SUPPLEMENT ARTICLE

Choice of Antiretroviral Drugs for Postexposure Prophylaxis for Adults and Adolescents: A Systematic Review

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Background. The choice of preferred regimens for human immunodeficiency virus postexposure prophylaxis (PEP) has evolved over the last 2 decades as more data have become available regarding the safety and tolerability of newer antiretroviral drugs. We undertook a systematic review to assess the safety and efficacy of antiretroviral options for PEP to inform the World Health Organization guideline revision process.

Methods. Four databases were searched up to 1 June 2014 for studies reporting outcomes associated with specific PEP regimens. Data on PEP completion and discontinuation due to adverse events was extracted and pooled estimates were obtained using random-effects meta-analyses.

Results. Fifteen studies (1830 PEP initiations) provided evaluable information on 2-drug regimens (zidovudine [ZDV]- or tenofovir [TDF]-based regimens), and 10 studies (1755 initiations) provided evaluable information on the third drug, which was usually a protease inhibitor. The overall quality of the evidence was rated as very low. For the 2-drug regimen, PEP completion rates were 78.4% (95% confidence interval [CI], 66.1%–90.7%) for people receiving a TDF-based regimen and 58.8% (95% CI, 47.2%–70.4%) for a ZDV-based regimen; the rate of PEP discontinuation due to an adverse event was lower among people taking TDF-based PEP (0.3%; 95% CI, 0%–1.1%) vs a ZDV-based regimen (3.2%; 95% CI, 1.5%–4.9%). For the 3-drug comparison, PEP completion rates were highest for the TDF-based regimens (TDF+emtricitabine [FTC]+lopinavir/ritonavir [LPV/r], 71.1%; 95% CI, 43.6%–98.6%; TDF+FTC+raltegravir [RAL], 74.7%; 95% CI, 41.4%–100%; TDF+FTC+ boosted darunavir [DRV/r], 93.9%; 95% CI, 90.2%–97.7%) and lowest for ZDV+ lamivudine [3TC]+LPV/r (59.1%; 95% CI, 36.2%–82.0%). Discontinuations due to adverse drug reactions were lowest for TDF+FTC+RAL (1.9%; 95% CI, 0%–3.8%) and highest for ZDV+3TC+ boosted atazanavir (21.2%; 95% CI, 13.5%–30.0%).

Conclusions. The findings of this review provide evidence supporting the use of coformulated TDF and 3TC/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.

Keywords. antiretroviral; adverse events; postexposure prophylaxis; tolerability; safety.

Guidelines for postexposure prophylaxis (PEP) to prevent human immunodeficiency virus (HIV) infection issued by the World Health Organization (WHO) in 2007 recommended zidovudine (ZDV) and lamivudine (3TC) as backbone drugs for PEP with a third drug, preferably ritonavir-boosted lopinavir (LPV/r), added according to exposure risk and the risk of viral drug resistance [1]. Since then, more data have become available on the safety and tolerability of newer antiretroviral drugs when used for treating HIV-infected individuals; recommendations for use in HIV-uninfected persons

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have evolved parallel to this development. PEP guidelines in the United States and Europe have recently been revised to recommend tenofovir (TDF) and emtricitabine (FTC) as preferred backbone drugs, with either a protease inhibitor [2] or an integrase inhibitor recommended as the third drug [3, 4].

The use of antiretroviral drugs for PEP differs from therapy in a number of important ways that can influence drug choice. PEP is given to HIV-uninfected immunocompetent individuals, for a limited duration (28 days), to individuals who may have been exposed to HIV as a result of an acute, and often traumatic, event (in particular sexual assault). Nevertheless, to improve access and simplify prescribing, particularly in resource-limited settings, it is desirable to align guideline recommendations regarding the use of antiretroviral drugs for PEP with those recommended for treatment.

To update WHO recommendations on drug choice for PEP, we undertook a systematic review to assess the safety and efficacy of antiretroviral options for PEP.

METHODS

Search Strategy and Study Selection Process

An initial search was carried out to assess outcomes associated with PEP among adults, irrespective of exposure type. Four databases—Medline via PubMed, Embase, the Cochrane Database of Systematic Reviews, and Lilacs—were searched from inception to 1 December 2013 according to a predefined protocol; this search was updated in PubMed to 1 June 2014. Abstracts of all conferences of the International AIDS Society were searched from 2010 to 2013, and the Conference on Retroviruses and Opportunistic Infections for 2014 (abstracts for prior conferences were not available online) [5].

Two investigators (N. F., C. I.), working independently, scanned all abstracts and independently assessed potentially eligible studies as full text. Consensus was sought prior to final inclusion; in case of disagreement, a third investigator (Z. S.) was consulted. Randomized trials and prospective observational studies reporting outcomes among >10 patients offered PEP were eligible for inclusion irrespective of exposure type provided that information was available on outcomes associated with specific PEP regimens. No language or geographical limits were applied.

Data were extracted independently and in duplicate using a piloted data extraction tool. Information was collected on study country, study population, exposure type, and regimens used. Owing to the difficulty in establishing efficacy of PEP in human studies (the HIV status of source and exposed is often not reported), the primary outcome for this review was discontinuation due to adverse events; secondary outcomes included PEP completion rates (defined as completing a full 28-day course of PEP), severe adverse events, and mortality due to adverse events. Studies were grouped to ensure comparability between regimens, and for the purposes of this review, lamivudine (3TC) and FTC were considered interchangeable, consistent with evidence from randomized trials [6]. Studies that reported outcomes for drugs that are no longer recommended for treatment were excluded from the final review. Data were also extracted to assess risk of bias according to predefined criteria indicative of study quality for randomized trials and observational studies (Supplementary Tables 1 and 2). The overall quality of the evidence for the outcome of treatment discontinuations due to adverse events was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [7].

Data Analysis

Point estimates and 95% confidence intervals (CIs) were calculated for the proportion of patients experiencing each outcome. Patients who discontinued PEP because it was subsequently found not to be needed (either because they were found to already be HIV infected or because the source was found to be HIV uninfected) were excluded from the denominator for assessing PEP completion rates. Data were transformed to stabilize the variance in the raw proportions and pooled after back-transformation using random-effects meta-analysis [8, 9]. Data from randomized trials and prospective observational studies were pooled together because adverse drug reactions are generally rare events, and no important differences in the reporting of these events have been observed between randomized trials and observational studies [10]. Because the drug comparisons of the proportion of patients experiencing adverse events are from separate cohorts, pooled relative-effect measures were not determined. All analyses were conducted using Stata version 12.0 (StataCorp, College Station, Texas) and GRADE Pro (www.gradeworkinggroup.org).

RESULTS

From an initial assessment of 97 studies reporting outcomes of individuals receiving PEP, 15 studies (1830 initiations) provided evaluable information on 2-drug regimens [11–25], and 10 studies (1755 initiations) provided information on the third drug [17, 26–34] across a range of exposures. The remaining studies were excluded for 1 or more of the following reasons: retrospective study design, outcomes not disaggregated by regimen, or regimens not reported. Data from studies reporting PEP outcomes using stavudine and nelfinavir were not included in this review because these drugs are no longer recommended for treatment [25, 26, 35]. Nevirapine was also excluded from review because, despite being widely used for treatment, there are established concerns regarding severe and potentially fatal adverse events attributed to nevirapine

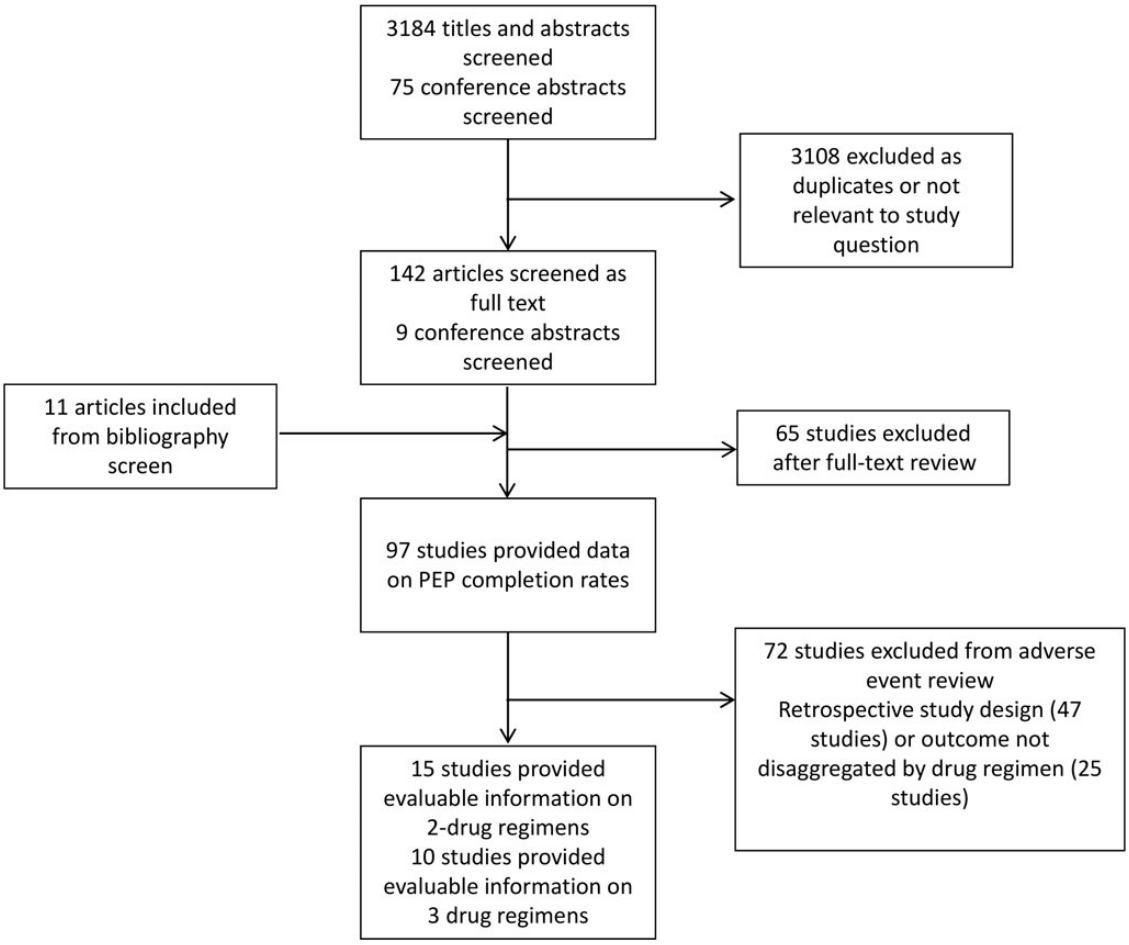

Figure 1. Study selection process. Abbreviation: PEP, postexposure prophylaxis.

when used as part of PEP [36]. Among the evaluated studies, 4 studies were randomized trials [11, 27, 28, 37] and the rest were prospective observational cohorts. The study selection process is outlined in Figure 1 and study characteristics are summarized in Table 1.

The overall quality of the evidence was rated as very low, with the main methodological concerns relating to inconsistency (ie, nonoverlapping CIs between studies led to uncertainty in pooled estimates) and imprecision (ie, wide CIs for individual estimates) (Supplementary Table 1).

For the 2-drug regimen comparisons, 12 studies (10 observational studies and 2 randomized controlled trials [RCTs] assessing adherence interventions) reported outcomes of ZDV and 3TC, and 3 observational studies reported outcomes of TDF and FTC. Pooled PEP completion rates were 78.4% (95% CI, 66.1%–90.7%) for people receiving a TDF-based regimen and 58.8% (95% CI, 47.2%–70.4%) for people receiving a ZDV-based regimen. Similarly, the pooled proportion of PEP discontinuation due to adverse events was lower among people taking TDF-based PEP (0.3%; 95% CI, 0%–1.1%) vs a ZDV regimen (3.2%; 95% CI, 1.5%–4.9%).

For the 3-drug comparison, 7 different comparisons were available: ZDV+3TC+atazanavir (ATV) (1 prospective cohort study), ZDV+3TC+boosted ATV (ATV/r) (2 prospective cohort studies), ZDV+3TC+TDF (1 prospective study), ZDV+3TC +boosted lopinavir (LPV/r) (4 prospective cohort studies and 1 RCT), TDF-+FTC+LPV/r (1 prospective cohort study and 1 RCT), TDF+FTC +raltegravir (RAL) (3 prospective cohort studies), and TDF+FTC-+boosted darunavir (DRV/r) (1 RCT). No studies provided evaluable data on the use of efavirenz in PEP. PEP completion rates were lowest for ZDV+3TC+LPV/r (59.1%; 95% CI, 36.2%–82.0%) and highest for the TDF-based regimens. Discontinuations were lowest for TDF+FTC+RAL (1.9%; 95% CI, 0%–3.8%) and highest for ZDV+3TC+TDF (18.7%; 95% CI, 11.8%–25.7%).

No studies reported any cases of mortality due to adverse drug events. PEP failure as determined by HIV seroconversion was rare, and could not be compared across regimens because of the paucity of events and different protocols for longer-term

Table 1. Characteristics of Included Studies

Study, First Author	Design	Setting	No. Receiving PEP	Exposure	Regimen
Abrahams [11]	RCT (adherence support)	South Africa	253	Sexual assault	ZDV+3TC
Garcia [12]	Prospective cohort	Brazil	278	Sexual assault	ZDV+3TC
Neu [18]	Prospective cohort	United States	33	Sexual assault	ZDV+3TC
Kim [14]	Prospective cohort	South Africa	195	Sexual assault	ZDV+3TC
Roland [37]	RCT (adherence support)	South Africa	457	Sexual assault	ZDV+3TC
Speight [22]	Prospective cohort	Kenya	88	Sexual assault	ZDV+3TC
Kahn [13]	Prospective cohort	United States	395	Nonoccupational	ZDV+3TC
Schechter [20]	Prospective cohort	Brazil	109	Nonoccupational	ZDV+3TC
Shoptaw [21]	Prospective cohort	United States	98	Nonoccupational	ZDV+3TC
Winston [25]	Prospective cohort	Australia	261	Nonoccupational	ZDV+3TC
Swotinsky [23]	Prospective cohort	United States	68	Occupational	ZDV+3TC
Wang [24]	Prospective cohort	United States	380	Occupational	ZDV+3TC
Landovitz [15]	Prospective cohort	United States	35	Nonoccupational	TDF+ FTC
Mayer [16]	Prospective cohort	United States	371	Nonoccupational	TDF+ FTC ZDV+3TC
McAllister [17]	Prospective cohort	Australia	125	Nonoccupational	TDF+ FTC TDF+FTC+RAL
Diaz-Brito [27]	RCT (drug regimens)	Spain	200	Occupational and nonoccupational	ZDV+3TC+ATV ZDV+3TC+LPV/r
Sonder [32]	Prospective cohort	Netherlands	292	Occupational	ZDV+3TC+ATV
Burty [26]	Prospective cohort	France	46	Occupational and nonoccupational	ZDV+3TC+ATV/r
Fätkenheuer [28]	RCT (drug regimens)	Germany	306	Occupational and nonoccupational	TDF+FTC+DRV/r TDF+FTC+LPV/r
Loufty [29]	Prospective cohort	Canada	347	Sexual assault	ZDV+3TC+LPV/r
Rabaud [31]	Prospective cohort	France	251	Occupational and nonoccupational	ZDV+3TC+LPV/r
Tan [33]	Prospective cohort	Canada	124	Occupational and nonoccupational	TDF+FTC+LPV/r
Tosini [34]	Prospective cohort	France	249	Occupational and nonoccupational	TDF+FTC+LPV/r ZDV+3TC+LPV/r
Mayer [30]	Prospective cohort	United States	100	Nonoccupational	TDF+FTC+RAL

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

monitoring after PEP provision. Pooled completion rates are summarized in Figure 2.

DISCUSSION

This is the first systematic review of completion and discontinuation rates associated with different specific regimens used for PEP. The outcomes of this review suggest that for the choice of first 2 drugs for PEP, TDF combined (preferably coformulated) with 3TC or FTC may improve completion rates and result in fewer treatment discontinuations due to adverse events and fewer new HIV infections compared to regimens including ZDV. This choice is further supported by the good tolerability of these drugs in trials of preexposure prophylaxis of HIV-negative individuals [38, 39].

The choice of third drug is less clear, and will depend on considerations of short-term tolerability (the main reason why first-generation nonnucleoside reverse transcriptase inhibitors were never recommended for PEP use), cost, availability, and the possible risk of transmitted drug resistance in certain contexts. In resource-limited settings, LPV/r and ATV/r are both recommended for the management of HIV-infected patients failing first-line antiretroviral therapy, and hence would be familiar drugs to use for PEP. Of the 2, boosted LPV/r is more widely available, has few concerns regarding drug–drug interactions, and from this review appears to be better tolerated in PEP, although this finding is based on very low-quality evidence.

In well-resourced settings, there has been a recent policy shift toward combining TDF and FTC with RAL as the third drug for PEP [3]. The findings of this review support this choice, although again the data are limited and the quality of the evidence is very low. The availability of RAL is much more limited in resource-limited settings, where this drug is more expensive and generally reserved for third-line antiretroviral therapy. Moreover, RAL is currently recommended to be prescribed twice daily, which may affect adherence [40]. Other drugs with good

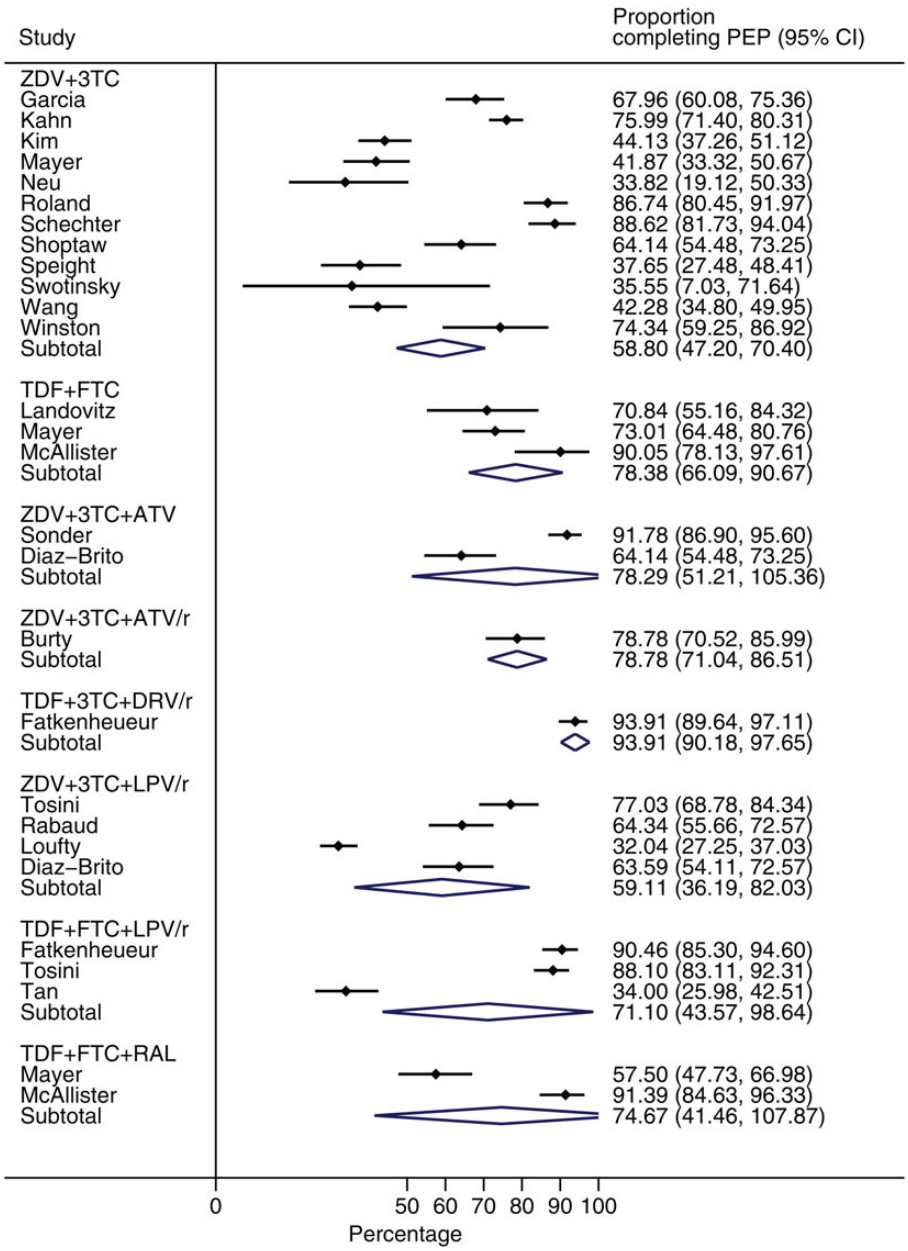

Figure 2. Pooled proportion of individuals completing postexposure prophylaxis (PEP). Not all studies [11] contributed data on completion rates. Abbreviations: 3TC, lamivudine; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; DRV/r, ritonavir-boosted darunavir; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; RAL, raltegravir; TDF, tenofovir; ZDV, zidovudine.

tolerability profiles, prescribed once daily, including elvitegravir/cobicistat, dolutegravir, and rilpivirine, each of which are recommended as first-line therapy in some countries (although the risk of severe hypersensitivity is not yet excluded in HIV-uninfected patients) [41], and low-dose efavirenz [42], may be future candidate drugs for PEP, but data on their use in HIV-uninfected individuals is needed to support the development of future recommendations.

Strengths of this review include a broad search strategy that identified a large number of studies reporting outcomes of people initiating PEP across a range of settings and exposures. Publication bias is a concern with all systematic reviews. We included conference abstract databases for recent years in an attempt to identify studies that may have been recently completed but not yet published in full. Another limitation is the limited amount of information informing reasons for differences in PEP

completion rates, which may be influenced by factors other than drug regimen including exposure type, adherence support, and prior use. The main limitation is that the majority of identified studies could not be included in the final analysis either because they were rated as having too high a risk of bias (retrospective study design) or did not provide sufficient information to associate outcomes with specific regimens. This underscores the need for high-quality studies to inform regimen choice for PEP and more careful reporting of outcome data disaggregated by PEP regimen. Another limitation relates to the fact that other factors may influence PEP completion rates, including exposure type and patient population (completion rates are known to be lower for exposures following sexual assault and for adolescents [5]). We were unable to assess this formally due to the limited number of studies contributing to each drug comparison, but 7 studies included in this review provided information on different regimens within the same patient population [17, 26, 27, 28, 30, 34, 37].

In conclusion, 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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