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► To cite this version:

Stéphane Blanche, Thorkild Tylleskär, Marianne Peries, Chipepo Kankasa, Ingunn Engebretsen, et al.. Growth in HIV-1-exposed but uninfected infants treated with lopinavir–ritonavir versus lamivudine: a secondary analysis of the ANRS 12174 trial. *Lancet HIV*, 2019, 10.1016/s2352-3018(18)30361-8 . hal-02095216

HAL Id: hal-02095216

<https://hal.umontpellier.fr/hal-02095216v1>

Submitted on 22 Oct 2021

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D-18-00399 R2

Comparison of growth in uninfected HIV-1-exposed infants treated with lopinavir-ritonavir versus lamivudine: a secondary analysis of the ANRS 12174 trial

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This work was presented in part at the 2017 Conference on Retrovirus and Opportunistic Infection,
Seattle, USA (poster #1912).

Funding

The French National Institute of Health and Medical Research–National Agency for Research on AIDS
and Viral Hepatitis (Inserm–ANRS) sponsored the study. Funding was provided by Inserm-ANRS
(ANRS 12174), including funds from the Total Foundation, European Developing
Countries Clinical Trials Partnership (EDCTP; grant number CT.2006.33020.004), and the Research
Council of Norway (GlobVac grant number 183600).

Acknowledgments

We acknowledge Pr Nicolas Molinari for his collaboration on the B-spline related analyses. We thank
all the women and their infants who agreed to participate in the trial.

Declaration of interests

We declare no competing interests.

Contributors

NN, TT, and PVdP designed the trial and wrote the final version of the protocol. JKT, MSM, NM, CK and MM coordinated the field and laboratory work in the four African study sites, collected the data and conducted enrolment and follow-up of participants. IE, TT, SB NN and PVdP designed the anthropometric study. MP and NN analysed the data. SB and MP wrote the first draft of the manuscript. SB coordinated the revised versions and was responsible for final content. All authors reviewed and approved the final version of the manuscript.

Research in context

Evidence before this study

The safety of antiretrovirals in very young children should be evaluated carefully. It may be different from that observed in adults, or even children, because of the immaturity of certain metabolic pathways during the first months of life, as well as more limited knowledge of the pharmacology. This concerns both mother-to-child transmission prophylaxis programs that include a post-natal treatment component for the child, as well as early treatment of HIV-infected children. The analysis is complex for the early treatment of HIV infection because it is not easy to distinguish the specific effect of a molecule within an association; In addition, HIV infection itself, particularly during the primary infection phase, may be accompanied by confounding symptoms. For various reasons, lopinavir boosted with ritonavir (LPV/r) remains one of the key molecules of the pediatric antiviral armamentarium in 2018, especially in countries with restricted access to treatment where a generic form is available. Unexpectedly and paradoxically, a slightly lower weight in the LPV/arm was reported in three out of four randomized studies in HIV-infected young children, despite a better virological outcome.

Added value of this study

Here lower weight gain under LPV/r was confirmed in the large ANRS 12174 randomized trial, which compared two monotherapies administered to uninfected newborns during the entire duration of breastfeeding, for a maximum of one year, for prophylactic purposes. The difference here is indisputable, since it was observed in the absence of HIV infection of the child and as a randomized monotherapy. The large number of children included in the trial allows for a robust statistical analysis.

Implications of all the available evidence

The lower weight gain under LPV/r indicates a persistent metabolic or nutritional effect in young children for which the mechanisms, as well as long-term clinical implications, need to be assessed.

Abstract:

Background: The tolerance of antiretroviral drugs by infants must be carefully evaluated. Lower weight gain under lopinavir/r-based combinations has been previously observed in HIV-1 infected children.

Methods: As a secondary analysis, we evaluated the growth of 1,273 HIV-1 exposed uninfected (HEU) infants enrolled in a multinational, randomized, double-blind, controlled trial of infant prophylaxis to prevent HIV-1 transmission by breastfeeding (NCT00640263). The 1:1 ratio randomization, stratified by country, occurred at seven days for either lamivudine or lopinavir/r prophylaxis until cessation of breastfeeding (maximum 12 months). Comparison of weight and height

are expressed as z-scores, using the least mean-squares method from the linear-mixed model and spline-regression model.

Findings: There was no difference in length-for-age z-scores (LAZ) between arms during the follow up but the weight-for-length z-score (WLZ) and weight-for-age z-score (WAZ) was consistently lower in the lopinavir/r than lamivudine arm: WAZ: -0.18 (95%CI: -0.30; -0.05, p=0.01) at 26 weeks and -0.24 (95%CI: -0.45; -0.05, p=0.02) at 50 weeks. The difference over time for the WLZ and WAZ was confirmed by linear mixed models, whereas spline regression models suggested that the phenomenon occurred early and remained constant thereafter (p=0.02 with a knot at 118 days for WAZ and p<0.0001 with a knot at 44 days for WLZ). The difference in WLZ was greater among girls.

Interpretation: Lower weight gain under lopinavir/r is indicative of a persistent impact that could have long-term deleterious effects. This merits attention given the early and lifelong ART recommendations for HIV-infected infants.

Funding: French National Agency for Research on AIDS and Viral Hepatitis (ANRS), the Total Foundation, the European Developing Countries Clinical Trials Partnership (EDCTP) and the Research Council of Norway.

Trial Registration: clinical trials.gov: NCT00640263

TEXT:

Introduction

The treatment of HIV-1-infected children with antiretrovirals is remarkably effective. Apart from the specific compliance difficulties of very young children and adolescents, clinical and virological efficacy is similar to that observed in adults.¹ The overall tolerance is remarkable, despite specific toxicity profiles for each class and each molecule of the same class.² The protease inhibitor (PI) lopinavir (LPV), pharmacologically boosted by ritonavir (LPV/r), is one of the key molecules of the pediatric

antiviral armament, due to its intrinsic antiviral efficacy and the high “genetic barrier” to viral resistance.³⁻⁵ Its use in low-income countries is increasing, as a generic pediatric formulation is now available.⁶ In addition to the inconvenience of the poor palatability of its oral solution, the tolerance of LPV/r is characterized, above all, by digestive disorders, such as nausea and diarrhea,³⁻⁴ and lipid perturbations, mainly hypertriglyceridemia.^{7,8} Unexpectedly, lower weight gain in children has been observed in the LPV/r based regimen of several randomized studies comparing it to nevirapine-based regimens, unrelated to virological outcomes.⁹⁻¹¹

The large randomized ANRS 12174 trial, comparing extended infant prophylaxis of either LPV/r or lamivudine – a nucleoside analogue lacking significant overt clinical toxicity¹² – in exposed, uninfected (HEU) newborns and infants for the prevention of HIV-1 transmission by breastfeeding offered a unique opportunity to precisely evaluate the impact of LPV/r on weight gain relative to that of another antiretroviral, without interference of either HIV infection or other drugs used in combination.

Methods

Study design and participants

The ANRS 12174 trial was a multinational, randomized, double-blind, controlled trial conducted in 1,273 mother-infant pairs in Burkina Faso, South Africa, Uganda, and Zambia between November 16 2009 and May 7, 2013 (clinical trials.gov NCT00640263). Complete details of the protocol and methodology according CONSORT guidelines have been published in detail elsewhere.^{13,14} In brief, the trial enrolled infants born to asymptomatic mothers who were not eligible for ART, according to WHO recommendations, at the time of the trial, *i.e.* CD4 blood count > 350 cells/ μ L. Mothers and infants followed the routine national prevention of mother-to-child transmission programs until trial inclusion at day seven after birth, including seven days of nevirapine treatment from the birth of the infants. Singleton infants were eligible if they had a negative HIV-1 DNA PCR at day 7. Pediatric liquid

formulations of LPV/r (Kaletra[®], Abbott, Chicago, USA) were given at a dose of 40 mg of LPV and 10 mg of ritonavir, twice a day, for infants weighing 2 to 4 kg or 80 mg/20 mg, twice a day, for infants weighing > 4 kg). These dose bands were proposed before WHO recommendations were available, based on a French population PK analysis¹⁴. A subsequent PK analysis revealed that this dosage led to a higher proportion of suboptimal exposure in children of less than 4 kg than those following the WHO recommendations.¹ The new formulation of dispersible granules was not available at time of the study. Generic lamivudine (from several manufacturers, depending on the country and period of the study) was given at 7.5 mg, twice a day, for infants weighing 2 to 4 kg, 25 mg, twice a day, for infants weighing 4 to 8 kg, or 50 mg, twice a day, for infants weighing > 8 kg). The prophylaxis was given from day 7 until the end of breastfeeding, plus one week with a maximum duration of 50 weeks. The trial protocol was approved by the National Ethical Committee for Health Research in Burkina Faso, the Biomedical Research Ethics Committee in Zambia, the Uganda National Council for Science and Technology, the Stellenbosch University Ethics committee, the Medicines Control Council in South Africa, and the Regional Committee for Medical Research Ethics of Norway. All participating mothers gave written informed consent.

Randomisation and masking

LPV/r or lamivudine were randomly assigned to participants in a 1:1 ratio to either drug with stratification by country. All bottles were masked with a study label that prevented the primary caregiver or parent from reading the original label. Drugs were renewed monthly by the trial pharmacists who weighed returned bottles to grossly assess adherence.

Procedures

According to WHO guidelines¹⁵, the trial physicians received extensive training for anthropometric measurement before the trial, using uniform standard procedures, and the same scales and height gauges at the four sites, and monitoring during the study. Child's length and weight twice were

measured twice, with a third measurement if the two measurements differed by greater than or equal to 0.8 cm for length and greater than or equal to 80 gram for weight.

Outcomes

As pre specified secondary outcome of the trial, the children's weight and height were compared between the groups of treatment. WHO Child Growth Standards were used to estimate the child's anthropometric status: length-for-age z-score (LAZ), weight-for-length z-score (WLZ), and weight-for-age z-score (WAZ). Children with a LAZ below -2 were considered to show severe stunting, a WLZ below -2, severe wasting, and a WAZ below -2, to be severely underweight.¹⁶

Data cleaning

The anthropometric data were cleaned through four steps: step 1) examination of potential weight/height outliers according to the age of the child; step 2) Consistency check between two reports of height and weight in the study CRF at each visit; step 3) examination of longitudinal data per child, i.e. the search for a large break in the weight/length curve during follow up; and step 4) determination of the z-scores according to the WHO Child Growth Standards.¹⁷ Measurements were considered to be potentially implausible according to the WHO if: 1) WAZ <-6 or > 5; 2) LAZ <-6 or > 6; 3) WLZ <-5 or > 5; or 4) WLZ > 3 and LAZ <-3. Extreme changes in LAZ and WLZ-scores of more than 2.5 between visits were also considered to be implausible. During the data cleaning process, all extreme values were assessed individually and all implausible measures considered as missing data. For the entire study, after adding all the weight and height measurements, as well as z-scores, the percentage of missing data was 1.2% (440 missing data points out of 35,980) for the LPV/r arm and 1.1% (392 missing data points out of 36,705) for the lamivudine arm.

Statistical analysis

We first used a modified intention-to-treat (ITT) analysis, including all children correctly enrolled with at least one anthropometric measurement during the follow up. Data were censored at the end of treatment or at the first HIV-1 PCR-positive test. A per-protocol (PP) analysis was performed for the subgroup of children with an estimated compliance > 80%. The descriptive analyses are presented as medians with interquartile ranges (IQRs) or means with standard deviations (SDs) for continuous variables and as frequencies with percentages for categorical variables. The analysis was first performed for the entire group, then by country and sex. We analyzed the continuous longitudinal data using first, a linear mixed effect model (PROC MIXED in SAS) to describe the three z-scores by the type of treatment over time. The covariance structure was assumed to be unstructured. Subject and time, in weeks, were added to the model as random effects to account for the correlation between repeated measurements on the same individuals. Treatment group, time, time squared, and interactions between time variables and treatment group were added as fixed effects. Model parameters were estimated using the Restricted Maximum Likelihood approach. Z-scores were compared between arms using the least square mean (LSM) from the linear mixed effect model method, at 6, 26, and 50 weeks after enrolment. The p value of the interaction between treatment and time from this model was used to determine whether the treatment affected the z-scores over time. Then, for each arm the average curve was fitted as a B spline with the same node (calculated from the spline regression on all data). For each arm, the difference between the slopes before and after the node was calculated. Then, these two differences were compared using the Wald test. We used a Generalized Linear Mixed Model (proc GLIMMIX in SAS) with binomial distribution and logit link function to assess the evolution of the categorical outcomes (low and severe stunting, wasting, and being underweight) over time. Subject and time, in weeks, were added to the model as random effects, and treatment group and time as fixed effects. The covariance structure was assumed to be unstructured. Model parameters were estimated using the Pseudo-Likelihood MMPL approach. Odds ratios are presented with the 95% confidence interval. A sensitivity analysis on continuous data was

performed on the children treated for at least 26 weeks. The data were analyzed using SAS Enterprise Guide V6.1 (SAS Institute Inc., Cary, NC, USA) and R V3.3.1 (R Foundation for Statistical Computing). The WHO SAS macro was used to calculate the indicators of the growth standard z-scores.¹⁶

Role of the funding sources

The sponsor and funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1,273 HIV-1 exposed but uninfected newborns were included in the trial; six were wrongly enrolled (protocol deviation) and one had no anthropometric data, leaving 1,266 newborns included in the analysis (630 in LPV/r group, 636 in lamivudine group, figure S1 in Appendix p1). The baseline characteristics of the 1,266 newborns and mothers were similar across the two arms (Table 1) and showed slight differences between countries (Table S1 in Appendix, p2). The median age of the mothers was 27.1 years (IQR: 23.8-31.2) in the LPV/r group and 27.0 (IQR: 22.9-30.9) in the lamivudine group. The median birthweight was 3.00 kg (IQR: 2.74-3.35) in the LPV/r group and 3.00 kg (IQR: 2.80-3.33) in the lamivudine group. As reported in the main trial article, grade 3-4 serious adverse events occurred without significant difference between the two arms.¹⁴ Anthropometric measurements were available for all 1,266 infants from 14,537 follow-up visits, *i.e.* 82% of expected visits. The median duration of prophylaxis was 41.3 weeks (IQR 28.9-47.3) for the LPV/r group and 42.1 weeks (IQR 32.9-48.1) for the lamivudine group. Few mothers reported poor feeding or poor appetite of their child during treatment (Min-Max: 0.3% at D7 – 5.1% at W46), with no difference between arms: three children in each group had a poor appetite at W6; only five children in the LPV/r group and one in the lamivudine group at W26 ($p=0.09$); and eight children in the LPV/r group and five in the lamivudine group at W50 ($p=0.47$). Although there was no difference in the LAZ between arms, the WLZ was lower in the LPV/r arm than the lamivudine arm, with differences of -0.22 (95%CI: -0.34; -0.09, $p=0.0006$) at 26 weeks and -0.25 (95%CI: -0.47; -0.04, $p=0.02$) at 50 weeks (Table 2). The WAZ was also consistently lower in the LPV/r than lamivudine arm with a difference of -0.18 (95%CI: -0.30; -0.05, $p=0.01$) at 26 weeks and -0.24 (95%CI: -0.45; -0.05, $p=0.02$) at 50 weeks. The difference over time was confirmed by linear mixed models for both the WLZ and WAZ ($p<0.0001$ and $p=0.002$ Table 2), whereas spline regression models suggest that this reduction occurred early and remained uncorrected thereafter ($p=0.02$ with a knot at 118 days for WAZ, and

$p < 0.0001$ with a knot at 44 days for WLZ (Figure 1). The risk of severe stunting and being underweight (z-score < -2) during the period of treatment in the LPV/r arm was not significantly different than that in the lamivudine arm: (OR=1.13; IC95%: 0.85-1.49, $p=1.13$ and OR 1.13; IC95%: 0.85-1.49, $p=0.41$, respectively). However, there was a marked trend for higher risk of wasting in the LPV/r arm: OR=1.39; IC95%: 0.99-1.93, $p=0.06$. The global impact of the treatment on the growth was not significantly modified by sex. However, there was a trend for the WLZ (p-value of the interaction sex*treatment: $p=0.26$ for LAZ, $p=0.07$ for WLZ and $p=0.83$ for WAZ). The difference in the WLZ was greater among girls than boys, with a difference of -0.29 (95%CI: $-0.58; 0.01$, $p=0.05$) for girls and -0.22 (95%CI: $-0.53; 0.09$, $p=0.18$) for boys at 50 weeks (Table 3). The decrease of z-score over time was confirmed by linear mixed models for the WLZ and was more significant for girls (girls: $p < 0.0001$; boys: $p=0.01$). Spline regression models suggest that the reduction in the WLZ occurred early among girls and remained constant thereafter ($p=0.001$ with a knot at 44 days, figure S2 in Appendix p 3). The Impact of LPV/r was higher in Burkina Faso and Uganda than in Zambia and South Africa for WAZ and LAZ but not for WLZ (p-value of the interaction sex*treatment: $p=0.02$ for LAZ, $p=0.87$ for WLZ and $p=0.03$ for WAZ) (Table S2). The reduction in WAZ over time was confirmed by a linear model in Burkina Faso ($p=0.0003$), and the reduction in LAZ was confirmed in Uganda ($p=0.02$). Eight of 10 and 9 of 10 statistically insignificant differences for LAZ and WAZ, respectively, disfavor LPV/r (Table S2 Appendix p4 and 5). The per-protocol analysis included 1,004 infants (481 in the LPV/r group and 523 in the lamivudine group) with an estimated adherence $>80\%$ based on the weight of the returned bottles. Similar to the ITT analysis, there was no difference in the LAZ between arms at 50 weeks in the per-protocol analysis, and the WLZ and WAZ were consistently lower in the LPV/r than lamivudine arm at 50 weeks, with differences similar to the ITT analysis. Moreover, the mixed and spline-regression models showed a trend for an effect of time on the LAZ ($p=0.01$ and $p=0.08$, respectively), in addition to the effect of time on the WAZ and WLZ described in the ITT analysis (Table S3 and Figure S3 in Appendix p6 and 7).

The sensitivity analyses conducted on children who were treated for at least 26 weeks did not show any differences in the results from mixed linear regressions in the ITT analysis.

Discussion

This large randomized trial compared two single-drug prophylactic regimens with either LPV/r or lamivudine in HIV-1 exposed, uninfected infants born to HIV-infected mothers. We observed lower WAZ and WLZ in the LPV/r group, starting early after initiating treatment in both the ITT and per-protocol analyses. The randomization of a large number of children regularly and precisely measured and weighed over a one-year period, after a rigorous training of the investigators, allowed us to avoid the imprecision inherent in measuring these parameters. Lamivudine-induced weight gain is possible, but our findings are consistent with those observed for HIV-1-infected children treated with a LPV /r-based combination, randomly compared to those treated with nevirapine, an antiretroviral drug from another class. In three of four randomized trials, a slightly lower WAZ in the LPV/r arm was similarly noted in the LPV/r group⁹⁻¹¹ (summary of the trials in Table S4 Appendix p8). It is not possible to distinguish between the respective roles of LPV and/or its pharmacological booster ritonavir, a former anti-HIV drug that also belongs to the PI class. A deleterious role of the excipient for LPV/r, which contains 42.4% alcohol and 15.3% propylene glycol by volume, cannot also be excluded. The new pediatric formulation of LPV/r as dispersible granules⁶ was not available at the time of the study and the impact on growth of the different galenic presentations remains to be evaluated. Reversibility and growth recovery after stopping treatment also needs to be assessed; a long-term follow-up study of these children is ongoing. Finally, the data are based on infants of less than one year of age and extrapolation to older children is not clear. Of note, there was no significant difference in growth in two other randomized studies comparing LPV/r to efavirenz.^{17,18} This discrepancy possibly reflects an age-related effect, as the LPV/r *versus* efavirenz trials were conducted in older children. In addition, efavirenz has a very different metabolic impact than nevirapine, even though they belong to the same class of antiretrovirals.¹⁹ The LPV/r weight-based

dosages were in the commonly used range. Blood levels of LPV measured in a subgroup of infants and published elsewhere were within the expected values for therapeutic efficacy, somewhat slightly under-dosed for one third of the children.²⁰ The observed difference in growth was more pronounced in girls. Contrary to previously published gender differences,²¹ the area under the curve and LPV/r residual levels was similar between boys and girls in this trial (unpublished, Frantz Foissac, personal communication).

The pathophysiological mechanisms leading to the observed weight difference remain to be elucidated. The loss of integrity of the digestive track is possible, given the mediocre intestinal tolerance of LPV/r. No difference in the incidence of digestive adverse events was observed in this trial.¹⁷ However, LPV/r induced endoplasmic reticulum stress and epithelial cell apoptosis in a mouse intestinal epithelial cell model, leading to the impairment of mucosal barrier integrity.²² Such an alteration could induce a subclinical malabsorption syndrome and lower than expected weight gain, although this is still speculation. A more trivial explanation could be that the bad taste of the oral suspension may have also reduced the appetite of the children, resulting in lower growth. However, the appetite of the children was not significantly different between the two arms, as evaluated by the mothers.

Another possibility could be dysfunction of one of the many metabolic pathways with which LPV and/or ritonavir interact. Lipid abnormalities and insulin resistance induced by PIs are well described,^{7,8} but a potential relationship between such alterations and lower weight gain is not clear. Cytochrome P450 (CYP) enzyme activity is strongly affected by PIs, as shown by the pharmacological role of ritonavir as a booster, which acts through the strong inhibition of CYP 3A4. PI-induced CYP inhibition and activation are mainly studied through the very large number of pharmacological drug-to-drug interactions they induce.²³ However, CYPs are present in many metabolic pathways that could theoretically impair growth when inhibited or activated by a specific drug. Genetic

polymorphisms should also be considered in CYP-related drug toxicity. Recently CYP 2C19 polymorphisms were shown to be associated with valproic acid-induced weight gain.²⁴ A role for food intake and energy balance via the role of CYP2C19 on testosterone and progesterone metabolism has been suggested. No less than seven adrenal enzymes belong to the cytochrome family²⁵ and hormonal disturbances induced by LPV/r have been described in newborns exposed pre- and postpartum,²⁶ as well as in pregnant women.²⁷⁻²⁸ However, the role of adrenal dysfunction in LPV/r-dependent alterations in weight gain is yet to be established. A prolonged elevated DHEA level, as observed during perinatal PI exposure, would, on the contrary, accelerate height as an androgen, which was not the case here. The difference observed between countries (more pronounced effect in Burkina Faso and Uganda than in Zambia and South Africa) cannot be explained by differences in per capita income or diet, as the trial was randomized. Although an effect on CYP is still speculative, a possible role of high CYP genetic diversity in Africa may be responsible.²⁹ This unexpected finding raises the question of the potential country-specific effect of feeding habits concurrent with LPV/r intake.

The difference in weight gain under LPV/r observed in our trial is modest and was not associated with significant morbidity during the first year of life. However, this finding is indicative of a persistent LPV/r-induced nutritional or metabolic impact that could have long-term deleterious effects under treatment. This effect deserves attention given the early and lifelong treatment recommendations for infected infants. It must be put in perspective with other advantages of the drug, mainly its strong genetic barrier to the risk of viral resistance, a point that is particularly important in children. The impact of other anti-HIV-1 protease Inhibitors on growth is also yet to be determined, as well as that of alternative drugs in the antiretroviral drug armamentarium.³⁰

References

- 1: WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. 2016 Recommendations for a Public Health Approach.
<http://www.who.int/hiv/pub/arv/arv-2016/en/> Accessed October 23, 2018
- 2: Kanters S, Vitoria M, Doherty M, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. *Lancet HIV*. 2016;3:e510-e520.
- 3: Sáez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2003; 22: 216–223
- 4: Sigaloff KC, Calis JC, Geelen SP, van Vugt M, de Wit TF. HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review. *Lancet Infect Dis*. 2011;11:769-79.
- 5: Frange P, Briand N, Avettand-fenoel V, et al. Lopinavir/ritonavir-based antiretroviral therapy in human immunodeficiency virus type 1-infected naive children: rare protease inhibitor resistance mutations but high lamivudine/emtricitabine resistance at the time of virologic failure. *Pediatr Infect Dis J*. 2011; 30: 684–688.
- 6: Nebot Giral A, Nöstlinger C, Lee J et al. Understanding the acceptability and adherence to paediatric antiretroviral treatment in the new formulation of pellets (LPV/r): the protocol of a realist evaluation. *BMJ Open*. 2017; 29:014528.
- 7: Rojas Sánchez P, Prieto L, Jiménez De Ory S et al. Madrid Cohort of HIV-1 Infected Children and Adolescents Integrated in the Paediatric Branch of the Spanish National AIDS Network (CoRISPe). Impact of lopinavir-ritonavir exposure in HIV-1 infected children and adolescents in Madrid, Spain during 2000-2014. *PLoS One*. 2017;12(3):e0173168.
- 8: Innes S, Abdullah KL, Haubrich R et al. High Prevalence of Dyslipidemia and Insulin Resistance in HIV-infected Prepubertal African Children on Antiretroviral Therapy. *Pediatr Infect Dis J*. 2016;35(1):e1-7.
- 9: Coovadia A, Abrams EJ, Stehlau R et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. 2010;304(10):1082-90.

- 10: Violari A, Lindsey JC, Hughes MD et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med.* 2012;366(25):2380-9.
- 11: Barlow-Mosha L, Angelidou K, Lindsey J et al. Nevirapine- Versus Lopinavir/Ritonavir-Based Antiretroviral Therapy in HIV-Infected Infants and Young Children: Long-term Follow-up of the IMPAACT P1060 Randomized Trial. *Clin Infect Dis.* 2016;63(8):1113-1121.
- 12 <https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv> Accessed August 19, 2018
- 13: Nagot N, Kankasa C, Meda N et al. PROMISE-PEP group. Lopinavir/Ritonavir versus Lamivudine peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: the PROMISE-PEP trial Protocol ANRS 12174. *BMC Infect Dis.* 2012 Oct 6;12:246.
- 14: Nagot N, Kankasa C, Tumwine JK et al. ANRS 12174 Trial Group. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet.* 2016;387(10018):566-73.
- 15: <http://www.who.int/childgrowth/training/en/> , Accessed October 23, 2018
- 16: de Onis M, Onyango A, Borghi E, Siyam A, Pinol AJ: WHO Child Growth Standards Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age Methods and development.: Department of Nutrition for Health and Development, World Health Organization; 2006.
- 17: Coovadia A, Abrams EJ, Strehlau R et al. Efavirenz-Based Antiretroviral Therapy Among Nevirapine-Exposed HIV-Infected Children in South Africa: A Randomized Clinical Trial. *JAMA.* 2015;314 (17):1808-17.
- 18: Murnane PM, Strehlau R, Shiao S et al. Switching to Efavirenz Versus Remaining on Ritonavir-boosted Lopinavir in Human Immunodeficiency Virus-infected Children Exposed to Nevirapine: Long-term Outcomes of a Randomized Trial. *Clin Infect Dis.* 2017; 65(3):477-485.
- 19: Van de Wijer L, Schellekens AFA, Burger DM, Homberg JR, de Mast Q, van der Ven AJAM. Rethinking the risk-benefit ratio of efavirenz in HIV-infected children. *Lancet Infect Dis.* 2016 May; 16(5):e76-e81.
- 20: Foissac F, Blume J, Tréluyer JM et al. Are Prophylactic and Therapeutic Target Concentrations Different?: the Case of Lopinavir-Ritonavir or Lamivudine Administered to Infants for Prevention of Mother-to-Child HIV-1 Transmission during Breastfeeding. *Antimicrob Agents Chemother.* 2017; 61(2). pii: e01869-16.
- 21: Umeh OC, Currier JS, Park JG, Cramer Y, Hermes AE, Fletcher CV. Sex differences in lopinavir and ritonavir pharmacokinetics among HIV-infected women and men. *J Clin Pharmacol.* 2011;51(12):1665-73.
- 22: Wu X, Sun L, Zha W et al. HIV protease inhibitors induce endoplasmic reticulum stress and disrupt barrier integrity in intestinal epithelial cells. *Gastroenterology.* 2010 ;138(1):197-209.

- 23: Li F, Lu J, Ma X. CYP3A4-mediated lopinavir bioactivation and its inhibition by ritonavir. *Drug Metab Dispos.* 2012; 40(1):18-24.
- 24: Noai M, Soraoka H, Kajiwara A et al. Cytochrome P450 2C19 polymorphisms and valproic acid-induced weight gain. *Acta Neurol Scand.* 2016; 133(3):216-23.
- 25: Miller WL. Steroidogenesis: Unanswered Questions. *Trends Endocrinol Metab.* 2017;28(11):771-793.
- 26: Simon A, Warszawski J, Kariyawasam D et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA.* 2011; 306(1):70-8.
- 27: Papp E, Mohammadi H, Loutfy MR et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis.* 2015;211(1):10-8.
- 28: Balogun KA, Guzman Lenis MS, Papp E et al. Elevated Levels of Estradiol in Human Immunodeficiency Virus-Infected Pregnant Women on Protease Inhibitor-Based Regimens. *Clin Infect Dis.* 2018 ;66(3):420-427.
- 29: Rajman I, Knapp L, Morgan T, Masimirembwa C. African Genetic Diversity: Implications for Cytochrome P450-mediated Drug Metabolism and Drug Development. *EBioMedicine.* 2017;17:67-74.
- 30: Shiao S, Abrams E J, Arpadi SM, Kuhn L Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? *Lancet HIV* 2018; 5: e250–58

Table 1. Characteristics of mothers and newborns at inclusion

	Lopinavir/r (n = 630)	Lamivudine (n = 636)
Mothers		
Age (years)	27.1 (23.8-31.2)	27.0 (22.9-30.9)
Parity	2.8 (1.5)	2.7 (1.5)
Gestational age at delivery (weeks)	38.4 (1.7)	38.5 (1.7)
Pre-delivery CD4 count (cells per μ L)	528 (430-667)	531 (437-673)
Plasma HIV-1 RNA		
- Undetectable	274 (44%)**	276 (45%)*
- Median (log ₁₀ copies per mL)	3.4 (2.9-3.9)	3.4 (3.0-3.9)
WHO clinical HIV-1staging		
- Stage I	612 (97%)	612 (96%) α
- Stage II	17 (3%)	22 (4%)
- Stage III-IV	0 (0%)	1 (<1%)
- Unknown stage	1 (<1%)	0 (0%)
Any PMTCT regimen		
- During pregnancy	607 (96%)	612 (96%)
- During labor	614 (98%)	626 (98%)
Highest education level completed		
- None	80 (13%)	85 (13%)
- Primary	234 (37%)	219 (34%)
- Secondary or tertiary	316 (50%)	332 (52%)
Newborns		
Boys	321 (51%)	335 (53%)
Girls	309 (49%)	301 (47%)
Birthweight (g)	3000 (2740-3350)	3000 (2800-3325)

Data are shown as the mean (SD), median (IQR), or n (%). α One Missing value,

**Nine missing values, * 19 missing values.

Table 2. Length-for-age (LAZ), weight-for-length (WLZ) and weight-for-age (WAZ), and least square means (Mean) z-scores at 6, 26, and 50 weeks (Intention-to-treat analysis).

	Lopinavir/r Mean(95% CI)	Lamivudine Mean (95% CI)	Difference (95% CI)	P value of the difference	P value of the reduction of the z-score over the time
LAZ N=12409*					
6 weeks	-0.88 (-0.96; -0.81)	-0.83 (-0.91; -0.76)	-0.05 (-0.16; 0.05)	0.35	0.17
26 weeks	-0.95 (-1.03; -0.87)	-0.91 (-0.99; -0.83)	-0.04 (-0.15; 0.07)	0.47	
50 weeks	-1.04 (-1.15; -0.92)	-0.92 (-1.03; 0.81)	-0.12 (-0.28; 0.05)	0.14	
WLZ N=12286**					
6 weeks	0.16 (0.08; 0.23)	0.18 (0.10; 0.25)	-0.02 (-0.12; 0.09)	0.73	<0.0001
26 weeks	0.01 (-0.08; 0.10)	0.22 (0.14; 0.31)	-0.22 (-0.34; -0.09)	0.0006	
50 weeks	-0.90 (-1.05; -0.74)	-0.64 (-0.79; -0.50)	-0.25 (-0.47; -0.04)	0.02	
WAZ N=12428α					
6 weeks	-0.53 (-0.60 ; -0.46)	-0.47 (-0.54; -0.40)	-0.06 (-0.16; 0.04)	0.26	0.002
26 weeks	-0.70 (-0.79; -0.61)	-0.53 (-0.62; -0.44)	-0.18 (-0.30; -0.05)	0.01	
50 weeks	-1.06 (-1.20; -0.92)	-0.81 (-0.95; -0.67)	-0.24 (-0.45; -0.05)	0.02	

Monthly visits completed during the treatment period: *85.4%, **84.5, α 85.5%.

Table 3. Weight-for-length z-score (WLZ) least square means (Mean) at 6, 26, and 50 weeks by sex (Intention-to-treat analysis).

	Lopinavir/r Mean(95% CI)	Lamivudine Mean (95% CI)	Difference (95% CI)	P value of the difference
WLZ				
Boys N=6395*				
Girls N=5891**				
6 weeks				
Boys	0.23 (0.12; 0.34)	0.15 (0.05; 0.26)	0.07 (-0.08; 0.23)	0.35
Girls	0.09 (-0.01; 0.19)	0.20 (0.10; 0.31)	-0.12 (-0.26; 0.03)	0.11
26 weeks				
Boys	0.04 (-0.09; 0.17)	0.16 (0.03; 0.28)	-0.11 (-0.29; 0.07)	0.22
Girls	-0.02 (-0.14; 0.09)	0.30 (0.19; 0.42)	-0.33 (-0.50; -0.16)	<0.0001
50 weeks				
Boys	-0.95 (-1.18; -0.73)	-0.74 (-0.96; -0.52)	-0.22 (-0.53; 0.09)	0.18
Girls	-0.83 (-1.04; -0.63)	-0.54 (-0.74; -0.34)	-0.29 (-0.58; 0.01)	0.05

Monthly visits completed during the treatment period: *85.1%, **83.9%.

Figure 1. Beta spline regression by arm for WLZ (A) and WAZ (B): red line for the lopinavir/r arm and blue line for the lamivudine arm (Intention-to-treat analysis).

