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Safety of antiretroviral therapy in the treatment of HIV/AIDS in children: systematic review and meta-analysis

*Renata Szpak[1], Natália F. Lombardi[1], Frederico A. Dias[2], Helena H.L. Borba[1], Roberto Pontarolo[3], and Astrid Wiens[3]**

[1]Postgraduate Program in Pharmaceutical Sciences, Federal University of Paraná; [2]Centro de Medicamentos do Paraná, Paraná State Health Secretariat; [3]Pharmacy Department, Federal University of Paraná. Curitiba-PR, Brazil

Abstract

The safety of using different antiretroviral therapies (ART) in pediatric HIV/AIDS patients is not well-established. Therefore, this study aimed to assess the safety of ART in children. A systematic review of randomized clinical trials (RCTs) was conducted to assess the safety of ART used by pediatric patients living with HIV/AIDS. The electronic search was conducted in PubMed and Scopus, in addition to a manual search. Studies were included if they assessed the safety of ART compared to placebo or another ART. Direct and indirect meta-analyses were conducted regarding safety outcomes. The systematic review included 21 RCTs. The studies included more than 5500 participants, and age ranged from 3 months to 18 years. The drugs evaluated were nucleoside reverse transcriptase inhibitors (NRTI); non-NRTI; and protease inhibitors. The predominant route of infection was vertical. Direct meta-analyses were performed for the outcomes sleep disorders, hepatobiliary disorders, respiratory disorders, hypertransaminasemia, neutropenia, hospitalization, and death. For these outcomes, no statistically significant differences were found. Indirect meta-analyses were performed for the outcomes anemia, gastrointestinal disorders, liver disorders, severe adverse events (AE), AE that led to changes in treatment, fever, and skin manifestations. However, no statistically significant differences were found for these outcomes. In this study, non-significant differences were detected in the safety of different ART used in pediatric individuals. The choice of appropriate therapy should be based on its efficacy and the individual characteristics of each patient.

Key words

HIV/AIDS. HIV/AIDS medicines. Child safety. Children's health.

Introduction

Before 2005, children infected with HIV, in the majority of countries, did not have adequate access to antiretroviral therapy (ART). Consequently, high childhood mortality rates were observed. With the expansion of the use of ART, the number of children who survive into adolescence and early adulthood is increasing[1].

The guidelines of the World Health Organization (WHO) recommend the use of ART soon after the

Correspondence to:
*Astrid Wiens
E-mail: astrid@ufpr.br

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diagnosis of HIV, regardless of the CD4 count, so that treatment of the infection begins in the early stages of infection[2]. According to the European Pediatric Network for the Treatment of HIV, the preferred scheme of ART's initially used in children are two or three reverse transcriptase inhibitors (nucleoside reverse transcriptase inhibitors [NRTI]), together with a protease inhibitor (PI) enhanced with ritonavir or non-NRTI (NNRTI)[3]. The initial treatment recommendation for HIV in children was updated by the WHO in 2019[4], and the first-line recommendation for children and adolescents is a therapeutic regimen with dolutegravir (DTG) in combination with a NRTI. As an alternative for DTG, raltegravir (RAL)-based regimen may be recommended for children, and efavirenz (EFV), at low dose in combination with an NRTI backbone for adolescents. A RAL-based regimen may be recommended as the preferred first-line regimen for neonates. The Department of Health and Human Services from the United States recommended as preferred regimens two NRTIs combined with either nevirapine (NVP) or RAL for newborns, with lopinavir/ritonavir (LPV/r) for neonates, with DTG for children aged 4 weeks-6 years, or with bictegravir (BIC) or DTG in 4-12 years old children. Alternative regimens include combination of two NRTI with atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), EFV, elvitegravir/cobicistat (EVG/c), or atazanavir/cobicistat (ATV/c)[5]. These regimes are associated with longer survival and lower incidence of opportunistic infections, among other complications associated with the virus[6].

Adverse events (AEs) associated with ART are considered the main cause of switching or withdrawal of therapy, together with non-adherence to treatment[7]. Gastrointestinal symptoms are among the most common AE associated with the use of ART, often compromising medication adherence[8]. Anemia, an event associated with HIV infection, if it persists after the use of therapy, can lead to late virological failure, a fact that can lead to resistance to the drugs used[9].

Previously systematic review assessed the safety of different ART therapies in adults or adolescents[10-12]; however, there are few studies evaluating the safety of ART in children with HIV/AIDS. Therefore, the aim of this study was to assess the safety of ART in children.

Methods

A systematic review was conducted to assess the safety of ART used by pediatric patients living with HIV/AIDS. The systematic review followed the criteria established by the Cochrane recommendations[13] and was reported according to PRISMA recommendations[14]. The protocol was registered in the PROSPERO database under number CRD42020124723.

Study search

Electronic searches were performed using PubMed and Scopus without date and language restrictions (last updated in May 2021). Descriptors related to the condition (HIV/AIDS), study type (randomized controlled trials; RCT), and ART approved in the United States[15] and Europe[3] were used. The detailed search strategy is described in table 1 of the Supplementary Material. Additionally, a manual search was performed in the references of included studies.

Eligibility criteria

The studies were included if they met all the eligibility criteria, according to the acronym PICOS:

- (P) Participants: pediatric patients living with HIV/AIDS.
- (I) Intervention: any ART, at any dose, by any route of administration or combination of medications used for HIV/AIDS.
- (C) Control: placebo or any ART, at any dose, by any route of administration or combination of drugs used for HIV/AIDS.
- (O) Outcomes: AEs or discontinuation due to AE.
- (S) Study design: RCT.

Studies written in non-Roman characters were excluded from this research.

Study selection

After the search, duplicates were excluded and the articles were screened with title and abstract evaluation and, if selected, were later read in full. The screening and eligibility steps were carried out by two independent reviewers, followed by consensus; in cases of disagreement, a third reviewer was consulted.

Data collection process

The articles included after the eligibility stage had their data extracted in duplicate for Microsoft Excel® tables developed specifically for this study. The data extracted from the studies were: characteristics of the

study (country/participating centers and duration), baseline characteristics of the patients included in each treatment arm (criteria for participating in the study, number of patients, sex, ethnicity, age, previous treatments, route of infection, CD4, and initial viral load), data related to the therapy (drugs, dose, and frequency), and safety results (discontinuation due to AE and AE).

Risk of bias in individual studies

The methodological quality of the included studies was assessed using the Jadad scale[16] and the Cochrane Collaboration tool was used to assess the risk of bias[17].

Meta-analysis

Direct and network meta-analyses were carried out using the Aggregate Data Drug Information System software applying the Monte Carlo method through Markov chains and a random-effects model. The results of the consistency model are expressed as odds ratios followed by the 95% credibility interval. In direct meta-analyses, heterogeneity was assessed by I^2 and was considered high when $I^2 > 75\%$[17]. The robustness of the networks was assessed using the node-splitting method, which verifies the agreement between direct and indirect comparisons. $p < 0.05$ indicates inconsistency in the meta-analysis, that is, a lack of robustness in the network[18]. Convergence was assessed using the Brooks Gelman–Rubin method and potential scaling factor[19].

Results

The systematic search retrieved 7.658 articles (Fig. 1), and through the manual search a further five articles were found. After removing duplicates and reading titles and abstracts, 160 articles were selected for full reading, of which 21 were included in the systematic review, totaling 5500 individuals.

Study characteristics

Of the 21 included studies, 12 were multicentric, five were conducted in one country and four did not report the study location (Table 2 of Supplementary Material). The most recurrent countries were African (43%). The duration of the studies ranged from 24 to 240 weeks, with eight studies being carried out in 48 weeks. The publication period ranged from 1997 to 2017.

In nine studies[20-28], one of the inclusion criteria was children clinically stable based on CD4 tests, viral load, or symptomatic diagnosis according clinical signs.

Children exposed to NVP as a way of preventing mother-to-child infection were included in three studies[29-31]. One study[32] was conducted in ART naïve children, and in other study[33] they could only have been exposed to ART in prophylactic form.

Most of the studies (86%) established a maximum and minimum age range, so the range was from 3 months to 18 years (Table 3 of Supplementary Material). All drugs were adjusted in relation to the dose according to the weight of the patients, and the pharmaceutical form was adjusted according to the particular needs of each patient.

The interventions used included drugs of the classes NRTI: zidovudine (AZT), abacavir (ABC), zalcitabine (ddC), didanosine (ddI), lamivudine (3TC), and stavudine (D4T); NNRTI: EFZ and NVP; and PI: LPV/r, ritonavir (RTV), and nelfinavir (NFV). In all control groups, placebo was associated with active therapy.

In all studies that reported the route of infection (n = 10)[20,23,25,30,34-38], the predominance was vertical contamination, whereas in one study[39], babies exposed to HIV were identified from programs to prevent vertical transmission. Exposure to previous therapies was reported in 10 studies[21-25,27-29,37,40], among them ABC, AZT, ddC, ddI, LPV/r, D4T, and 3TC. Two studies[34,36] reported the use of previous therapies but did not specify which ones.

Safety

Considering all studies, in 143 children, therapies were switched due to AE. In one study[20], four children changed their therapy due to AE, so that one replaced AZT with d4T due to anemia and three replaced NVP with EFZ due to skin rash. In two studies[23,34], therapeutic substitution due to AE was also reported, with therapies based on AZT and ddI. Two studies[35,36] reported switches in AZT therapy. AE that led to switches in treatment were observed in nine more studies[20,22,23,25,34-36,38,40]. Two of them[22,25] had the drug LPV/r in common.

In eight studies, it was possible to observe AE classified as severe, that is, grade III (severe) and IV (very severe). The most common drug that lead to this outcome was LPV/r[20,22,23,34-36,38,40]. Hospitalization was observed in four studies (110 patients), in two studies in patients who used LPV/r[25,39], and in the others LPV/r or EFZ[22,29].

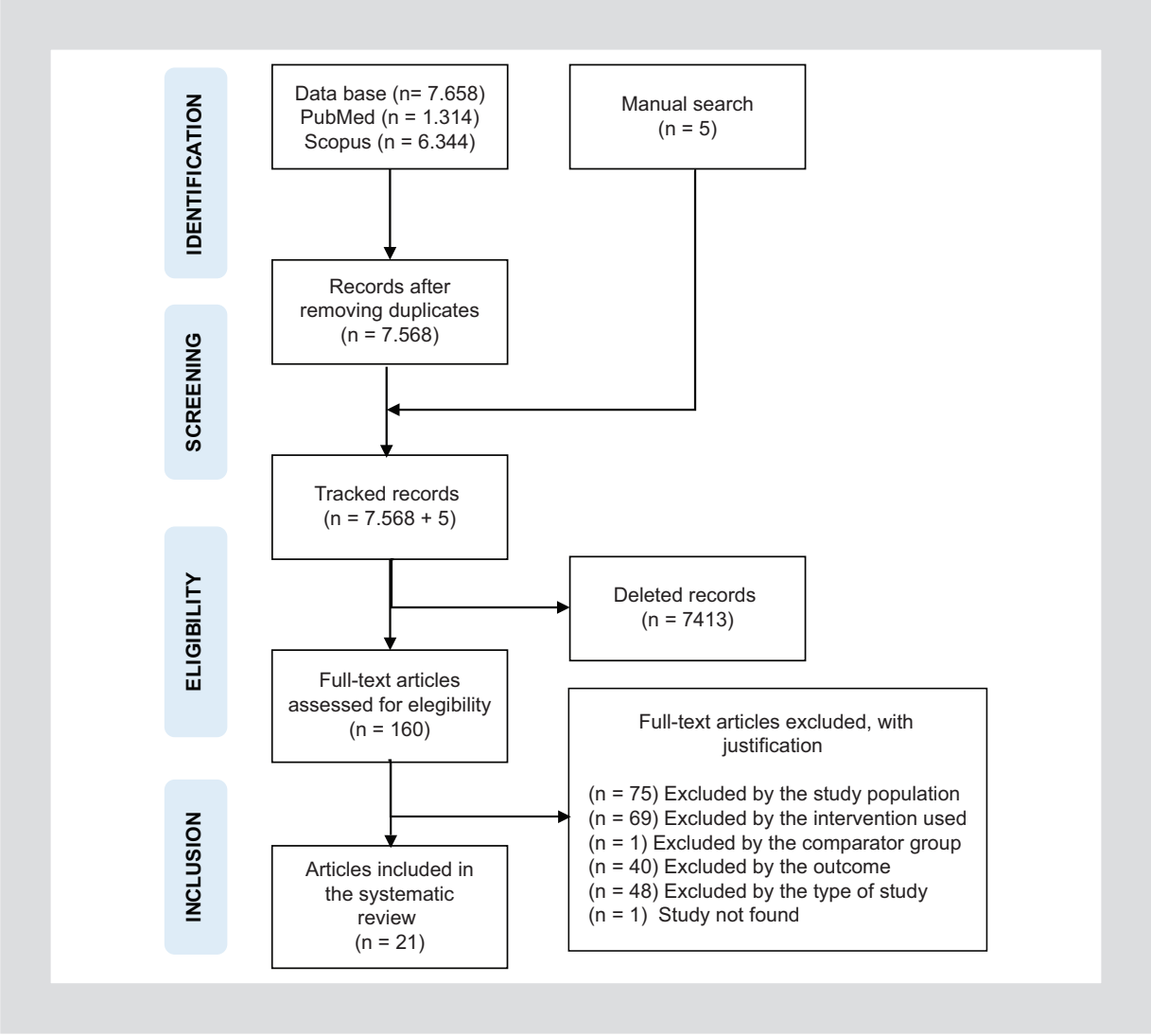

Figure 1. *Flowchart of randomized clinical trials (RCT).*

Regarding laboratory disorders, the most common AE was neutropenia (321 patients), followed by anemia (190 patients)[20-24,26,27,29,30,33,34,36,37,39,40]. The most common clinical disorder among the studies was skin manifestations (264 patients with skin rash), followed by gastrointestinal disorders (172 patients)[20-22,24,25,27-30,32,33,36-38].

In three studies, hepatobiliary disorders were observed[21,25,34]; two of them used two NRTI or NRTI + placebo. Disorders of the nervous system were observed in common in three studies, two of which had the same association[21,25,36]. Sleep disorders were observed in two studies using a combination of two NRTI and as a third drug, that is, LPV/r or EFZ. One of the studies showed that 29% of the patients who had this event were in the EFZ group[22,29].

One study[29] reported that 34% of patients had respiratory problems and both groups used NRTI + NRTI + EFZ or LPV/r therapy. The outcome of fever was also highlighted in this study.

Ten studies presented the outcome of death (117 patients)[21,28,30,33-37,39,40]. Three reported that there were no deaths[20,22,29] and in eight studies this outcome was not reported[23-27,31,32,38] (Tables 4 and 5 of Supplementary Material).

Direct meta-analysis

Five studies were included for direct meta-analyses[21,22,29,30,33]. It was not possible to present the results separately for each treatment combination

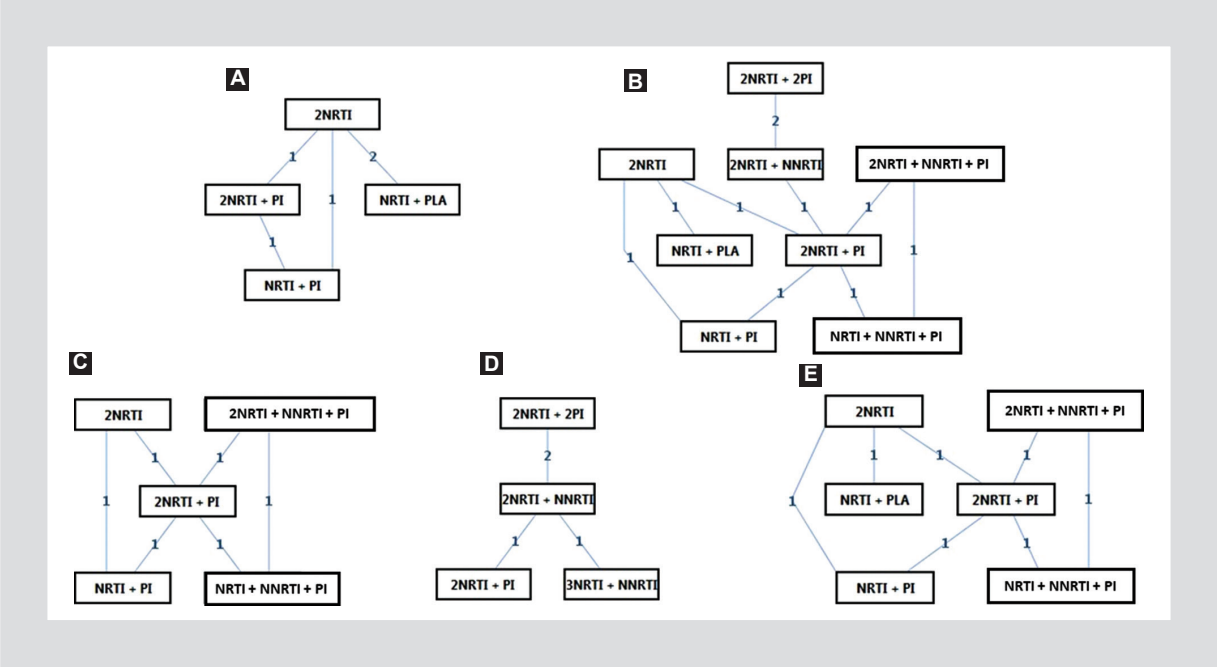

Figure 2. *Comparison networks included in the analyses.* **(A)** *Anemia;* **(B)** *gastrointestinal disorders;* **(C)** *liver disorders;* **(D)** *severe EA III/IV;* **(E)** *fever and cutaneous manifestations. *Number present in the lines represents the number of studies that present the same comparison. NRTI: nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PLA: placebo.*

due to the great diversity of combinations found between the studies. For this reason, the data were grouped into classes of drugs. For the outcomes sleep disorders, respiratory disorders, hypertransaminasemia, hospitalization, death, and neutropenia, the comparison performed was the intervention group using two NRTIs combined with one NNRTI versus the control group using two NRTIs with one PI. For the outcome of hepatobiliary disorders, the comparison performed was NRTI + placebo versus 2NRTI. No comparison was statistically significant between the treatments evaluated (Figs. 1-6 of the Supplementary Material).

Indirect meta-analysis

For the outcomes anemia, gastrointestinal disorders, neutropenia, liver disorders, respiratory disorders, severe AE III/IV, AE that led to treatment switching, fever, and skin manifestations, indirect meta-analyses were performed (Fig. 2). Eleven studies were included in the meta-analyses[21,22,24,27-30,33-35,38]. No comparison was statistically significant between the different treatments (Figs. 7-13 and Tables 6-12 of the Supplementary Material).

Assessment of quality and risk of bias

The average Jadad score was 2.4 (ranging from 1 to 3) (Table 13 of the Supplementary Material). Regarding the risk of bias (Suppplementary figures 14 and 15), for the domains of generating the random sequence and hiding the allocation, more than 50% of the studies did not clearly describe the process. The dominance related to the blinding of the participants and evaluators of the outcome was predominantly high risk, as most of the studies were non-blinded. For the domain of incomplete outcomes, the risk was low, since most of the articles provided all the proposed results. The domain regarding the reporting of selective outcomes was not clear in most studies. Finally, for the domain of other sources of bias, 50% of the studies were funded by the pharmaceutical industry.

Discussion

In this study, the predominant route of infection in pediatric subjects was vertical. The prevention of mother-to-child transmission of HIV is one of the greatest achievements in pediatric research and is crucial to the management of infected women during

pregnancy[41]. A systematic review assessed the reasons for low adherence by pregnant women to ARV therapies for the prevention of mother-to-child vertical transmission, including studies conducted in sub-Saharan Africa. As a result, the authors found that little knowledge of HIV/ART/vertical transmission, low levels of maternal education, psychological problems after diagnosis of the infection, stigma, and fear of disclosure of status to partners, family, or community were the main reasons for low adherence, contributing to the increase in cases of the disease in the pediatric population[42].

A cohort study found that babies born from women with HIV who used prophylaxis with AZT to prevent vertical transmission had higher risks of developing neonatal anemia[43]. In the present study, 50% of children with anemia had AZT as a component of ART. This event was not observed with other therapies. The use of AZT was also associated with severe neutropenia in adults in a retrospective study[44]. In the current study, 63% of patients who had neutropenia used AZT as one of their antiretroviral agents. In a cross-sectional study that evaluated cytopenia in HIV-infected children, anemia was the most common disorder, followed by neutropenia. Severe immunosuppression and younger age were significantly associated with anemia. The study also pointed out, for patients using ART, the presence of a rash, fever, pneumonia, gastroenteritis, and diarrhea[45]. In this meta-analysis, the incidence of anemia or neutropenia was not statistically significant for any of the evaluated classes. This could be better assessed if it were possible to conduct meta-analyses with specific therapies instead of grouping them into therapeutic classes. Apparently, by evaluating therapeutic classes, this outcome is associated with a similar safety between groups.

A previously meta-analysis[46] compared the efficacy and safety of ABC containing regimens in comparison with other NRTIs as first-line treatment for HIV-infected children and adolescents. Experimental and observational studies were included in the study. No significant differences between the two groups were found regarding AE and death. In our study, comparisons were made between classes of drugs, but there were also no statistically significant differences between the therapeutic classes for any of the evaluated outcomes.

In other systematic review evaluating the efficacy and safety of NVP and EFZ, it was observed that NVP was more associated with skin rash and EFZ with mental functions[47]. In the present study, 28% of patients who had skin-related problems, such as skin rash, had NVP in their therapeutic regimen. One of the included studies[22] pointed out that 44.7% of patients on EFZ therapy had the same problem. In addition, 81% of all patients who had sleep disorders had EFZ as part of their therapeutic regimen. However, in the direct or indirect meta-analyses performed in our study, it was not possible to see statistically significant differences in these assessed outcomes.

After acquire HIV, children should start ART therapy as soon as possible and should be monitored regarding the safety. For some drugs recommended in guidelines, few RCTs conducted only in children were found, especially for the most recent drugs. Several studies found in the literature did not define a specific age range, that is, they included adults and children in the same analysis, hindering the interpretation of the results[12,48]. In a long-term study[49], NVP-based regimens were compared to LPV/r regimens, to better understand the comparative effect of these 2 ART regimens in an HIV-infected pediatric population after 5 years follow-up. After this period, LPV/r was associated with fewer deaths compared to NVP-based ART. DTG was evaluated in a study that included African children. The treatment was considered safe, without AE attributed to DTG[50]. RAL safety was evaluated in another study which enrolled children and adolescents and was considered safe, and there were no treatment-related discontinuations or deaths in the 48-week study[51].

Conclusion

This systematic review is the first to include all approved therapies for the treatment of HIV/AIDS in pediatric patients. Although some AEs had been observed with the RCTs individually, when the meta-analyses were conducted, the differences were not significant between the evaluated groups. However, this information should be interpreted with caution and reviewed periodically, as at this time, there are few RCT evaluating the safety of children using ART, and for some safety outcomes, it was not possible to perform the meta-analysis. As new studies emerge, this information should be updated. Therefore, to date, no differences have been observed, in the safety profile of the different classes of ART. This is an important information to guide clinicians and decision-makers in choosing the safest treatment.

Limitations

This study has some limitations. Due to the lack of studies with the same drugs and the same outcomes,

for the meta-analyses, the drugs were grouped into therapeutic classes, making it impossible to assess the differences in the safety of particular therapies. Another limitation is the divergence between doses and pharmaceutical forms of drugs administered to children. In all studies, the drugs were administered orally; however, the studies used pills, capsules, or syrups, and the dose varied according to weight, age, and local recommendations.

Supplementary data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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