41%)</p> <p>Factors associated with adherence using TVD+LPV/r as a reference value:</p> <p><u>CBV+LPV/r</u> AOR, 0.58; CI: 0.44 to 0.75, $P < 0.001$</p> <p><u>TVD+RAL</u> AOR, 1.15; CI: 0.83 to 1.59, $P = 0.406$</p> <p><u>Other regimens</u> AOR, 0.66; CI: 0.48 to 0.89, $P = 0.007$</p> <p><u>Male</u></p>	<p><i>“PEP regimen was significantly associated with adherence to treatment. Patients were more likely to be adherent to TVD-based regimens which are known to have better tolerability than CBV-based regimens. Ten patients seroconverted during the follow-up period after taking PEP; however, only a single case of PEP failure was observed as the remaining cases did not reduce at-risk behaviors and increased possible re-exposure to HIV. PEP is therefore a successful method to prevent HIV infection after sexual exposure.” (p.7)</i></p>

Table A6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
<p>AOR, 1.94; CI: 1.46 to 2.59, <i>P</i> < 0.001</p> <p><u>Age (per additional year)</u></p> <p>AOR, 1.02; CI: 1.01 to 1.03, <i>P</i> < 0.001</p> <p><u>1st PEP consult</u></p> <p>AOR, 1.31; CI: 1.09 to 1.57, <i>P</i> = 0.004</p> <p><u>Moderate/high exposure risk</u></p> <p>AOR, 1.05; CI: 0.69 to 1.60, <i>P</i> = 0.799</p> <p><u>Seroconversion</u></p> <p>N = 11 patients (n = 1 not treated as source considered to be HIV-negative; n = 9 patients that exhibited high-risk behavior following treatment; n = 1 patient considered a pure treatment failure)</p> <p>All 11 patients who seroconverted completed treatment; 9 were compliant, and treatment adherence was not available for 1 patient.</p>	

AOR = adjusted odds ratio; CBV = Combivir (zidovudine-lamivudine); CI = confidence interval; LPV/r = lopinavir/ritonavir; NNRTI = Non-nucleoside reverse-transcriptase inhibitors; PEP = post-exposure prophylaxis; RAL = raltegravir; TVD = Truvada (tenofovir-emtricitabine).

Appendix 5: Additional References of Potential Interest

Abstract

Li HC, Cheng YP, Yang CJ. Safety, tolerability and effectiveness of HIV non-occupational prophylaxis in Taiwan. *J Int AIDS Soc.* [Internet] 2014 [cited 2017;17(4 Suppl 3):19736. Available from:

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RCTs with Comparisons between Protease Inhibitors

Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. *J Antimicrob Chemother.* 2016 Jul;71(7):1987-93.

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RCT with Comparison between a Protease Inhibitor and a CCR5 Coreceptor Antagonist

Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus maraviroc each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. *J Antimicrob Chemother.* 2016 Jul;71(7):1982-6.