SUPPLEMENT ARTICLE

# Choice of Antiretroviral Drugs for Postexposure Prophylaxis for Children: A Systematic Review

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***Background.*** This systematic review aimed to assess the safety and efficacy of antiretroviral options for postexposure prophylaxis (PEP). Recognizing the limited data on the safety and efficacy of antiretroviral drugs for PEP in children, this review was extended to include consideration of data on the use of antiretroviral drugs for treatment of infants and children living with human immunodeficiency virus.

***Methods.*** The PEP literature was assessed to identify studies reporting safety and completion rates for children given PEP, and this information was complemented by safety and efficacy data for drugs used in antiretroviral therapy. The proportion of patients experiencing each outcome was calculated and data were pooled using random-effects meta-analysis.

***Results.*** Three prospective cohort studies reported outcomes of children given zidovudine (ZDV) plus lamivudine (3TC) as a 2-drug PEP regimen. The proportion of children completing the full 28-day course of PEP was 64.0% (95% confidence interval [CI], 41.2%–86.8%), whereas the proportion discontinuing due to adverse events was 4.5% (95% CI, .4%–8.6%). One randomized trial compared abacavir (ABC) plus lamivudine (3TC) and ZDV+3TC as part of a dual or triple first-line antiretroviral therapy regimen; this study showed better efficacy in the ABC-containing combinations and no difference in the time to first serious adverse event. Three randomized trials compared lopinavir/ritonavir (LPV/r) to nevirapine (NVP) for antiretroviral therapy and showed a lower risk of treatment discontinuations associated with LPV/r vs NVP (hazard ratio, 0.56 [95% CI, .41–.75]) but no difference in drug-related adverse events. The overall quality of the evidence was rated as very low.

***Conclusions.*** This review supports ZDV+3TC+LPV/r as the preferred 3-drug regimen for PEP in children.

***Keywords.*** antiretroviral; children; postexposure prophylaxis; tolerability; safety.

Postexposure prophylaxis (PEP) following human immunodeficiency virus (HIV) exposure is an important intervention to prevent HIV infection in infants and children, who may be exposed to HIV following accidental exposure such as through community-acquired needle-stick injuries [1–3] or premastication [4], or following sexual assault [5–7].

Postnatal prophylaxis as part of the package to prevent mother-to-child transmission (PMTCT) is the most accepted and widely used postexposure prophylaxis intervention in infants and young children; however, using PEP in other scenarios is often forgotten or delayed due to concerns in administering antiretrovirals in an HIV-uninfected child and lack of drugs in the age-appropriate formulation for immediate use [3]. Development of simplified evidence-based guidelines is a critical step to enable delivery of PEP interventions to children at risk.

For adults, recent guidelines for HIV PEP recommend tenofovir combined with lamivudine (3TC) or emtricitabine (FTC) as the backbone 2-drug regimen, with the addition of either a protease inhibitor (PI) or an integrase inhibitor as the third drug [8]. However, lack of availability of age-appropriate pediatric formulations can limit the use of antiretroviral medicines for children. In resource-limited settings, alignment of antiretroviral drugs used for PEP with those used for

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postnatal prophylaxis or antiretroviral therapy (ART) could be of value in ensuring availability and reliable procurement for this intervention.

To establish World Health Organization (WHO) recommendations on drug choice for PEP in children, we undertook a systematic review to assess the safety and efficacy of antiretroviral options for PEP. Recognizing the limited data on the safety and efficacy of antiretroviral drugs for PEP in children, this analysis was extended to include a review of data on the use of antiretroviral drugs for treatment of infants and children living with HIV.

## METHODS

Two separate systematic reviews were conducted to assess the evidence supporting antiretroviral drug choice for PEP. In the first review, the PEP literature was assessed to identify studies reporting safety and completion rates for children given PEP. In the second review, safety and efficacy data for drugs used in ART were assessed. For both reviews, studies needed to report outcomes associated with specific drug regimens among children aged ≤10 years; this age was chosen as children aged >10 years can receive the same antiretroviral drugs as adults.

For the first review, we extracted data from all prospective studies reporting outcomes among children that were identified as part of an overarching review of PEP outcomes across all populations. This review included any randomized and nonrandomized study that reported completion rates for PEP regardless of exposure type, age, or geographical location, and without language restrictions provided that >10 patients were offered PEP; studies reporting outcomes for PMTCT and related infant prophylaxis were excluded. For the second review, we systematically evaluated efficacy and drug safety data from randomized trials comparing different nucleoside reverse transcriptase inhibitor (NRTI) backbones or first-line nonnucleoside reverse transcriptase inhibitor (NNRTI)– and PI-based regimens as part of ART for children <3 years old and >3 years old [9]. This review, originally conducted to inform the WHO 2013 antiretroviral consolidated guidelines, was subsequently updated to inform PEP guidelines; detailed descriptions of the search strategies and databases screened have been described previously [9, 10]. For both reviews, study selection and data extractions were conducted in duplicate, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting criteria [11].

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 [12].

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 pooled following appropriate transformation using random-effects meta-analysis [13, 14]. All analyses were conducted using Stata software version 12.0.

## RESULTS

For the systematic review of PEP studies, 3 prospective cohort studies were identified from a total of 97 studies screened. These studies reported outcomes of children (age range, 1–18 years) given zidovudine (ZDV) plus 3TC as a 2-drug PEP regimen following mass needle-stick injury in South Africa [7] and Canada [1] and sexual assault in Malawi [5]. In these studies, the proportion of children completing the full 28-day course of PEP was 64.0% (95% CI, 41.2%–86.8%), whereas the proportion discontinuing PEP due to adverse events was 4.5% (95% CI, .4%–8.6%). The overall quality of the evidence was rated as very low.

For the review of treatment studies evaluating efficacy and safety of different NRTI backbones, 1 randomized trial was identified. This study compared abacavir (ABC) plus 3TC and ZDV+3TC as part of a dual or triple first-line ART regimen for children; this study showed better efficacy in the ABC-containing combinations ($P = .01$ for change in HIV RNA up to 48 weeks) and found no difference in the time to first serious adverse event (log-rank $P = \cdot 51$). However, 1 death and 1 treatment discontinuation due to ABC-related hypersensitivity reaction were reported [15].

For the choice of third drug in children aged <3 years, 3 studies compared lopinavir (LPV/r) to nevirapine (NVP) [16–18]. These randomized trials showed a lower risk of treatment discontinuations associated with LPV/r vs NVP (hazard ratio, 0.56 [95% CI, .41–.75]); there was no difference in the risk of drug-related adverse events associated with NVP (relative risk [RR], 1.21 [95% CI, .88–1.65]). In children aged >3 years, the only randomized study that investigated efficacy and safety of PI-based vs NNRTI-based first-line regimens showed no difference in efficacy and safety between the 2 arms [19].

Trials reporting data on efficacy and discontinuation of antiretrovirals used for treatment of HIV infection have limited generalizability to the use of antiretrovirals for PEP. In addition, the number of subjects included and the number of events observed reported in both reviews were very small. For this reason and the uncertainty resulting from significant indirectness and imprecision, the overall quality of the evidence was rated as low to very low.

## DISCUSSION

This systematic review was carried out to inform recommendations for PEP for children as part of the 2014 WHO

guidelines for PEP. These guidelines are based on a public health approach, with the aim of harmonizing PEP regimens across age groups and aligning with recommendations for ART.

There is very little evidence in the literature to guide drug choices for PEP, especially for children. All identified PEP studies used ZDV+3TC as a 2-drug PEP regimen; reassuringly, reported PEP completion and discontinuation rates were better than for adults, although the quality of the evidence is very low [10].

Current pediatric recommendations for treatment of HIV-infected children recommend ABC+3TC as a preferred regimen for children aged 3–10 years mainly to optimize NRTI sequencing, as superiority of ABC over other NRTIs was not shown in a recently completed randomized controlled trial [20]. This trial has also contributed to the emerging body of evidence suggesting that ABC-associated hypersensitivity reaction is rare in the African population [21]. ABC+3TC and ZDV+3TC are equally recommended for children 3 years and younger due to the protective effect played by LPV/r in selecting resistance mutations [22]; however, higher rates of hypersensitivity reaction were observed with ABC in non-African children, and ZDV may be preferred in these settings. Due to a slow transition to ABC-containing regimens, the higher cost, and potential concerns for hypersensitivity reaction, ZDV+3TC is currently the backbone regimen most commonly used for treatment; therefore, alignment of PEP with drugs used for ART is considered more feasible. Alignment with adult PEP regimens would have been of value; however, while the concerns for bone toxicity that limit use of TDF in children are not relevant in the context of short-term use for PEP, TDF is not considered a preferred drug due to the lack of TDF pediatric formulations that are currently not produced by generic manufacturers and not available in most countries.

There were no data from the PEP literature to inform the choice of third drug. Efficacy data from randomized trials assessing different regimens for treatment in children aged <3 years favor LPV/r over NVP, with no significant difference in safety profile. This choice is further supported by results from a recent randomized trial that found no significant difference in efficacy and tolerance comparing LPV/r and 3TC as part of postnatal prophylaxis [23], and LPV/r appears to be preferred by health workers [24]. LPV/r syrup has poor palatability and requires cold chain until dispensing, but this is anticipated to improve with the availability of new solid formulations that can be sprinkled on food.

Although alignment of PEP regimens with current postnatal prophylaxis recommendations which favor NVP would overcome the challenge of ensuring cold chain requirements and availability of LPV/r in the existing formulation at the point of use, the experience with using NVP in young children beyond the first year of age is fairly limited. Where LPV/r is not a feasible option, NVP is a safe alternative in the first 2 years of life, but is discouraged in older children due to concerns of severe hypersensitivity reactions in HIV-uninfected individuals [25].

LPV/r was also considered a viable option for children aged >3 years due to the similar efficacy and safety profile demonstrated in the only randomized trial available in this age group [18]. Alignment with PEP recommendations for younger children and adults, for whom ritonavir-boosted PI is the preferred third drug to construct a PEP regimen, is considered of

| Weight (kg) | | Age | Zidovudine + Lamivudine fixed-dose combination tablets (ZDV+3TC) | | | | Lopinavir/ritonavir (LPV/r) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Tablet, dispersible 60 mg+30 mg pack of 60 | | Tablet, scored, 300 mg+150 mg pack of 60 | | Oral liquid 80/20 mg/mL** 5X60mL bottles | | Tablet 100/25 mg pack of 60 | | Tablet 200/50 mg pack of 120 | |
| min | max | Range | am | pm | am | pm | am | pm | am | pm | am | pm |
| 3 | 5.9 | 0-6 months# | 1 | 1 | NR | NR | 1 mL | 1 mL | NR | NR | NR | NR |
| 6 | 9.9 | 6 months-1 year# | 1.5 | 1.5 | NR | NR | 1.5 mL | 1.5 mL | NR | NR | NR | NR |
| 10 | 13.9 | 1 – 3 years§ | 2 | 2 | NR | NR | 2 mL | 2 mL | 2 | 1 | NR | NR |
| 14 | 19.9 | 3 – 6 years§ | 2.5 | 2.5 | NR | NR | 2.5 mL | 2.5 mL | 2 | 2 | 1 | 1 |
| 20 | 24.9 | 6 – 9 years | 3 | 3 | NR | NR | 3 mL | 3 mL | 2 | 2 | 1 | 1 |
| 25 | 34.9 | 9–14 years | 4 | 4 | 0.5 | 1 | 4 mL | 4 mL | 3 | 3 | 2 | 1 |
| 35 | | >14 years | 5 | 5 | 1 | 1 | 5 mL | 5 mL | 4 | 4 | 2 | 2 |

**LPV/r oral liquid requires refrigeration at 2-8°C, therefore is not suitable for supply to areas where the cold chain cannot be maintained OR inclusion in kits such as post-sexual assault kits that are supplied in the context of emergencies.

# In settings where LPV/r syrup is not available, or cold storage facilities are not available, use Nevirapine as follows:

**Nevirapine oral liquid 10 mg/mL or Nevirapine 50 mg dispersible tablets**

0-6 months: 5mL or 1 tablet every 12 hours (twice daily)

6 months -1 year: 8 mL or 1.5 tablets every 12 hours (twice daily)

§ LPV/r tablets must be swallowed and should not be crushed or dissolved in liquid. Children who are unable to swallow LPV/r tablets should use LPV/r liquid. Note that LPV/r oral liquid contains >42% alcohol and may not be suitable for school-aged children.

All the medicines can be taken with or without food.

**Figure 1.** Weight- and age-band dosing for preferred antiretrovirals (ARVs) to be used for postexposure prophylaxis (as endorsed by the World Health Organization Paediatric ARV Working Group). Abbreviations: 3TC, lamivudine; LPV/r, lopinavir/ritonavir; NR, not recommended; ZDV, zidovudine.

value to streamline procurement and simplify PEP approaches across subpopulations.

Although there is a clear rationale to use other drugs such as ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or raltegravir, no comparative evidence is currently available in children, and lack of or limited access to age-appropriate formulations remains a barrier to their use in most resource-limited settings. In adults, a combination containing TDF, FTC, and raltegravir (RAL) is a well-tolerated PEP regimen with fewer side effects compared with PI-containing regimens as noted in observational PEP studies in adults. FTC is currently Food and Drug Administration approved in children from birth. TDF and RAL are currently FDA approved for use in children aged ≥2 years. Raltegravir brings the added benefits of its integrase inhibitor activity in preventing integration of HIV genetic material to the host genome in a postexposure scenario. As pediatric formulations for newer, more tolerable, and more potent antiretrovirals become more widely available for younger children in resource-limited settings, consideration should be given to including them in future PEP guidelines.

In conclusion, this systematic analysis supports the use of ZDV+3TC+LPV/r as the preferred 3-drug regimen for HIV PEP. These drugs should be administered according the WHO weight-band dosing schedule except for emergency situations, when age-based dosing can be used if weight is unavailable (Figure 1).

## Notes

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