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Antiretroviral treatment and its impact on oral health outcomes in 5 to 7 year old Ugandan children

A 6 year follow-up visit from the ANRS 12174 randomized trial

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Abstract

Background: Antiretroviral therapy for HIV in sub-Saharan Africa has transformed the highly infectious virus to a stable chronic condition, with the advent of Highly active antiretroviral therapy (HAART). The longterm effects of HAART on the oral health of children are understudied.

Objective: To compare the effect of lopinavir-ritonavir and lamivudine on oral health indicators (dental caries, gingivitis, tooth eruption, and oral health related quality of life) in 5 to 7 year old HIV-1 exposed uninfected children from the ANRS 12174 trial.

Methods: This study used data collected in 2017 among children aged 5 to 7 years from the Ugandan site of the ANRS 12174 randomized trial (ClinicalTrials.gov no: NCT00640263) implemented between 2009 and 2012 in Mbale district, Eastern Uganda. The intervention was lopinavir-ritonavir or lamuvudine treatment to prevent vertical HIV-1 transmission. One hundred thirty-seven and 139 children were randomized to receive lopinavir-ritonavir or lamivudine treatment at day 7 postpartum to compare efficacy of prevention

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of vertical HIV-1 transmission. At follow up, the children underwent oral examination using the World Health Organization methods for field conditions. The oral health related quality of life was assessed using the early childhood oral health impact scale. Negative binomial and logistic regression were used for the analysis of data.

Main outcome measures: Dental caries, gingivitis, tooth eruption, and oral health related quality of life) in 5 to 7 year old HIV-1 exposed uninfected children.

Results: The prevalence of dental caries was 48% in the study sample: 49% in the lopinavir-ritonavir arm and 48% in the lamivudine treatment group. The corresponding mean decayed missing filled teeth and standard deviation was 1.7 (2.4) and 2.3 (3.7) The mean number (standard deviation) of erupted permanent teeth was 3.8 (3.7) and 4.6 (3.9) teeth in the lopinavir- and lamivudine group, respectively. The prevalence of reported impacts on oral health was 7% in the lopinavir-ritonavir and 18% in the lamivudine group. Gingivitis had a prevalence of 7% in the lopinavir-ritonavir and 14% lamivudine treatment group. The regression analysis revealed 70% less reported impacts on oral health in lopinavir-ritonavir group than the lamivudine treatment group with an incidence rate ratio of 0.3 (95% confidence interval: 0.1–0.9).

Conclusions: HIV exposed uninfected infants in the lopinavir-ritonavir group reported less impacts on oral health than the lamivudine treatment group. Dental caries, gingivitis, and tooth eruption were not significantly affected by the treatment lopinavir-ritonavir or lamivudine.

Trial Registration ClinicalTrials.gov identifier: NCT00640263.

Abbreviations: ART = antiretroviral treatment, cART = combined antiretoviral treatment, CI = confidence interval, dmft/s = decayed missing filled teeth/surfaces, HAART = highly active antiviral treatment, HIV = human immune virus, IRR = incidence rate ratio, OHRQoL = oral health related quality of life, PIs = protease inhibitors, PROMISE-PEP = promoting infant health and nutrition in Sub African Africa: safety and efficacy-pre exposure propylaxis, REC = Regional Ethical Committee.

Keywords: antiretroviral, children, clinical trial, dental caries, gingivitis, oral health related quality of life, public health

1. Introduction

Human immune virus (HIV) treatment programs in sub-Saharan Africa have transformed HIV infection from being a highly lethal infectious disease to a condition with many similarities to other chronic diseases.[1] Especially, the introduction of highly active antiretroviral therapy (HAART) using 3 or more antiretroviral drugs in combination, has led to significant declines in HIV-associated morbidity and mortality.[2] Among the commonly used antiretroviral drugs are the nucleoside reverse transcriptase inhibitor like lamivudine and the protease inhibitors (PIs) like lopinavir-ritonavir.[3] Both drugs have been used as first- or second-line treatment options, for children, adolescents, and adults.[4,5]

It is important to investigate the long-term safety aspects of antiretroviral drug regimens in order to maximise control of HIV while at the same time minimizing adverse events. The ANRS 12174 multi-center trial investigated consequences of providing lopinavir/ritonavir versus lamivudine to exposed uninfected infants and reported less weight gain at 50 weeks among infants given lopinavir–ritonavir compared to infants receiving lamivudine. This indicates a negative growth effect that could have adverse health- and developmental consequences among infants given lopinavir-ritonavir.[6] Recently, another study from ANRS 12174 found that lopinavir-ritonavir was associated with dose-dependent adrenal dysfunction in infants.[7]

A study from Iran compared adult persons with HIV receiving HAART to HAART naïve controls and reported no differences related to crown and root caries.[8] Similar conclusions were also reported from the United states in an HIV cohort of women.[9] However, from Thailand it has been reported that HIV infected adults with long-term use of HAART (commonly non PI based regimens) showed a greater risk of having gingival bleeding on probing and oral lesions than their counterparts on short – term HAART.[10] In contrast, Bretz et al found that adult patients who received antiretroviral therapy (ART) had a less occurrence of dental caries than patients not taking these medications.[11] The studies involving children with regard to HIV infection have focused on reporting the prevalence of oral lesions and not the effect of HAART on oral health outcomes These studies reported high prevalence of dental caries.[12,13] However 1 study from the Unites States involving youth aged between 10 and 18 years explored the association between combination antiretroviral therapy (cART) and oral health outcomes (dental and periodontal) lesions and found that youth who had received combination antiretroviral treatment containing integrase inhibitors had significantly higher number of teeth with untreated active caries than those with cART without intergrase inhibitors. This study also found that the youth with later initiation of PIs had significantly higher decayed, missing filled teeth/surfaces (DMFT/S) scores than the youth initiating PI at an earlier stage.[14] Other oral health conditions like reduced salivary flow rates and salivary gland engorgement have also been associated with HAART and specifically with PI based HAART.[10,15]

The literature regarding the association of HAART with oral conditions shows mixed findings. The long-term impact of exposure to HAART on children's oral health status is understudied and requires more documentation. The purpose of this study was to compare the effect of lopinavir-ritonavir and lamivudine on oral health indicators (dental caries, gingivitis, tooth eruption, and oral health related quality of life) of 5 to 7 year old HIV exposed uninfected children from the ANRS 12174 trial.

2. Methods

2.1. Study setting and design

This study presents data for analysis of secondary outcomes from the Ugandan mother-children pairs participating in the ANRS 12174 randomized trial (ClinicalTrials.gov no: NCT00640263) implemented between 2009 and 2012 and the ANRS 12341 follow-up study carried out between March 2017 and February 2018 in Mbale district, Eastern Uganda.[16]

In summary, the ANRS 12174 promoting infant health and nutrition in Sub African Africa: safety and efficacy-pre exposure propylaxis (PROMISE-PEP) trial was a multicenter randomized trial recruiting women in antenatal clinics at 4 African sites: Ouagadougou University Teaching Hospital (urban site in Burkina Faso), East London Hospital Complex (urban site in South Africa); Mbale Regional Referral Hospital (semi-rural site in Uganda); and Lusaka University Teaching Hospital (urban site in Zambia). The aim was to compare lopinavir–ritonavir with lamivudine (given from day 7 after birth until either 50 weeks or 1 week after cessation of breastfeeding) on the rate of HIV-1 transmission and adverse events among HIV-1-exposed uninfected infants in Africa. The participating mothers followed routine national prevention guidelines until day 7 postpartum when their new-borns were randomized to either lopinavir–ritonavir (Kaletra, Abbott, Chicago) or generic lamivudine. Detailed information about this trial has been published previously.[17] The inclusion criteria for the infants were: being singleton; breastfed at day 7 by their mothers; a negative HIV-1 DNA PCR at day 7; and having received any prevention of mother to child treatment. For the mothers the criteria were: being 18 years or older, having intention to continue breastfeeding, HIV-1 infected, and not eligible for ART at the time of the study (clinically determined or because CD4 count <350 cells per μL), not intending to move out of the area in the next year, and gave consent to participate for herself and her infant. The exclusion criteria were: new-borns who had clinical signs or biological abnormalities of grade 2 or higher on the US National Institutes of Health Division of AIDS adverse events grading tables, with exceptions for hemoglobin (not included if hemoglobin <120 g/L) and absolute neutrophil count (not included if neutrophils <1200 cells per μL [1.20×10^9/L]); or if they presented with serious congenital malformations or birthweight was 2.0 kg or lower.

During the ANRS 121741 PROMISE- PEP trial 7 day old babies were randomized to the lopinavir–ritonavir or lamivudine in a 1:1 ratio (Fig. 1). The study participants and data collectors, data managers, and statisticians were masked to the allocation arm. However, given the poor palatability of lopinavir-ritonavir, some parents might have known their child's treatment allocation. The infants received locally available pediatric liquid formulations of either lopinavir–ritonavir (Kaletra, Abbott); 40 mg of Lopinavir and 10 mg of ritonavir, twice a day if weighing 2 to 4 kg, and 80 mg and 20 mg, twice a day if weighing >4 kg) or generic lamivudine (7.5 mg twice a day if weighing 2–4 kg, 25 mg twice a day if weighing 4–8 kg, and 50 mg twice a day if weighing >8 kg).

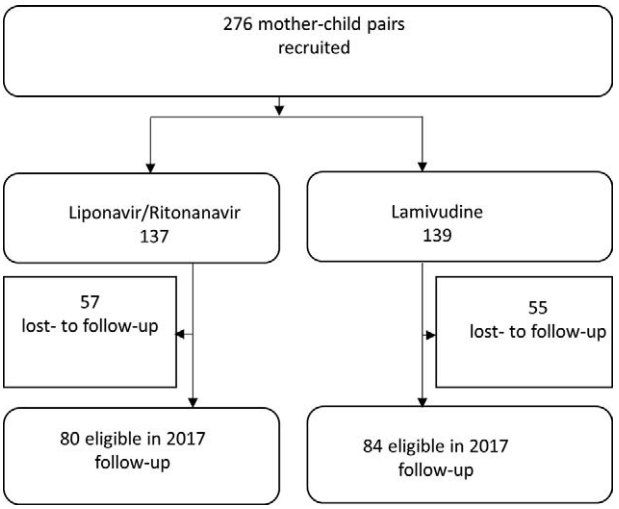

Figure 1. Trial profile.

Two hundred seventy-six infants were recruited to the Ugandan site of the ANRS 121741 PROMISE-PEP trial with 137 (50%) randomized to lopinavir–ritonavir and 139 (50%) to lamivudine. In 2017, in a follow-up visit at the age of around 6 years, 166 children were followed-up. Two of the children were excluded due to HIV seroconversion with 164 eligible for enrollment. The loss to follow-up was 42% and 40% in the Lopinavir-ritonavir and lamivudine groups, respectively. The reasons for loss to follow were relocation and child deaths (Fig. 1).

2.2. Primary outcomes

The outcomes of this study were: dental caries experience, gingivitis, oral health related quality of life, number of retained primary and erupted permanent teeth.

2.3. Interview with mothers at baseline (7 days post-partum) and follow-up (2017)

Data at baseline and follow-up was collected using semi-structured interviews with mothers in the local language (Lumasaaba). Details of data collection and capture are described elsewhere.[16,18] The oral health questionnaire used at follow-up has been developed and tested previously in a similar population.[19] The oral health data was entered in Epidata software (www.epidata.dk). The interview schedule included questions about socio-demographic characteristics in terms of age, sex, marital status, level of education, and type of income. A wealth index based on ownership of household assets, such as furniture, electricity, type of water source, roof material, and type of toilet assessed at the baseline interview, was constructed and categorized into wealth quintiles. This socio-economic asset index was initially categorized into quintiles ranging 1 to 5 (most poor–least poor) and then recoded into the 2 categories (ie, the poorest and least poor) for analysis. The oral health related quality of life (OHRQoL) was assessed at follow up in 2017 using.[20] a slightly modified and abbreviated version of the Early Childhood Oral Health Impact Scale scale previously assessed for its psychometric properties among preschool children in Uganda.[21] The scale, consists of the child impact section and family impact section, which are proxy measures of children's OHRQoL with parents as respondents to assist children in evaluating their own quality of life. The child impact section, was assessed using 5 of its original 9 questions, covering the original 4 subdomains: symptoms, function, psychology, self-image, and child social interaction. The family impact section was assessed using the original 4 questions covering 2 domains of family distress and family function. Response categories were rated on a 5-point Likert scale. Total OHRQoL scores were constructed by adding the Child and Family impact scores. A dichotomy variable in terms of "0" equal to no total OHRQoL impact and "1" equal to at least 1 OHRQoL impact was constructed for analyses.

2.4. Clinical oral examination of children at follow-up visit (2017)

The clinical oral examination was performed by 2 experienced dental surgeons (NB and MM). Dental caries were assessed on fully erupted primary teeth using the decayed, missing, and filled teeth index (dmft) in accordance with the World Health Organization guidelines for field conditions.[22] A tooth was documented as decayed if it was visually cavitated with the aid of a dental mirror and periodontal probe. A tooth was qualified as missing when extracted due to caries, as confirmed by the mother. In the present analysis, dmft was used as a count variable and a dichotomous variable. The count variable was the sum of the decayed, missed or filled teeth. The dichotomized variable was categorized as absent for dmft count equal to "0" and present for dmft count greater than "0." To assess gingivitis of the children, the modified community periodontal index was used.[22] Each tooth was scored according to the presence or absence of gingival bleeding, indicative of presence or absence of gingival inflammation, using a periodontal probe across the gingival margins of the teeth.

The retained primary teeth and permanent dentition were assessed by manually counting the retained primary and fully erupted permanent teeth.

2.5. Reliability measurements

Duplicate clinical examinations were carried out after 2 weeks by dental surgeons (NB and MM) with 26 children not involved in the original study cohort but considered to be representative of the study participants. The calibration exercise comparing dmft scores for each primary tooth within and between examiners revealed intra- and inter-rater reliability of median Kappa (interquartile range) of 0.6 (0.5–0.7) and 0.7 (0.5–0.8), respectively. The corresponding scores for the DMFT of caregivers were 0.7 (0.5–0.9) and 0.6 (0.4–0.8), respectively.

2.6. Data cleaning and statistical analysis

The statistical package Stata/SE 16 (Stata Corp LLC, College Station, TX) was used for analysis. To compare baseline characteristics at randomization in the study sample at follow-up, means for continuous and proportions for categorical variables were used. Negative binomial regression with incidence rate ratio (IRR) and 95% confidence intervals (CIs) was used to assess the effect of lopinavir-ritonavir or lamivudine on dmft count and OHRQOL impacts. Logistic regression with odds ratios and 95% CIs was used to assess the effect of lopinavir-ritonavir or lamivudine on gingivitis, OHRQoL, and dental caries experience (dmft >0). To adjust for potential differences in loss-to-follow- up between study groups an inverse probability weight method with a probit regression was used to predict risk of lost-to-follow-up based on social economic position, years of education, and site of residence. The median of the inverse probability weight was 1.8

2.7. Ethics

Ethical approval for the study was granted by the Makerere University School of Medicine Research Ethics Committee (REC REF 2018-030) and the Uganda National Council for Science and Technology (HS 2373), and Regional Committees for Medical and Health Research Ethics, Western Norway [(REK) (2017/760/REC Sør-Øst)]. Signed or thumb-printed informed consent was obtained from each mother before study participation. The consent procedure was approved by the ethics committees.

3. Results

3.1. Sample characteristics

The baseline characteristics of the 164 children analyzed at follow-up, paralleled those at baseline and there were similar numbers of participants in the lopinavir–ritonavir (n = 80) and lamivudine (n = 84) treatment groups, respectively. With regard to loss to follow-up, the number lost was similar across the treatment groups with respect to both the categorical and continuous variables. However, loss to follow up was more likely among slightly younger women and women with higher viral load. Median maternal age (interquartile range) in the study group at baseline was 27 (23–28) and 28 (23–30) in the lopinavir-ritonavir and lamivudine treatment groups, respectively. Corresponding figures among those lost to follow up were 25 (23–28) and 25 (22–28) years. The viral load in the study group at baseline was 150 (150–338) and 150 (150–1396) viral copies/μL in the lopinavir-ritonavir and lamivudine treatment groups, respectively. Corresponding figures among those lost to follow up were 228 (150–3376) and 293 (150–3476) viral copies/μL (Table 1).

As indicated in Table 2, the average age of the children at follow was 6 years across the treatment groups. The prevalence of dental caries was 48% (dmft >0) in the total study group and 49% and 48% in the lopinavir-ritonavir and lamivudine treatment groups, respectively. The corresponding mean dmft and standard deviation values were 1.7 (2.4) and 2.3 (3.7). The pattern of mean dmft was similar across the treatment groups with most of anterior teeth in the upper jaw and molars depicting higher frequency as is the usual pattern of dmft experience (Fig. 2). The average number of retained primary teeth was comparable across treatment groups and amounted to 17 teeth. The lopinavir group had on average a lower number of erupted permanent teeth than the lamivudine group with a mean number (standard deviation) of 3.8 (3.7) and 4.6 (3.9) teeth, respectively (Fig. 3). A small percentage of mothers, (13%), reported impacts on oral health, with 7% and 18% in the lopinavir-ritonavir and lamivudine groups, respectively. The prevalence of gingival bleeding was 12% in the study sample with 7% and 14% in the lopinavir-ritonavir and lamivudine treatment groups, respectively.

Negative binomial regression did not indicate statistically significant differences between the treatment groups with respect to dental caries experience, gingivitis, retained primary teeth, and erupted permanent teeth. The corresponding IRRs, with 95% CIs were 0.7 (0.4–1.3), 0.3 (0.05–1.8) and 0.8 (0.6–1.2), respectively. There were 70% less impacts reported in lopinavir-ritonavir group than in the lamivudine treatment group with IRR of 0.3 (95% CI: 0.1–0.9) (Table 3).

Logistic regression showed no significant differences between the treatment groups with respect to dental caries experience, gingivitis, and oral health related quality of life. The corresponding odds ratio (95% CIs): were 1.0 (0.6–2.0), 0.6 (0.2–1.5) and 0.4 (0.1–1.0) respectively (Supplemental Digital Content [Additional file], Table SI, http://links.lww.com/MD/E914).

Table 1

Baseline characteristics (number and percentage [n and %]) among those included and lost to follow-up by treatment arm.

Categorical variables	lopinavir-ritonavir n (%)	Lamivudine n (%)	Loss to follow-up lopinavir-ritonavir n (%)	Loss to follow-up lamivudine n (%)
Eligible mother infant pairs	80 (49)	84 (51)	57 (42)	55 (39)
Marital status				
Married/cohabiting	69 (86)	73 (87)	42 (73)	42 (76)
Socio-economic status quintile				
1–2 (poorest)	52 (65)	51 (61)	47 (82)	41 (75)
3–5	28 (35)	33 (39)	10 (17)	13 (24)
Education level				
None	4 (5)	3 (3)	4 (7)	2 (4)
Primary	48 (60)	47 (56)	34 (60)	34 (63)
Secondary or more	28 (35)	34 (40)	19 (33)	18 (3
HIV clinical staging				
Stage I	75 (94)	75 (89)	52 (91)	52 (94)
Stage II	5 (6)	8 (9)	5 (9)	3 (5)
Stage III	0 (0)	1 (1)	0 (0)	0 (0)
Detectable viral load				
Yes	58 (72)	50 (63)	33 (57)	34 (64)
Child sex				
Girls	42 (52)	40 (47)	34 (60)	30 (54)
Continuous data	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Maternal median age (yr)	27 (23–30)	28 (23–30)	25 (23–28)	25 (22–28)
Maternal body -mass index day 7 (kg/m^2)	23 (21–24)	23 (20–24)	22 (20–24)	22 (21–25)
Maternal CD4 cell count day 7	523 (432–617)	527 (441–612)	524 (417–643)	515 (418–6625)
Maternal HIV viral copies/μL	150 (150–338)	150 (150–1396)	228 (150–3376)	293 (150–3476)
Child median birth weight (grams)	3000 (2750–3300)	3100 (2930–3350)	3000 (2700–3300)	3000 (2800–3400)

IQR = interquartile range.

4. Discussion

According to the present findings, having received lopinavir-ritonavir or lamivudine during the trial period did not have a significant long term effect on children's dental caries experience, gingivitis, the number of retained primary- and erupted permanent teeth at follow-up. In contrast, children receiving lopinavir-ritonavir were less likely than their counterparts receiving lamivudine to experience oral impacts or reduced oral health related quality of life at follow up.

Table 2

Summary data; mean, standard deviation (SD), number (n), and proproptions (%) in the total group and by treatment allocation at follow-up.

Variable	All n = 164	Lopinavir-ritonavir n (%)	Lamivudine n (%)
Continuous variables (mean, SD)			
Mean child age (SD)	6.0 (0.7)	6.0 (0.8)	6.0 (0.5)
Mean no of erupted permanent teeth (SD)	4.2 (3.8)	3.8 (3.7)	4.6 (3.9)
Mean no of retainedprimary teeth (SD)	17 (7.2)	17 (2.4)	17 (9.8)
dmft* score	2.0 (3.2)	1.7 (2.4)	2.3 (3.7)
Categorical	n (%)		
dmft >0			
Yes	79 (48%)	39 (49)	40 (48)
Gingival bleeding present			
Yes	19 (12)	7 (9)	12 (14)
Child impact score >0			
Yes	19 (12)	5 (6)	14 (17)
Family impact score >0o			
Yes	11 (7)	2 (2)	9 (11)
Child and family impact score >0			
Yes	21 (13)	6 (7)	15 (18)

* Decayed, missing filled teeth.

The random assignment of children is a strength of this study as randomized trial designs minimize the risk of confounding. Furthermore, the dental examiners and research assistants were blind to the allocation status of study participants limiting possible measurement bias.

Due to the long follow-up time, there was attrition, which reduced the sample size. This could have led to unequal groups and a problem with differential loss to follow up. However, we compared baseline characteristics in the available study sample and those lost to follow-up and as reported the treatment groups remained comparable indicating that the randomization had been maintained. Also, the reduced sample size could involve the epidemiological possibility of type II errors. The non-statistically significant differences were predominantly smaller. We acknowledge the limitation that assessment of dental caries at cavity level under field conditions without using x-rays might lead to underestimation of dental caries prevalence as the early incipient lesions are left out.

It is difficult to compare the findings of this study with other studies. This is because most of the literature focuses on persons with HIV infected on ART while our study involved HIV exposed uninfected children who had received lopinavir-lopinavir or lamuvudine to prevent vertical transmission. A study from the US focusing on the effect of cART on oral outcomes (dental caries

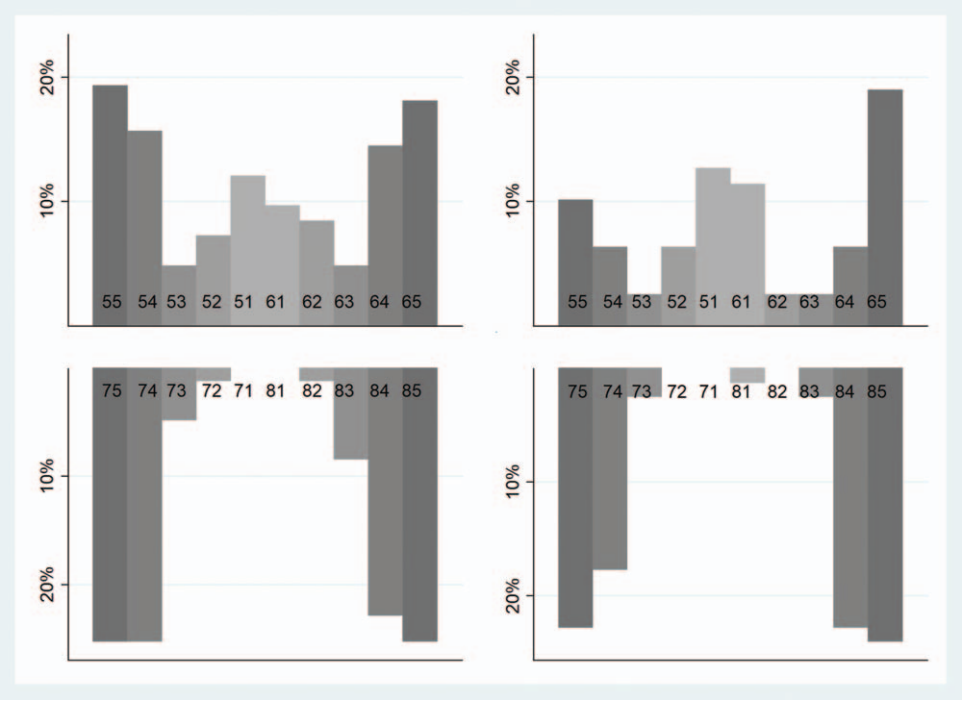

Figure 2. Distribution of mean dmft (decayed, missing filled teeth) by tooth type in the maxilla for lopinavir-ritonavir (top left) and lamivudine (top right) group. Also distribution of mean dmft in mandible lopinavir-ritonavir (bottom left) and lamivudine group (bottom right).

and periodontal) found that perinatally HIV infected youth initiated later on PIs had significantly higher DMFT/S scores than periantally HIV youth initiated to the PIs at an earlier age.[14] However, this study unlike our study whose children were taking HAART as prophlaxis to prevent vertical transmission, excluded children who were taking HAART as propylaxis Thus, our study is one of the first to investigate the potential effect of antiretroviral drugs on children's oral health independent of HIV infection. So far research findings are mixed with some studies indicating that HAART is not associated with dental caries[8,9] while other studies have found both negative[11] and positive associations between HIV infected people on HAART and dental

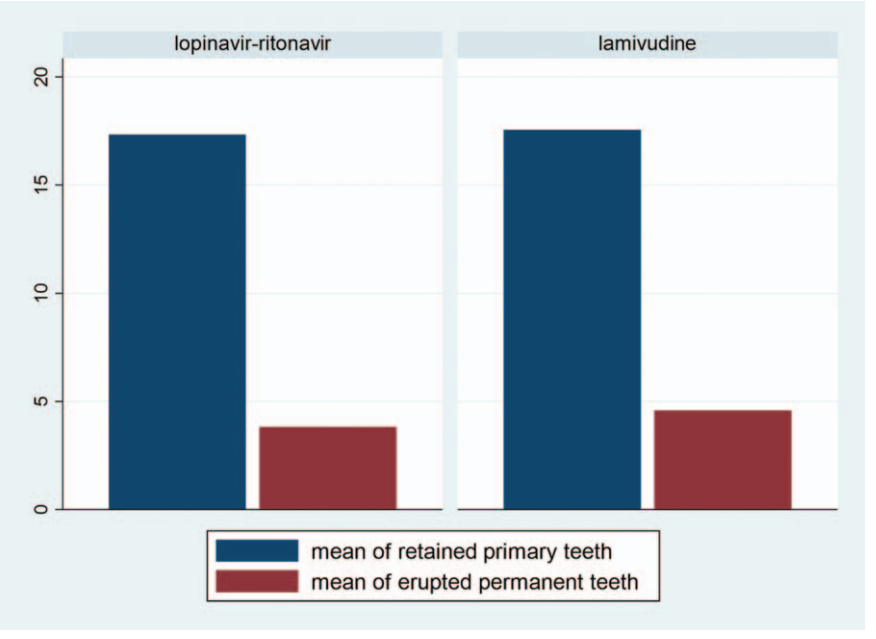

Figure 3. Average numbers of retained primary teeth and erupted permanent teeth in lopinavir-ritonavir and lamivudine treatment groups.

Table 3

Dental caries experience, oral health related quality of life, retained primary teeth, and number of erupted permanent teeth by treatment group using negative binomial regression.

	Dental caries experience	Oral health related quality of life	Retained primary teeth	Erupted permanent teeth
Neg Binomial reg	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Lopinavir-ritonavir	0.7 (0.4–1.3)	0.3 (0.1–0.9)	1.0 (0.9–1.1)	0.8 (0.6–1.2)
Lamivudine	1	1	1	1

CI = confidence interval, IRR = incidence rate ratio.

caries.[10,23,24] Thus, Kalanzi et al and Glick et al published case reports that recommended further studies. In other studies involving the ANRS 12174 trial participants, Blanche et al observed less weight gain in infants given lopinavir–ritonavir while Kariyawasam et al. found lopinavir–ritonavir to be associated with dose dependent adrenal dysfunction.[7]

A possible explanation for lesser-reported oral impacts reported in the lopinavir-ritonavir group could be due to higher prevalence of gingivitis, dental caries, and number of teeth in the lamivudine group compared to the lopinavir-ritonavir group although this was not statistically significant. It has been established in the literature that oral health impacts are associated with clinical findings but is also influenced by social and cultural factors.[21,25]

Further research is recommended to further clarify the relationship of HAART on oral health of children.

5. Conclusions

HIV exposed uninfected infants in the lopinavir-ritonavir group reported less impacts on oral health than their counterparts in the lamivudine treatment group. Dental caries, gingivitis, and tooth eruption were not significantly affected by lopinavir-ritonavir or lamivudine pre exposure prophylaxis.

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