Optimization of antiretroviral therapy in HIV-infected children under 3 years of age: a systematic review

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Background: Treatment of young HIV-infected children is challenging because of rapid disease progression, high viral loads and few drug options. This review was undertaken to update evidence on the management of young HIV-infected children and to inform the development of the 2013 WHO guidelines for antiretroviral therapy (ART) in low and middle-income countries.

Design: A systematic review and meta-analysis.

Methods: We identified and critically assessed randomized controlled trials that evaluated treatment strategies in perinatally HIV-infected infants and young children (aged <3 years).

Results: Eight studies were included. Antiretroviral therapy (ART) initiation in asymptomatic infants led to 74% reduction in mortality or disease progression [hazard ratio 0.36, 95% confidence interval (CI) 0.18–0.74, $P = 0.0002$]. Regardless of previous exposure to prevention of mother to child transmission (PMTCT), treatment failure at 24 weeks was more likely in children starting nevirapine-based than in those starting lopinavir/ritonavir (lopinavir/r)-based ART (hazard ratio 1.79, 95% CI 1.33–2.41, $P = 0.0001$). Infants starting lopinavir/r-based ART and substituting lopinavir/r with nevirapine once virologic suppression was achieved were less likely to experience viral load more than 50 copies/ml (hazard ratio 0.62, 95% CI 0.41–0.92, $P = 0.02$) but more likely to have confirmed virologic failure (>1000 copies/ml) than those remaining on lopinavir/r (hazard ratio 10.19, 95% CI 2.36–43.94, $P = 0.002$). Children receiving induction-maintenance ART (four-drug NNRTI-based regimen for 36 weeks followed by three-drug ART) showed better short-term immunologic and virologic responses, but no long-term benefits. The only trial comparing continuous ART from infancy with interrupted ART beyond infancy was terminated early because the duration of treatment interruption was less than 3 months in most infants.

Conclusion: ART initiation in asymptomatic infants reduces morbidity and mortality. Lopinavir/r-based first-line ART is superior to nevirapine-based regimens in young children, regardless of PMTCT exposure, but lopinavir/r use is challenging. Substituting lopinavir/r with nevirapine following virologic suppression may be feasible where viral load testing is available. Considering current evidence, induction-maintenance and treatment interruption strategies are not recommended. This review contributed to the evidence base for the 2013 WHO guidelines on antiretroviral therapy, which recommend that all children below 3 years start lopinavir/r-based ART and that lopinavir/r can be substituted with nevirapine once sustained virologic suppression is achieved.

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Background

In the absence of antiretroviral therapy (ART), over 50% of HIV-infected infants progress to AIDS and death by 2 years of age [1]. The introduction of ART has dramatically improved health outcomes of HIV-infected children [2]; however, at the end of 2012, only 35% of eligible children in low and middle-income countries (LMICs) had initiated ART [3].

There has been a general shift in paediatric treatment recommendations towards earlier initiation of ART [4,5], recognizing that the goals of treatment are not only to reduce opportunistic infections and mortality but also to maximize long-term growth, neurodevelopment and immunologic health [6,7]. Although early initiation of ART may be beneficial for infants and young children (<3 years of age), lifelong treatment is problematic, given the limited availability of appropriate drugs, long-term toxicities, difficulties with adherence, risk of resistance and cost of such a strategy [8]. Although over 20 antiretroviral drugs are licensed worldwide for the treatment of HIV-infected adults, many are unlicensed or do not have appropriate formulations for young children. For example, the only available protease inhibitor for young children currently is lopinavir/r, which is formulated either as a poorly palatable liquid requiring a cold-chain or as tablets that cannot be crushed. Even where appropriate formulations are available, optimal dosing can be uncertain as drug metabolism varies with age, particularly in infants. Furthermore, ART efficacy may be affected by maternal transmission of drug-resistant virus or postnatal selection of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance [9–11], potentially compromising the response to nevirapine-containing first-line treatment regimens [12,13].

The challenges of treating young children therefore mean that alternative ART approaches need to be considered. For example, switching from lopinavir/r to nevirapine once virologic suppression is achieved may enable a more feasible ART regimen to be used in long term. An induction-maintenance ART strategy, whereby a more potent regimen is used initially followed by maintenance ART with a standard 3-drug regimen, is another potential approach in young children. Finally, initiation of early ART followed by a period of treatment interruption may allow the child to be protected during the period of greatest risk for HIV disease progression and mortality, but enable time off therapy beyond 1–2 years of age to reduce toxicity, cost and risk of resistance [8].

This systematic review and meta-analysis, which is an update of a previous review [14], aimed to summarize the evidence on optimization of ART in HIV-infected children less than 3 years of age to inform the development of the 2013 WHO guidelines for ART in LMICs. We reviewed randomized controlled trials that assessed the efficacy of early ART initiation in HIV-infected children less than 3 years of age compared with deferred ART, started according to clinical or immunologic criteria; the question of what ART regimen to start with, comparing efficacy and toxicity of NNRTI and protease inhibitor based regimens; and the efficacy and safety of alternative strategies to optimize antiretroviral treatment: an induction-maintenance approach to ART initiation, treatment interruption or ART switch strategies (substituting lopinavir/r with nevirapine vs. continuing lopinavir/r once virologic suppression is achieved).

We present here an abbreviated version of this systematic review; the full review has recently been published elsewhere and contains details of the protocol, search strategy and study inclusion and exclusion criteria [14].

Materials and methods

We included randomized controlled trials conducted in perinatally HIV-infected children under 3 years of age that evaluated the following interventions: use of early compared with deferred ART; use of NNRTI vs. protease inhibitor based regimens, in combination with any nucleoside reverse transcriptase inhibitor (NRTI) backbone; substitution of lopinavir/r with nevirapine following initiation with PI-based regimens; interruption of treatment, compared with continuous early ART; induction-maintenance treatment, that is initiating ART with four antiretroviral drugs for an induction period, then moving to maintenance treatment with a standard three-drug regimen [14].

Planned primary outcome measures were mortality and disease progression (defined as occurrence of new AIDS events: Center for Disease Control (CDC) Class C, or WHO stage 4 disease; and other serious HIV-related events: CDC Class B or WHO stage 3 disease). The planned secondary outcome measures were an increase in $CD4^+$ T-cell count percentage from ART initiation (as defined by each study); virologic suppression (HIV RNA viral load below the level of assay detectability, typically 400 or 50 copies/ml plasma); virologic failure (as defined by each study, typically over 1000 copies/ml plasma); change in growth from baseline values following ART initiation (absolute weight and height percentiles or Z-scores); neurodevelopmental outcome (as defined by each study, for example Griffiths Mental Development Scales Scores); serious adverse events (SAEs) and drug-related adverse events according to the National Institute of Allergy and Infectious Diseases (NIAID) SAE grade 1–4 rating criteria [15]. Depending on the data available in the study report or provided by investigators, the outcome definitions described above were modified

for analysis and pooling. When data on only one trial were available for a question, individual trial results were described.

The original search was conducted on 1 November 2010 and was updated on 1 August 2012. We sought to identify relevant studies from 1997 to the search date, regardless of language or publication status, by searching the Cochrane HIV/AIDS Review Group Trials Register, Cochrane Library, PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the following specific search terms supplementary data, http://links.lww.com/QAD/A496 were used: infant, child, p(a)ediatric, HAART, antiretroviral agents, early ART, deferred ART, HIV infection, HIV, acquired immunodeficiency syndrome, NNRTIs, NRTI, protease inhibitor, protease inhibitors, randomized controlled trial and controlled clinical trial. Abstracts from the World AIDS Conference, International AIDS Society conference and Conference on Retroviruses and Opportunistic Infections were also screened. We searched for unpublished and ongoing studies using prospective clinical trial registries, and by contacting research organizations and experts in the field.

Two authors (M.P. and A.J.P.) independently screened records identified by the search. Studies were identified if they met the eligibility criteria. M.P. and A.J.P. independently extracted, cross-checked and assessed data, with any disagreement resolved by consensus with a third author (E.J.A.). If insufficient data were available in the study report, further information was sought from the publication authors. Methodological quality was assessed using the Cochrane risk of bias tool [16].

Where more than one trial was identified for the questions being addressed, the hazard ratios or relative risks (RRs) for each outcome were combined in a meta-analysis to give a pooled hazard ratio or RR, using the fixed-effects model (FEM). A random-effects model (REM) was also used to test the robustness of the results. If heterogeneity was detected and could not be explained by subgroup analyses, then sensitivity analyses were conducted.

Results

In the updated search, 881 records were identified; of the 735 remaining after duplicates were removed, four additional studies were eligible for inclusion in this review (Fig. 1). Four further records were identified in conference proceedings, for a total of eight records. A total of 12 full text studies were excluded because direct comparison with a control arm without intervention was not reported; infants or young children less than 3 years of age were not included or very poorly represented; children enrolled in the studies were not ART-naive or definitions of the interventions being evaluated significantly differed from the ones the review intended to examine. Characteristics of included studies are summarized in Table 1 [17–24].

Risk of bias in included studies

Sequence generation was computerized and performed centrally by the trial statistician in all studies. Allocation was adequately concealed using opaque envelopes or electronic interfaces, opened at the time of randomization in all studies. Participants were not blinded to treatment allocation, but the study endpoints were unlikely to be affected by unmasking. Blinding of outcome assessment was only reported for the CHER trial [17]; however, for the remaining studies, endpoint assessments relied mainly on laboratory measurements, which are unlikely to be affected by unmasking. Incomplete outcome data were reported for NEVEREST [18], wherein a modified intent-to-treat analysis was conducted, but few patients were excluded. An intent-to-treat analysis of all patients was performed for CHER, P1060 cohorts 1 [19] and 2 [20], ARROW [21] and OPH-03 [22], such that attrition bias is unlikely to significantly affect the results. No loss to follow-up was reported for PEHSS [25].

The primary outcome was prespecified in study protocols and provided in study reports or by the investigators, so selective reporting of this outcome is unlikely. Virologic and immunologic outcomes were reported in all studies. P1060 cohorts 1 and 2 were terminated early, as recommended by the DSMB; despite prespecified stopping criteria being applied, potential biases arising from early termination should be considered. The CHER trial was modified to recall and evaluate all deferred arm infants for initiation of immediate ART on advice of the DSMB. Similarly, early termination was recommended by the DSMB in OPH-03 due to the high rate of restarting ART in the interruption arm; the short time spent off ART in the this arm may have reduced the ability to detect differences in growth between groups. PEHSS was originally designed as a feasibility study and was not powered to assess differences in mortality between arms. Similarly, PROMOTE was designed to assess malaria outcomes and was therefore not powered to compare virologic responses between lopinavir/r and nevirapine-based regimens. NEVEREST randomized children who had already achieved virologic suppression, which may limit its generalizability.

Effects of interventions

When to start

Two studies assessed when to start treatment. The pooled hazard ratio for time to death of 0.36 (95% CI 0.18–0.74) indicates a 64% relative reduction in mortality among

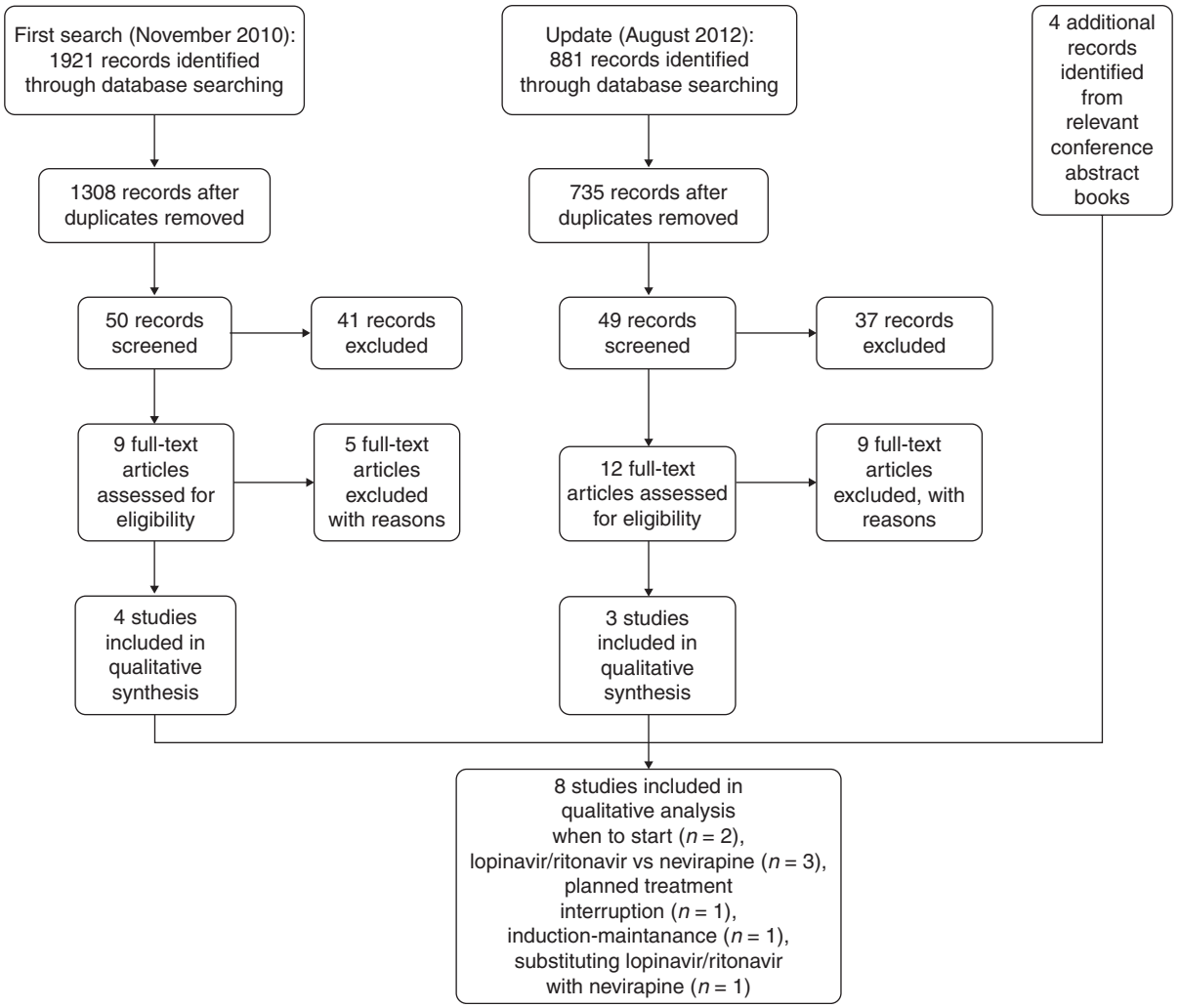

Fig. 1. PRISMA flowchart of study selection process.

infants starting early lopinavir/r-based ART compared with those starting deferred ART once clinical or immunologic criteria were met (Table 2). The combined outcome of mortality or disease progression could only be assessed for CHER. Treatment initiated at 6–12 weeks of age in asymptomatic infants with good immunologic status was associated with a 75% reduction (hazard ratio 0.25, 95% CI 0.12–0.51, $P = 0.0002$) in time to mortality or disease progression, compared with deferred treatment. However, no randomized trial data demonstrate the comparative efficacy of starting vs. deferring treatment in children who first present beyond early infancy. Immunologic response was not combined in a meta-analysis, as the two studies provided different endpoints.

What to start

Three studies assessed what antiretroviral regimen to start in children less than 3 years of age (Table 1). No study was powered to assess mortality or disease progression as independent endpoints. In meta-analysis, the hazard for treatment failure (a composite of virologic failure or discontinuation of the study drugs for any reason, including death) was 1.79 (95% CI 1.33–2.41) times higher in children starting nevirapine than in those starting lopinavir/r-based regimens ($P < 0.0001$). When considering only the two cohorts of P1060, the findings were consistent across studies, indicating that results are similar for NNRTI-exposed and -unexposed children. There was no clear difference in effect by age group, with a similar risk of treatment failure among children starting nevirapine-based regimens above or below 12 months. Results were similar when an REM was used (Table 2).

The hazard for virologic failure was overall 1.84 (95% CI 1.29–2.63) times higher for children starting nevirapine than those starting lopinavir/r-based regimens ($P = 0.0008$) (Fig. 2). The hazard ratio for virological failure (or death) in the nevirapine compared with lopinavir/r group was greater in children below 12 months, than in those above 12 months, with no differences between trials within these age groups (Fig. 3).

Table 1. Summary of characteristics of included studies.

Trial	Country	Question	Participants	Trial details
CHER [17]	South Africa	When should antiretroviral therapy be started in young children?	377	Asymptomatic HIV-infected infants aged 6–12 weeks, with $CD4^+$ cell count ≥25%, were randomized to immediate ART for 40 weeks; immediate ART for 96 weeks; deferred ART according to WHO criteria. First-line ART regimen comprised zidovudine, lamivudine, lopinavir/r. Primary outcomes: time to death or failure of first-line ART (defined as failure to reach $CD4^+$ T-cell count ≥20% by week 24 of ART; decrease to $CD4^+$ cell count <20% after week 24; progression to CDC severe stage B or stage C clinical events; toxicity requiring ≥1 drug substitution within the same class, a switch to a new class or permanent discontinuation of treatment).
PEHSS [24]	South Africa		63	HIV-infected infants were enrolled at birth to a pilot feasibility study of early ART strategies, with randomization to immediate ART for 1 year; immediate ART for 12–18 months with up to 3 structured treatment interruptions; deferred ART according to WHO criteria. First-line ART regimen comprised zidovudine, lamivudine, nevirapine and NFV, with nevirapine discontinued once virologic suppression (VL <50 copies/ml) achieved. Primary outcome: proportion of infants progressing to AIDS by 3 years of age (not yet reported). Clinical, virologic and immunologic outcomes have been reported.
P1060 [19,20]	South Africa, Zimbabwe, Zambia, Malawi, Uganda, Tanzania, India	What antiretroviral therapy should be started in young children?	164 (cohort 1) and 288 (cohort 2)	Two parallel trials of first-line treatment regimens in children below 3 years of age who qualified for ART by WHO criteria. Children in cohort 1 ($n = 164$) had previously been exposed to sd-nevirapine; children in cohort 2 ($n = 288$) had not previously been exposed to sd-nevirapine. Children were randomized to zidovudine, lamivudine, nevirapine or zidovudine, lamivudine, lopinavir/r. Primary outcome: Treatment failure by 24 weeks, defined as permanent discontinuation of the treatment regimen for any reason, including death, toxic effects and virologic failure (confirmed viral load <1 $\log_{10}$ copies/ml below the study-entry level at 12–24 weeks, or confirmed viral load >400 copies/ml at 24 weeks).
PROMOTE-PEDS [23]	Uganda		185	Children age 2 months–5 years who were either ART-naive, or who were currently suppressed on NNRTI-based ART, were randomized to either an NNRTI-based or a PI-based regimen. The study was designed to investigate the impact of ART regimen on incidence of malaria. 185 children were enrolled and randomized to NNRTI-based ($N = 93$) or PI-based ($N = 92$) ART at median age 3.1 years (range 0.3–6.0 years). Protocol-defined analyses included evaluating the noninferiority of lopinavir/r compared with NNRTI-based ART, with virologic and immunologic endpoints. In posthoc analyses, similar endpoints to the P1060 trial were assessed in PROMOTE-PEDS for children <3 years of age.
NEVEREST [18]	South Africa	Can lopinavir/r be substituted with nevirapine in young children achieving virologic suppression?	323	Children under 2 years of age, previously exposed to sd-nevirapine, started a first-line ART regimen comprising d4T, lamivudine, lopinavir/r. 195 infants who maintained viral load <400 copies/ml for >3 months were randomized to continue lopinavir/r or change to nevirapine. Primary outcome: Viral load >50 copies/ml at 52 weeks. Safety endpoint: Confirmed viral load >1000 copies/ml.
ARROW [21]	Uganda, Zimbabwe	Can an induction-maintenance strategy (starting treatment with a 4-drug NNRTI-based regimen) be used in young children?	1206	Open randomized parallel-group trial of ART-naive children age 3 months–17 years (31% below 3 years of age). The trial had a factorial design, with randomization 1 : 1 at ART initiation to either clinically driven or laboratory along with clinical monitoring, and open-label randomization to one of three ART regimens: Arm A started abacavir, lamivudine and NNRTI, whilst Arms B and C started abacavir, lamivudine, zidovudine and NNRTI. After 36 weeks, Arm B children stopped zidovudine and Arm C children stopped the NNRTI. Primary endpoint: change in $CD4^+$ cell count at weeks 72 and 144. Secondary endpoints included new WHO 3/4 event or death; new or recurrent WHO 3/4 event or death; new WHO stage 4 event or death; new or recurrent WHO stage 4 event or death; mortality; viral load; weight, height and BMI; and grade 3/4 adverse events or SAEs.
OPH-03 [22]	Kenya	Can ART be started during infancy and later interrupted?	42	Open, randomized trial recruiting infants who started ART below 13 months of age, had been on ART >24 months and had $CD4^+$ cell count >25% and normalized growth. Infants were randomized to continue ($n = 21$) or interrupt ($n = 21$) treatment at a median (IQR) age of 29 (29–34) and 30 (29–35) months, respectively. The primary endpoints were weight-for-height *Z*-scores (WHZ) and serious adverse events.

ART, antiretroviral therapy; IQR, interquartile range; SAEs, serious adverse events.

Table 2. Summary of results.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
Early vs. deferred antiretroviral treatment				
Mortality	2 (17, 24)	440	Hazard ratio (IV, Fixed, 95% CI)	0.36 [0.18, 0.74]
Mortality or disease progression	1 (17)	377	Hazard ratio (IV, Fixed, 95% CI)	0.25 [0.12, 0.51]
Nevirapine-based vs. lopinavir/r-based first-line antiretroviral therapy				
Treatment failure (virologic failure or treatment discontinuation)	3 (19, 20, 23)	583	Hazard ratio (IV, Fixed, 95% CI)	1.79 [1.33, 2.41]
Treatment failure (virologic failure or treatment discontinuation)	2 (19, 20)	452	Hazard ratio (IV, Fixed, 95% CI)	2.01 [1.47, 2.77]
Infants (less than 12 months old)	2 (19, 20)	200	Hazard ratio (IV, Fixed, 95% CI)	2.03 [1.24, 3.32]
Children (older than 12 months)	2 (19, 20)	251	Hazard ratio (IV, Fixed, 95% CI)	2.00 [1.32, 3.03]
Virological failure or death	3 (19, 20, 23)	583	Hazard ratio (IV, Fixed, 95% CI)	1.84 [1.29, 2.63]
Virological failure or death	2 (19, 20)	452	Hazard ratio (IV, Fixed, 95% CI)	2.28 [1.55, 3.34]
Infants (less than 12 months)	2 (19, 20)	200	Hazard ratio (IV, Fixed, 95% CI)	3.88 [2.06, 7.30]
Children (older than 12 months)	2 (19, 20)	251	Hazard ratio (IV, Fixed, 95% CI)	1.67 [1.03, 2.70]
Change in $CD4^+$ T-cell count% from baseline	3 (19, 20, 23)	356	Mean difference (IV, Fixed, 95% CI)	1.18 [−0.50, 2.86]
Change in weight *z*-score from baseline	3 (19, 20, 23)	360	Mean difference (IV, Random, 95% CI)	0.19 [−0.23, 0.61]
Change in height *z*-score from baseline	3 (19, 20, 23)	374	Mean difference (IV, Fixed, 95% CI)	0.16 [−0.01, 0.32]
Adverse events	3 (19, 20, 23)	506	Risk ratio (M-H, Fixed, 95% CI)	1.21 [0.88, 1.65]
Switch to nevirapine vs. continue on lopinavir/r				
Virologic failure (any VL >50 copies/ml)	1 (18)		Hazard ratio (IV, Fixed, 95% CI)	0.62 [0.41, 0.92]
Virologic failure (confirmed VL >1000 copies/ml)	1 (18)		Hazard ratio (IV, Fixed, 95% CI)	10.19 [2.36, 43.94]
Decline by 10% in $CD4^+$ T-cell count% at week 52	1 (18)	195	Risk ratio (M-H, Fixed, 95% CI)	0.22 [0.07, 0.74]
Decline by 1 *z*-score in weight-for-age at week 52	1 (18)	195	Risk ratio (M-H, Fixed, 95% CI)	0.32 [0.11, 0.94]
ALT increase (Grade 3/4)	1 (18)	195	Risk ratio (M-H, Fixed, 95% CI)	1.80 [0.55, 5.97]
Neutropenia (grade 3/4)	1 (18)	195	Risk ratio (M-H, Fixed, 95% CI)	1.72 [0.42, 6.99]
Induction-maintenance strategy				
Increase in $CD4^+$ T-cell count% from baseline at week 36	1 (21)	228	Mean difference (IV, Fixed, 95% CI)	2.90 [0.80, 5.00]
Increase in $CD4^+$ T-cell count % from baseline at week 72	1 (21)	225	Mean difference (IV, Fixed, 95% CI)	0.60 [−1.56, 2.76]
Increase in $CD4^+$ T-cell count % from baseline at week 144	1 (21)	228	Mean difference (IV, Fixed, 95% CI)	0.50 [−1.70, 2.70]
Virologic response (VL <400 copies/ml) at 24 weeks	1 (21)	268	Odds ratio (M-H, Fixed, 95% CI)	1.99 [1.09, 3.62]
Virologic response (VL <400 copies/ml) at 36 weeks	1 (21)	312	Odds ratio (M-H, Fixed, 95% CI)	1.28 [0.73, 2.23]
Virologic response (VL <400 copies/ml) at 48 weeks	1 (21)	195	Odds ratio (M-H, Fixed, 95% CI)	0.96 [0.50, 1.83]
Virologic response (VL <400 copies/ml) at 144 weeks	1 (21)	199	Odds ratio (M-H, Fixed, 95% CI)	1.03 [0.51, 2.07]
Mortality	1 (21)		Hazard ratio (IV, Random, 95% CI)	0.71 [0.16, 3.21]
New WHO 4/death event-free survival	1 (21)		Hazard ratio (IV, Fixed, 95% CI)	0.73 [0.25, 2.12]
New WHO 3/4/death event-free survival	1 (21)		Hazard ratio (IV, Fixed, 95% CI)	0.98 [0.51, 1.90]
Planned treatment interruption strategy				
Change in WAZ z-score	1 (22)	31	Mean difference (IV, Fixed, 95% CI)	−0.13 [−0.31, 0.05]
Change in HAZ z-score	1 (22)	31	Mean difference (IV, Fixed, 95% CI)	−0.10 [−0.33, 0.13]
Change in WHZ z-score	1 (22)	31	Mean difference (IV, Fixed, 95% CI)	−0.11 [−0.32, 0.10]
Serious adverse events	1 (22)	42	Odds ratio (M-H, Random, 95% CI)	1.00 [0.06, 17.12]

CI, confidence interval; HAZ, heigh for age z-score; IV, inverse variance method; M-H, Mantel-Haenszel method; VL, viral load; WAZ, weight for age z-score; WHZ, weight for height z-score.

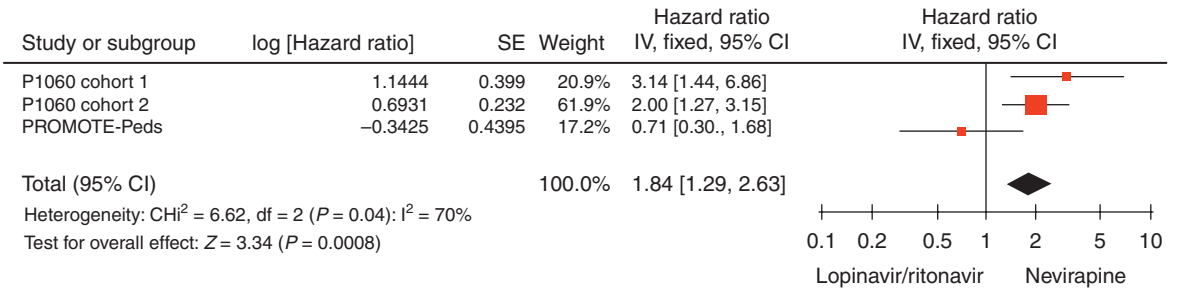

Fig. 2. Forest plot of virologic failure or death: nevirapine-based vs. lopinavir/r-based first-line antiretroviral therapy.

There was weak evidence of greater increases in CD4%, weight-for-age Z-scores and height-for-age Z-scores in the nevirapine compared with lopinavir/r arms. Adverse events associated with treatment were similar between groups (Table 2).

Substituting lopinavir/ritonavir with nevirapine

One trial, NEVEREST [18], addressed the question of lopinavir/r substitution. Children substituting nevirapine for lopinavir/r had a lower risk of having at least one viral load greater than 50 copies/ml but a higher risk of confirmed virologic failure (>1000 copies/ml), than those remaining on lopinavir/r. CD4% increase was lower in the lopinavir/r than in the nevirapine group. Weight-for-age Z-scores were similar on average, but fewer children in the nevirapine group experienced a decline in weight-for-age. Grade 3 or 4 elevations in ALT were more common in the nevirapine group, but events were rare and no association was found with study arm. Similarly, grade 3 or 4 neutropenia was rare and similar across arms (Table 2).

Induction-maintenance

One trial, ARROW [21], investigated an induction-maintenance ART strategy; we report results for the subset of 370 (31%) children below 3 years of age. There was no significant difference between groups in mean CD4% change from baseline at 72 or 144 weeks (Table 2); however, at 36 weeks, there was a greater CD4% increase in the four-drug, compared with three-drug, arms. At 24 weeks, virologic response was better in children receiving four-drug than in those receiving three-drug regimens; however, this effect was not maintained at 48 weeks. There were no differences between groups in mortality, disease progression or growth (Table 2).

Planned treatment interruption

Although three trials investigated planned treatment interruptions, only one, OPH-03 [22], was designed to directly compare continuous ART from infancy vs. interruption. Growth and SAEs were similar between arms (Table 2); however, the trial was stopped early because 14 out of 21 (67%) children in the interruption arm had to restart ART within 3 months.

Discussion

Paediatric HIV remains an important public health problem, with an estimated 700 infants newly infected each day [3]. Historically, clinicians have varied in their practice regarding when to start ART in young children. Furthermore, decisions around which ART regimen to start are complicated by drug resistance in the context of nevirapine exposure, few drug choices, uncertain dosing and long-term toxicities. However, as reviewed here, there are now trial data to inform treatment choices and management strategies for infants and young children.

The question of when to start ART has been clarified by the CHER trial [17], which showed significantly reduced morbidity and mortality among infants randomized to immediate vs. deferred lopinavir/r-based ART. The results of CHER were felt to be relevant to all settings, as reflected by changes in United States [26], European [27] and WHO guidelines [5] to recommend initiation of ART early in infancy. However, in many settings, early infant diagnosis (EID) of HIV is delayed or even unavailable, and loss-to-follow-up is high [28], demonstrating the importance of an effective PMTCT/EID programme if infants are to benefit from early ART. Infants in CHER started ART at 6–12 weeks of age;

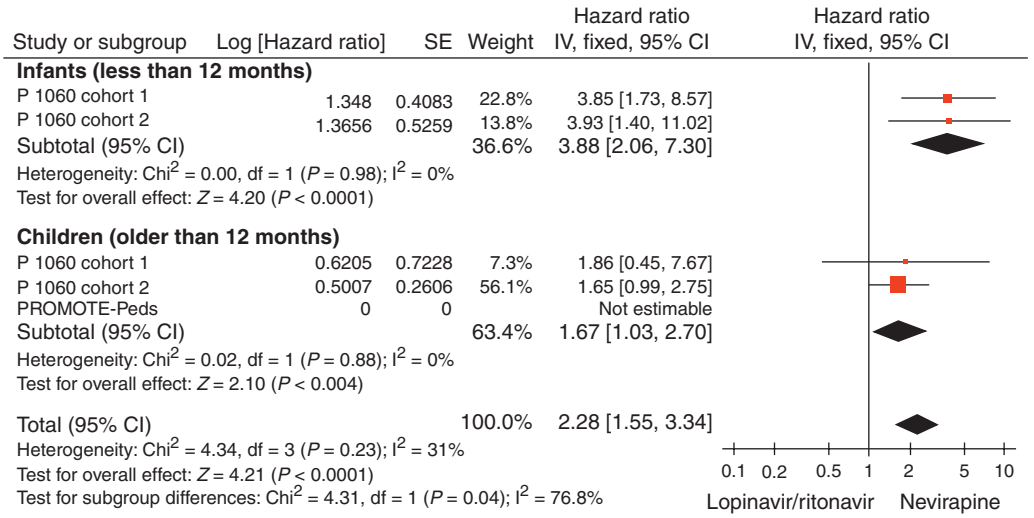

Fig. 3. Forest plot of age subanalysis for virologic failure or death: nevirapine-based vs. lopinavir/r-based first-line antiretroviral therapy.

whether there would be additional benefit to very early initiation of ART (close to birth), as has been hypothesized following report of a 'functional cure' in an HIV-infected infant in the United States [29], remains unclear. However, with an increased interest in some settings of moving EID closer to birth, studies are currently underway to evaluate this strategy. The CHER trial does not resolve the issue of when to treat young children beyond early infancy. Revised 2013 WHO guidelines [4] recommend ART initiation for all children below 5 years of age, with the goal of simplifying paediatric treatment (particularly in the absence of $CD4^+$ cell count testing) and facilitating rapid scale-up of ART for children in LMIC, but there are no clinical trial or cohort data to support this approach. The PREDICT trial, which randomized children age 1–12 years (26% below 3 years of age) with $CD4^+$ T-cell counts of 15–24% at enrolment, to early vs. deferred (once $CD4^+$ T-cell count <15%) ART, found no difference in AIDS-free survival at 144 weeks [30]. A causal modelling analysis of data from 2934 children in the International Epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) cohort, comparing immediate ART (according to 2013 WHO guidelines) with ART initiation according to immunologic thresholds (<750 cells/μl or <25%, as per 2010 WHO guidelines), estimated no mortality difference between strategies up to 3 years [31]. In Europe [27] and USA [26], where treatment is individualized and monitoring and follow-up are generally easier, guidelines continue to recommend age-related clinical and immunologic thresholds for ART initiation in young children beyond infancy.

The P1060 trials addressed what ART to start, recruiting both nevirapine-exposed (cohort 1) and nevirapine-unexposed (cohort 2) children. In both cohorts, there was a higher treatment failure rate among children randomized to a nevirapine-based than those randomized to a lopinavir/r-based regimen. The primary endpoint was a fairly short-term (24 week) composite of virologic failure or discontinuation of the study treatment for any reason, including death. After stratifying by age, the combined analysis of P1060 cohorts 1 and 2 did not show any difference between children younger or older than 12 months for the primary endpoint; however, a considerable difference was detected for the secondary endpoint comprising virologic failure or death. This difference between primary and secondary endpoints may be explained by a higher number of interruptions due to toxicity in children older than 12 months in the nevirapine arm.

It remains unclear why lopinavir/r should be superior to nevirapine even in children not previously exposed to NNRTIs for PMTCT. There are several theoretical explanations, including the low genetic barrier to resistance and once-daily 'lead-in' dosing of nevirapine, which may be problematic in the context of high viral loads during infancy. It is possible that infants without documented NNRTI exposure were actually carrying NNRTI-resistant virus, as reported in observational studies and surveillance data from South Africa and Zimbabwe [32,33]. A posthoc analysis of data from PROMOTE-Peds in Uganda [23] showed no significant difference between nevirapine and lopinavir/r regimens for children less than 3 years of age, using the same endpoints as P1060. However, PROMOTE-Peds was neither designed nor powered to address this question. There are several practical disadvantages to lopinavir/r over nevirapine, including cost, palatability, cold-chain requirements and available formulations [8]. Despite these caveats, P1060 provided high-quality randomized data from sub-Saharan Africa showing superiority of lopinavir/r over nevirapine for young children. WHO 2013 guidelines therefore recommend lopinavir/r-based ART for all infants and young children; however, where use of lopinavir/r is not feasible, nevirapine-based ART should be initiated. Studies are underway to evaluate more palatable sprinkle formulations of lopinavir/r.

An alternative to long-term lopinavir/r, investigated in NEVEREST, is to start ART with lopinavir/r and switch to nevirapine (maintaining the NRTI backbone) once virologic suppression is achieved. Children switching to nevirapine were more likely to maintain viraemia below 50 copies/ml than those continuing lopinavir/r; however, virologic failure (>1000 copies/ml) was more common in those who switched. The apparent inconsistency between these findings may be due to suboptimal adherence among infants continuing lopinavir/r, leading to occasional blips of HIV viraemia, whereas virologic failure was more common with nevirapine because of its low genetic barrier to resistance. This switch strategy has been included as an option for young children in WHO 2013 guidelines [4], in settings in which virologic monitoring is feasible.

ARROW is the only randomized trial to compare an induction-maintenance approach in children, approximately one-third of whom were below 3 years of age. There was some benefit during the induction phase with four drugs, with greater virologic suppression (at week 24) and $CD4^+$ T-cell count increase (at week 36), particularly among children with low baseline $CD4^+$ T-cell counts; however, there were no long-term benefits. Whether sustained benefits would have been seen with a longer induction period (beyond 36 weeks) is unclear. However, four-drug regimens represent an additional burden on ART costs, and currently, an induction-maintenance strategy is not recommended in light of the limited, short-term gains observed in this trial.

Only one trial (OPH-03) compared the current standard management approach (early lifelong ART for infants) with treatment interruption beyond infancy. Disease

progression was rapid after ART interruption, with two-thirds of children restarting ART within 3 months. Two South African trials (PEHSS [24] and CHER [34]), which started treatment in healthier infants and had different designs but a similar rationale to OPH-03, also found that young children starting early, time-limited ART and then interrupting needed to restart sooner than would be feasible in a public health approach, where close follow-up and monitoring of children off ART is challenging.

In summary, there is an unequivocal benefit to early treatment initiation in HIV-infected infants. WHO 2013 guidelines have extended the recommendation for universal early ART to include all children below 5 years of age, to simplify paediatric treatment programmes and facilitate rapid scale-up. Findings from the P1060 trials have led to a change in recommended first-line ART for children below 3 years of age, which is now lopinavir/r-based where feasible. Few high-burden countries are currently using first-line protease inhibitors in young children; adopting these new recommendations will therefore require significant expansion of lopinavir/r provision and development of better formulations. The role of newer drug classes, such as integrase inhibitors, has yet to be evaluated in young children, but could provide an alternative to NNRTI or protease inhibitor based first-line regimens. Given the findings of the induction-maintenance and treatment interruption trials, these strategies are not currently recommended. Further data are needed to determine which children would most benefit from substituting lopinavir/r with nevirapine or efavirenz and to evaluate the impact of this strategy on virologic control and treatment sequencing. There is an urgent need for further research into the programmatic and economic consequences of early ART; development of better drug formulations; monitoring of long-term toxicities; and evaluation of alternative treatment approaches for infants and young children in LMICs.

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M.P. and A.J.P. were the lead authors. M.P. and A.J.P. scrutinized identified studies for eligibility, extracted data and assessed the methodological quality of included studies. M.P. performed the analysis. All authors critically reviewed the manuscript before submission.

Conflicts of interest

A.J.P. is a coinvestigator on the PEHSS and ARROW trials. E.J.A. is a coinvestigator on the P1060 and NEVEREST trials.

No additional conflicts to declare.

None declared.

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