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ANTIVIRAL AGENTS

Efficacy of Three Antiretroviral Regimens Initiated during Pregnancy: Clinical Experience in Rio de Janeiro

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ABSTRACT Few studies have compared the clinical efficacy and adverse events of combined antiretroviral therapy (cART) regimens in pregnant women seeking obstetrical care. The objective of this study was to compare the efficacy (virus load response), adverse events, and obstetrical and neonatal outcomes of three different regimens of cART in HIV-infected pregnant women initiating treatment in Rio de Janeiro, Brazil. This was a retrospective cohort study of cART-naive pregnant women who initiated either ritonavir-boosted protease inhibitors (atazanavir or lopinavir), efavirenz, or raltegravir plus a backbone regimen. From 2014 to 2018, 390 pregnant women were followed over time. At baseline, the median viral load (VL) for HIV was 4.1 log copies/ml. Among participants who received cART for 2 to 7 weeks, the VL decline was greater for raltegravir (2.24 log copies/ml) than for efavirenz or protease inhibitors ($P < 0.001$). Virologic suppression was achieved in 87% of women on raltegravir near delivery versus 73% on efavirenz and 70% on protease inhibitors ($P = 0.011$). Patients on raltegravir achieved virologic suppression faster than those on other regimens ($P = 0.019$). Overall, the HIV perinatal infection rate was 1.5%. This clinical study compared three potent and well-tolerated cART regimens and demonstrated that a higher proportion of participants on raltegravir achieved an undetectable HIV VL near delivery ($P = 0.011$) compared to the other arms. These findings suggest that raltegravir-containing regimens are optimal regimens for women with HIV initiating treatment late in pregnancy.

KEYWORDS HIV, integrase inhibitors, raltegravir, protease inhibitors, efavirenz, mother-to-child transmission, obstetrics, pregnancy, cesarean, nonnucleotide reverse transcriptase inhibitors, perinatal transmission

As of 2020, there were 38 million people living with HIV worldwide, of whom approximately 25.4 million had access to antiretroviral therapy (ART) (1). The World Health Organization and most guidelines worldwide recommend universal treatment for all people living with HIV (2–7). Globally, approximately 80% of pregnant women have access to ART (8), while the use of combined ART (cART) has reduced vertical transmission (VT) in nonbreastfeeding women to <1% (9). cART regimens inhibit HIV from infecting new cells by targeting different phases of the viral life cycle (10). The main goal for the prevention of mother-child transmission (PMTCT) is the use of potent cART regimens to reduce HIV viral load (VL) in order to decrease the risk of VT. Three different regimens of ART: non-nucleoside reverse transcriptase inhibitors, protease inhibitors (PIs), and integrase inhibitors, along with a two-nucleoside reverse transcriptase inhibitor (NRTI) backbone, are the pillars of prevention of HIV VT worldwide (3–7).

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These regimens have distinct adverse event rates of and virologic suppression profiles in nonpregnant populations.

Despite the widespread use of efavirenz (EFV), ritonavir-boosted lopinavir (LPV/r), ritonavir-boosted atazanavir (ATV/r), and raltegravir (RAL), there have been relatively few comparisons of the efficacy, tolerability, and frequency of adverse events among these ART regimens when used during pregnancy. At our institution, the main regimens recommended are RAL, EFV, LPV/r, and ATV/r plus ART backbone regimens. The purpose of this study was to compare the efficacy and frequency of adverse events among women living with HIV (WLH) initiating one of three distinct cART regimens during pregnancy in Rio de Janeiro (11).

RESULTS

Between 8/2014 to 10/2018, 696 WLH registered for care at our prenatal clinic. For the cART efficacy analysis, 306 patients were excluded as seen in Fig. 1A. Among the excluded 14 women who switched cART during gestation, 10 did so for drug side effects, 2 for patient preference, 1 for virologic failure, and 1 for cART discontinuation against medical advice. The final sample size for the efficacy analysis was 390 mother-infant pairs. The NRTI backbone used most frequently was lamivudine plus tenofovir (3TC+TDF) (56%) with the remaining mothers taking zidovudine plus 3TC (ZDV+3TC) (44%). During the study, the standard of care cART regimen changed over time; in the first 2 years, protease inhibitor (PI)-based therapy was the preferred regimen.

The median age of 390 study participants was 26 years (interquartile range [IQR], 22 to 31 years), and the median gestational age at study entry was 19 weeks (IQR, 14 to 25 weeks), as seen in Table 1. The median gestational age differed among patients in the three regimen arms ($P = 0.04$). Women in the EFV group enrolled at a lower gestational age than those in the RAL group ($P = 0.02$). Further, women in the EFV group had more prenatal visits than those in the LPV/r and ATV/r group ($P = 0.02$). Baseline CD4 cell counts and HIV VL were comparable between patients receiving the three regimens. At baseline, the overall median HIV VL was 4.1 $\log_{10}$ copies/ml, and the median CD4 cell count was 437 cells/mm^3.

Overall, across the three cART regimens, the median duration of cART exposure was 17 weeks. However, duration differed among regimens ($P = 0.017$, Table 2), with the median duration of RAL treatment lasting 14 weeks versus 18 weeks for EFV ($P = 0.04$) and LPV/r or ATV/r ($P = 0.019$). In terms of efficacy, 75.1% of participants achieved suppression near delivery below the assay detectable range of 40 copies (cp)/ml. Patients in the RAL arm had a higher proportion of virologic suppression (87.2%) than patients in the EFV (72.9%) or LPV/r and ATV/r arms (69.8%) ($P = 0.011$, Table 2). The virologic response for RAL in weeks 2 to 7 of treatment was far greater among patients receiving this drug than in the EFV- or PI-based regimen arms ($P = 0.019$) (Fig. 2). In particular, the log reductions in VL were 2.24 for RAL, 1.76 for EFV, and 1.83 for LPV/r and ATV/r (Fig. 2). After week 7, there was no difference among regimens in regard to rate of virologic suppression. The time to virologic suppression was significantly shorter for RAL than for the other cART regimens ($P < 0.0001$). The number of elective cesarean sections (C-sections) was lower in the RAL treatment arm for this reason, since more patients in this arm achieved virologic suppression. Of the 147 elective C-section deliveries performed in study participants, 29% were in patients in the RAL arm, as opposed to 39% in the EFV arm and 42% in the PI arm. The difference in the rate of C-sections among arms was not significant.

Ninety percent of 470 participants had no drug-related adverse events during pregnancy, as seen in Fig. 1B (see also Table S1 at http://fullertl.bol.ucla.edu/BenamorSupportingInformation.pdf), which demonstrates good tolerability overall. None of the noted adverse events was severe. The most common adverse events discontinuing a study regimen were nausea/vomiting (6%) and dizziness (2%) (see Table S1 in the supplemental material).

The overall VT rates were 1.5% 6/390 [2.7% with EFV ($n = 5$), 1.5% with RAL ($n = 1$), and 0 with PI-based regimens ($P = 0.19$)]. Four mothers who transmitted HIV to their

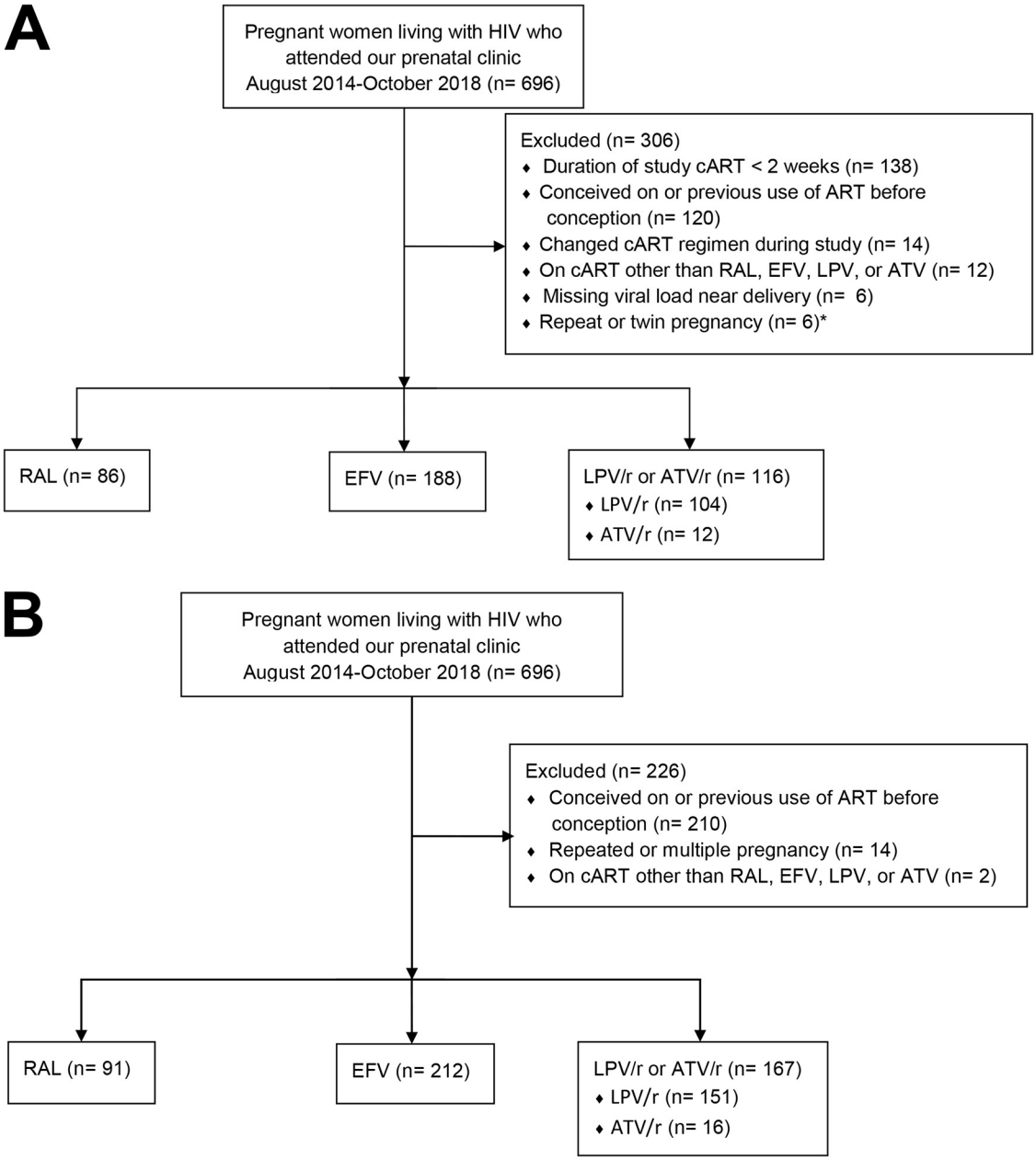

FIG 1 (A) Flow chart of participants enrolled in the efficacy, obstetric, and neonatal outcomes analysis ($n = 390$ final participants). *, some participants met multiple exclusion criteria. (B) Flow chart of participants enrolled in the analysis of adverse events ($n = 470$ final participants).

infants had genotypic tests performed during pregnancy. Three did not have any resistance mutations detected, and one had resistance to EFV detected close to delivery. Among the six mothers who transmitted HIV to their infants, only one had achieved virologic suppression by the time of delivery. Two of the six cases represented *in utero* transmission because the infant had detectable VL at birth. Details on the six episodes of HIV transmission are presented in Table S2 (http://fullertl.bol.ucla.edu/BenamorSupportingInformation.pdf). In addition to the timing of initiation of cART during pregnancy, nonadherence to cART may have played a role in some cases where patients initiated treatment relatively early in pregnancy but still transmitted infection to their infants, with a high virus load levels detectable close to delivery. Rates of preterm birth, low birth weight, and neonates small for gestational age did not differ

TABLE 1 Baseline sociodemographic, immunological, and virologic characteristics of the study cohort of pregnant women living with HIV in Rio de Janeiro, 2014 to 2018 ($n = 390$)

Variables	No. (%) for various cART regimens[a]				P[b]
	Total	RAL	EFV	LPV/r or ATV/r	
Age ($n = 388$)					0.54
<20	51 (13.1)	13 (15.1)	23 (12.2)	15 (12.9)	
20–29	213 (54.6)	45 (52.3)	112 (59.6)	56 (48.3)	
30–39	119 (30.5)	27 (31.4)	52 (27.7)	40 (34.5)	
>40	5 (1.3)	1 (1.2)	1 (0.5)	3 (2.6)	
Ethnicity ($n = 385$)					0.23
White	89 (22.6)	24 (27.9)	34 (18.1)	30 (25.9)	
Nonwhite	297 (76.2)	67 (70.9)	152 (80.9)	84 (72.4)	
Not reported	5 (1.3)	1 (1.2)	2 (1.1)	2 (1.7)	
Marital status ($n = 384$)					0.053
Single/widowed/divorced	163 (41.8)	43 (50)	39 (43.1)	39 (33.6)	
Married/stable union	221 (56.7)	41 (47.7)	75 (55.9)	75 (64.7)	
Unknown	6 (1.5)	2 (2.3)	2 (1.1)	2 (1.7)	
Education ($n = 379$)					0.001
0–4 yrs	19 (4.9)	1 (1.2)	6 (3.2)	12 (10.3)	
5–9 yrs	161 (41.3)	26 (30.2)	77 (41)	58 (50)	
10–14 yrs	189 (48.5)	50 (58.1)	97 (51.6)	42 (36.2)	
>15 yrs	10 (2.6)	1 (1.2)	5 (2.7)	4 (3.4)	
Not reported	11 (2.8)	8 (9.3)	3 (1.6)	0 (0)	
Syphilis coinfection[c] ($n = 362$)	36 (9.2)	5 (5.8)	17 (9)	14 (12.1)	0.42
Median no. of prenatal visits (IQR)[d]	8 (6–10)	7 (6–10)	8 (6–10)	7 (5–9)	0.02
Median % CD4 (IQR) ($n = 390$)	25.6 (19.2–33.5)	26.3 (18.9–32)	25.4 (19.2–33.8)	25.6 (19.2–33)	0.97
CD4 (counts/mm^3)					0.73
<200	50 (12.8)	11 (12.8)	26 (13.8)	13 (11.2)	
≥200 to <500	180 (46.2)	42 (48.8)	80 (42.6)	58 (50)	
≥500	160 (41)	33 (38.4)	82 (43.6)	45 (38.8)	
Median VL $\log_{10}$ cp/ml (IQR) ($n = 390$)	4.1 (3.4–4.7)	4.1 (3.4–4.5)	4.05 (3.4–4.6)	4.15 (3.5–4.8)	0.48
Median gestational age in yrs (IQR) at cART initiation ($n = 380$)	19 (14–25)	21 (14–29)	19 (14–25)	18 (14–24)	0.04

[a]Values represent the number (%) of patients unless noted otherwise in column 1.
[b]cART regimens were compared using chi-squared tests for discrete outcomes and ANOVA or the Kruskal-Wallis test for continuous variables.
[c]As determined using a VDRL nontreponemal test and confirmed by a fluorescent treponemal antibody absorption test.
[d]IQR, interquartile range.

significantly among regimens (Table 2). Stillbirths (one EFV and two LPV/r or ATV/r) and perinatal mortality (one RAL and one LPV/r or ATV/r) were also the same across regimens (Table 2).

DISCUSSION

This clinical study of pregnant women living with HIV, which compared patients receiving RAL-, EFV-, or PI-based regimens, found that all three regimens were potent against HIV. However, RAL-based regimens induced a 2.24-$\log_{10}$ reduction in maternal VL in the first 2 to 7 weeks of treatment, which was significantly greater than the virologic decline observed for the other regimens. The average duration of RAL exposure was 2 weeks shorter than that of the other regimens. However, the proportion of women who achieved virologic suppression below the threshold of detection near delivery on RAL was higher than the proportion of women who were on EFV- or PI-based regimens. The overall HIV VT rate of 1.5% described in this study was consistent with that of recent studies from developed countries (12, 13).

Our findings regarding virologic response of the three different cART regimens are supported by previous studies in pregnant populations, which evaluated distinct outcomes from that of our study. In IMPAACT NICHD P1081, an open-label trial in 408 ART-naive pregnant women, which compared the virologic suppression of RAL and EFV-containing regimens, 94% of women in the RAL group and 84% of women in the

TABLE 2 Maternal, obstetric, and neonatal outcomes for cART regimens of the study cohort of pregnant women living with HIV in Rio de Janeiro, 2014 to 2018 ($n = 390$)

Variable	No. (%) for various cART regimens[a]				P[b]
	Total	RAL	EFV	LPV/r or ATV/r	
Maternal and obstetric outcomes					
VL undetectable near delivery[c] ($n = 390$)	293 (75.1)	75 (87.2)	137 (72.9)	81 (69.8)	0.011
Vaginal delivery	163 (41.8)	42 (48.8)	75 (39.4)	46 (39.7)	0.1574
Emergency C-section	58 (14.9)	12 (13.9)	30 (16)	16 (13.8)	
Elective C-section	147 (37.7)	25 (29.1)	73 (38.6)	49 (42.2)	
C-section type unknown	6 (1.5)	4 (4.7)	2 (2.3)	0 (0)	
Mode of delivery unknown	16 (4.1)	3 (3.5)	8 (4.3)	5 (4.3)	
Stillbirth	3 (0.8)	0 (0)	1 (0.5)	2 (1.8)	0.33
Median VL $\log_{10}$ cp/ml (IQR) near delivery (34–36 wks)	2.2 (1.8–2.9)	1.8 (1.7–1.9)	2.1 (17–2.8)	2.4 (2.1–2.9)	0.568
Median (IQR) change in CD4 cell count from baseline ($n = 356$)	4.2 (0.2–8.4)	4.4 (0–8.1)	3.7 (0–8.2)	4.2 (1.4–8.7)	0.714
Median wks cART exposure (range)	18 (11–22)	14 (9–20)	18 (10–23)	18 (13–23)	0.017
Neonatal outcomes					
Neonatal mortality ($n = 388$)	2 (0.5)	1 (1.2)	0 (0)	1 (0.9)	0.378
HIV vertical transmission ($n = 380$)	6 (1.5)	1 (1.3)	5 (2.7)	0 (0)	0.19
Low infant birth wt (<2,500 g) ($n = 366$)	45 (11.5)	5 (5.8)	22 (11.7)	18 (15.5)	0.11
Preterm birth (<37 wks gestation) ($n = 361$)	37 (9.5)	6 (7)	15 (8)	16 (13.8)	0.163
Small for gestational age ($n = 307$)	38 (9.7)	8 (13.6)	15 (9.9)	14 (14.4)	0.15
Mean birth wt (g) (CI)[d]	3,029 (2,975–3,082)	3,143 (3,035–3,251)	3,024 (2949–3,099)	2,966 (2,66–3,066)	0.08

[a]Values represent the number (%) of patients unless noted otherwise in column 1.
[b]cART regimens were compared using chi-squared tests for discrete outcomes and ANOVA or the Kruskal-Wallis test for continuous variables.
[c]Viral load near delivery and weeks of cART exposure were available for all participants (no data were missing).
[d]CI, 95% confidence interval.

EFV group achieved undetectable viral loads at delivery (14, 15). The P1081 trial assessed virologic efficacy in 408 patients, and another study in Brazil comparing LPV/r and RAL reported similar findings (16). The results of our study are consistent with those reported for the Dolphin trial since the proportion of participants in the integrase inhibitor RAL arm achieving virologic suppression was also higher than the proportion of patients achieving suppression in the EFV arm (17, 18).

In the present study, pregnant women had a median duration of cART exposure of 18 weeks. When stratified for time of cART exposure and type of ARV regimen used, the subset of women who used ART for 2 to 7 weeks in the RAL arm, had a 2.24-$\log_{10}$

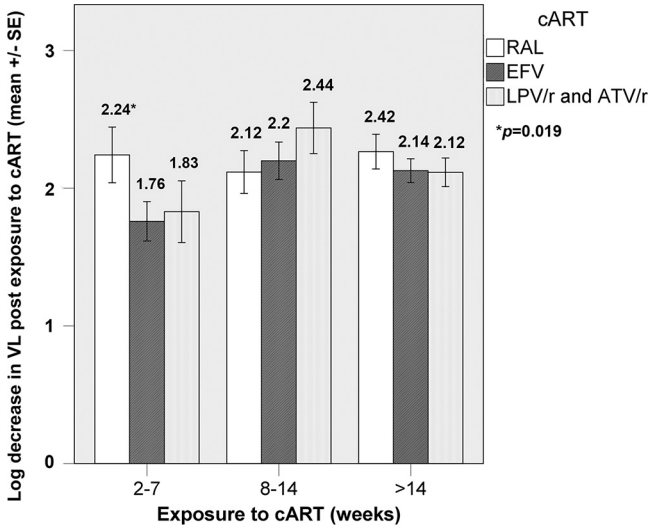

FIG 2 Comparison of virologic suppression during pregnancy among patients in different regimens.

decrease in HIV VL, which was significantly higher than that of women in the other two arms (EFV and LPV/r or ATV/r). A study in ART-naive nonpregnant populations comparing RAL and EFV-containing regimens demonstrated that the proportion of patients achieving HIV VL below the detectable threshold was greater in the RAL arm at weeks 2, 4, and 8 (19). An observational study of nonpregnant participants in the United States reported that the time to undetectable viremia was significantly shorter for RAL than for regimens that did not contain integrase inhibitors (20). In our population, RAL had the highest rates of HIV suppression and a higher rate of VL reduction than other regimens. The highest proportion of women with undetectable VL levels near delivery in our study was in this arm.

As for drug related adverse events, as in a previous trial conducted in Brazil (16), boosted protease inhibitors had a higher proportion of side effects than RAL, but for all of the three regimens the proportion of adverse events was low. The most common adverse event among participants who discontinued any study regimen was nausea and/or vomiting. However, since nausea and vomiting are very common in pregnancy, we cannot differentiate adverse events caused by pregnancy from those associated with a particular cART regimen. Dizziness was the second most common adverse event in the EFV group (2%), which was comparable to other studies (14, 21).

The overall HIV VT across regimens was 1.5%. Five of six pregnant women who transmitted had detectable HIV VL near delivery and one was undetectable. Of interest, five of the six transmission episodes occurred in the EFV arm. In addition, these women had other risk factors for vertical transmission: 4/6 were late presenting pregnant women, while the mother with an undetectable HIV VL had active syphilis coinfection, which has been shown to be associated with VT (12, 22). Infection likely occurred before birth in two of the six cases as the infants had detectable VL at birth. One transmitting mother developed EFV drug resistance detectable at the time of delivery. At study entry, maternal virus was sequenced, and the genotype assay detected no mutations associated with EFV resistance. Genotypic resistance may have occurred during pregnancy possibly due to poor cART adherence (23). We found no relationship between PIs and preterm delivery, but other studies have reported such an association (24).

The strengths of this study include a large sample size of patients seeking clinical care at a single HIV-referral institution. One of the study limitations was that this was not a randomized clinical trial but an observational cohort of patients monitored over the years, subject to evolving antiretroviral guidelines which shifted over time from ritonavir boosted protease inhibitors to efavirenz and later raltegravir. Nevertheless, one advantage of this observational clinical scenario is that it confirms whether findings of clinical trials can be duplicated in clinical settings when the rigors of randomization and study window visits are lifted, which is what we concluded in the present analysis. Although there could be a concern for recruitment bias in observational cohort studies, because cART therapy in Brazil is provided by the Single Unified Brazilian Health Care System (SUS), practitioners adhere more rigorously to national guidelines in order to enable dispensation of prescriptions from public pharmacies. In this sense, prescribing patterns are somewhat rigid and do not tend to deviate from national guidelines, almost as in a randomization assignment. Adherence monitoring in our study was based on comparing baseline VL to VL near delivery. Participants whose VL increased by at least 1 log were considered nonadherent. Furthermore, analysis of pharmacy records of patients referred to our center indicates that 72% conceived on ART and 82% refilled their prescriptions postpartum (25). In summary, RAL resulted in a a better early virologic response and was better tolerated than other regimens in our patient population. Taken together, these findings suggest that RAL-containing regimens are a preferred option for women living with HIV who present late in pregnancy in clinical practice.

MATERIALS AND METHODS

This was a retrospective cohort study of pregnant WLH who were ART naive and who were monitored with their neonates at a reference center for HIV PMTCT in Rio de Janeiro, Brazil (Hospital Federal dos Servidores do Estado). A detailed description of our institution's cohort has been previously

published (11). In the present study, patients were followed between August 2014 and October 2018. For all patients who were referred to our center, the HIV diagnosis was confirmed using the Brazilian Ministry of Health algorithm (26). Participants were prescribed either RAL 400 mg twice daily, EFV 600 mg once daily, LPV/r 400/100 mg twice daily (increased to 600/150 mg during the third trimester of pregnancy), or ATV/r 300/100 mg once daily plus a two-NRTI backbone, which was either zidovudine (ZDV) 300 mg twice daily plus lamivudine (3TC) 300 mg once daily or tenofovir (TDF) 300 mg once daily plus 3TC 300 mg once daily.

The ART regimen was chosen based on national guidelines, which changed during the course of the study. During the first half of the study, Brazilian guidelines recommended RAL solely for late-presenters (after gestational week 28). During the final years of the study, starting in 2017, national guidelines were changed to recommend the use of RAL for all pregnant women. Since antiretrovirals are provided free of care in Brazil under the Single Unified System (SUS) through hospital-based pharmacies, cART regimens prescribed to patients follow strict adherence to national guidelines. During routine medical visits, physicians filled out medical records using standardized forms. Standardized case report forms were filled out with data obtained during these visits and were used to populate our center's database. The aforementioned data were entered into the database, anonymized, and subsequently were utilized in the present analysis. The center had SOPs (site operating procedures) developed for data management and a quality assurance/quality control (QAQC) procedure through which data collected from all patients is subject to the same stringent review.

During medical visits, data on maternal demographics were collected, including maternal age at cohort entry, ethnicity, gestational age, and years of education, as well as medical history. Trimestral ultrasound evaluations were carried out, and laboratory data were collected, including treponemal and nontreponemal tests, urine cultures, CD4 T cell percentages and absolute counts, and IgG and IgM levels for anti-HAV and hepatitis B markers (HBsAg, Anti-HbsAg, and Anti-HBc). In addition, we also extracted the data concerning the following tests: transaminases, bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase.

HIV RNA VL cp/ml were measured at entry, 2 to 4 weeks after initiation of cART, subsequently once per trimester, and then near delivery (34 to 36 weeks; Abbott Real Time; Abbott Molecular, Inc.). The lower limit of quantification (LLQ) was $<$40 cp/ml. Genotyping drug resistance tests were carried out for individuals with an HIV VL of $>$1,000 cp/ml at entry and/or in case of virologic failure. The drug regimen was decided in accordance with the patient and her physician and taking into consideration national guidelines. The efficacy endpoint was the proportion of women with HIV RNA VL above the LLQ.

The guidelines for ART-naive pregnant women in Brazil are to start ART after the first trimester, with the exception of symptomatic patients or a low CD4 count ($<$350 cells/mm^3 at the time of conduct of the study) (27). Women with nonsingleton pregnancies or repeated pregnancies were excluded from the data set. For the efficacy analysis, the inclusion criterion was for the patient to be cART naive and under cART for at least 2 weeks before the measurement of VL at 34 to 36 weeks of gestation, maintaining cART until delivery. Patients who used a three-drug antiretroviral regimen consisting of nevirapine (NVP), ZDV, and 3TC and those who used a four-drug regimen were excluded from the analysis because this subset comprised a very small number of patients. Individuals who switched or abandoned cART were excluded from the efficacy analysis. Exclusion criteria also included missing data on HIV VL near delivery (Fig. 1A).

C-section to prevent VT was performed based on the VL obtained from 34 to 36 weeks of gestation, and the VL cutoff was any detectable copies or unknown VL near delivery. During the study, women used intravenous ZDV during labor, irrespective of VL. The neonates received ZDV suspension during the first 4 weeks of life. In addition, neonates whose mothers had a VL near delivery that was either unknown or greater than 1,000 cp/ml received a dose of NVP within 48 h postpartum, a second dose 72 h later, and a third dose 96 h after the second dose. All infants were formula fed and received trimethoprim-sulfamethoxazole prophylaxis after completion of the 4 weeks of ZDV until HIV infection was ruled out. No mothers breastfed their infants.

Clinical and laboratory data on infants was collected at delivery and during postpartum visits, including birth weight, the Capurro index (similar to Ballard), and data on Small for Gestational Age (SGA), defined as below the 10th percentile for weight and length (28). The quantitative HIV RNA VL was measured at birth (0 to 72 h postpartum) and at $\geq$2 months. In this study, infant HIV infection was defined as at least two HIV RNA VL tests above the low quantification limit. The HIV-exposed uninfected status was defined as two or more HIV RNA VL tests below the low quantification limit, one at age 1 month and one at age 4 months or older.

Differences in baseline social and demographic characteristics among regimens were compared using Pearson's chi-squared test for categorical variables, analysis of variance (ANOVA) for continuous variables that were normally distributed, and Kruskal-Wallis tests for continuous variables that were not normally distributed (29). When the ANOVA P value was $<$0.05, indicating a difference among the three regimens, we determined which pairs of regimens differed significantly from one another using Tukey's HSD test. Cochran-Haensel-Mantel tests were used to compare changes in HIV VL among regimens stratified by weeks of exposure. We assessed whether the cART regimens differed in time to suppression using a log-rank test with SPSS 19. The study was approved by the local Institutional Review Board protocol CAAE 18275819.9.0000.5252.

Data availability. To protect the confidentiality of individual patients, data on neonatal and obstetrical outcomes will be aggregated by antiretroviral regimen and deposited in Dryad (https://datadryad.org/stash/share/3tHyz-rhXbLiaDmhVJ1crJtdQlPEsDZcRTNJDufBtVA) within 6 months of acceptance. SPSS scripts have been uploaded to GitHub (https://github.com/trevon79/AAC).

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We declare that there are no competing interests.

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