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MAJOR ARTICLE

Efficacy and Safety of DRG/3TC for Prophylaxis of HIV Perinatal Transmission: A Pilot Study (PREGNANCY)

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Background. The prevention of perinatal human immunodeficiency virus (HIV) transmission depends on the safe and effective use of antiretroviral therapy (ART). Simplifying treatment reduces drug exposure for both mother and child. We evaluated the safety and efficacy of dolutegravir (DTG) plus lamivudine (3TC) for antiretroviral-naive pregnant women with HIV.

Methods. This proof-of-concept trial enrolled ART-naive pregnant women ≥15 years old with HIV infection and a gestational age between 14 and 28 weeks. Participants received a fixed-dose combination of DTG/3TC. Baseline HIV genotyping was performed. Participants were monitored at baseline, every 4 weeks, and at delivery. Infants were assessed at birth, 4 weeks, and 6 weeks of age. Outcomes included the proportion of women achieving an undetectable HIV type 1 plasma viral load (<50 copies/mL) at delivery, therapy modification frequency, perinatal HIV transmission rate, and adverse events.

Results. Between January 2019 and March 2021, 20 women were enrolled. At baseline, the median CD4 cell count was 401.6 ± 113.6 cells/μL, increasing to 690.2 ± 266 cells/μL at delivery. Median viral load was 9514 copies/mL. All women achieved an undetectable viral load after an average of 40 days. No cases of perinatal HIV transmission were detected. No therapy modifications were necessary during the study, and no adverse events were related to the ART.

Conclusions. In this pilot trial, DTG/3TC demonstrated safety and efficacy, with all participants achieving viral suppression before delivery. There were no cases of perinatal HIV transmission and no drug-related adverse events. DTG/3TC can be an option for initial treatment of drug-naive pregnant women with HIV.

Keywords. dolutegravir; double therapy; HIV; perinatal transmission.

Perinatal transmission of human immunodeficiency virus (HIV) is a significant public health problem. Each year, approximately 1.3 million pregnancies occur in women with HIV worldwide [1], with perinatal transmission being the leading cause of pediatric HIV [2]. Perinatal HIV transmission occurs in pregnant and breastfeeding women with HIV who have not been diagnosed or have not yet started antiretroviral therapy (ART), who interrupted treatment, or who became infected during pregnancy or breastfeeding [3].

In Brazil, 114 cases of HIV infection in children aged <9 years were reported as cases of vertical transmission in 2022, representing 0.3% of all cases with known exposure. This is the same proportion of cases when compared to 2019 [4]. To achieve the goal of eliminating vertical transmission (ie, <1 case per 100 000 live births), the use of safe and effective antiretroviral drugs during pregnancy and breastfeeding is crucial [2, 5]. Studies show that using ART correctly reduces the risk of perinatal HIV transmission from pregnant and nonlactating women to the fetus to <1% [2].

According to the Brazilian Ministry of Health, the recommended treatment for pregnant women who are diagnosed with HIV and require ART in the country should consist of 3 drugs. Two of these drugs should be nucleoside reverse transcriptase inhibitors (NRTIs) and the third should be from a different class of antiretroviral drugs, such as an integrase inhibitor (INI), a ritonavir (RTV)–boosted protease inhibitor (PI), or a non-NRTI (efavirenz [EFV]). The recommended regimen should be taken once daily. The combination of tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) is the preferred option in the NRTI class. Dolutegravir (DTG), darunavir 800 mg/day boosted by RTV 100 mg, and EFV are the preferable choices in the INI, PI + RTV, and reverse transcriptase inhibitor categories (TDF with 3TC and DTG) [6]. DTG-based ART leads to a rapid decrease in the plasma levels of HIV type 1 (HIV-1) RNA. Due to its effectiveness in virological suppression, tolerability, and high barrier to resistance, DTG is a

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preferred first-line ART and is recommended as preferred regimen in pregnancy by Brazilian guidelines [7–9].

Recently, some studies have demonstrated that 2-drug ART regimens that include DTG are just as effective as 3-drug regimens when initiated in either antiretroviral-naive or fully suppressed individuals [10, 11]. This simplification in ART reduces the number of drugs an individual with HIV is exposed to, with the aim of reducing long-term toxicity [12–17]. If utilized in pregnancy, 2-drug regimens could have a similar benefit in reducing the number of drugs the fetus is exposed to in utero [11]. However, there is still a lack of information regarding the efficacy of 2-drug ART in preventing perinatal HIV transmission. Therefore, this study aims to gather initial evidence on the safety and effectiveness of DTG/3TC when initiated in antiretroviral-naive pregnant women with HIV.

METHODS

Study Design

This single-arm, proof-of-concept trial (ClinicalTrials.gov identifier NCT04808973) was done in Salvador, Bahia, Brazil. Women followed in the HIV outpatient clinics of a public reference center were prescribed DTG/3TC (fixed-dose combination) and followed up to the end of gestation. Infants born from participants were followed up to 6 weeks after birth.

Study Population

The study population was obtained considering 2 different phases. In the first, a total of 10 pregnant women were included in a single arm and were followed until delivery. After the last participant delivered, the study was reviewed by a data and safety monitoring board. Once the first phase was successfully completed, without any safety signal, the study was resumed, and 10 additional participants were included in a second phase.

Participants were included if they had confirmed HIV infection, a plasma viral load of at least 1000 copies/mL, gestational age between 14 and 28 weeks (confirmed by ultrasound), age ≥15 years, and not previously exposed to ART. All eligible pregnant women diagnosed during the study period were invited to enter the study. Only 2 of them refused to participate, because they lived in neighboring cities and could not attend the study visits.

The criteria for gestational age entry were established due to residual concerns during the study design. These included a safety signal on potential neural tube defects (NTDs) associated with early DTG use in pregnancy (periconception use), as well as the theoretical risk of delayed viral suppression if medication was initiated later in pregnancy [18].

Exclusion criteria for this study included the presence of genotypic resistance mutations to 3TC or DTG; active hepatitis B or C; anemia; the presence of any congenital abnormality on ultrasound; use of concomitant medications with potentially relevant drug–drug interactions, requiring adjustment of the DTG dose or which could lead to toxicity; increases in serum alanine aminotransferase (ALT) levels of >5 times the upper limit of normal (ULN) or ALT of ≥3 times the ULN and bilirubin of 1.5 times the ULN (with 35% direct bilirubin);, a history or clinical suspicion of unstable liver disease; subjects with severe liver failure (class C) as determined by the Child-Pugh classification; the presence of severe preeclampsia or other pregnancy-related events such as kidney or liver abnormalities; and any patient or disease-related condition that, in the opinion of the investigator, would prohibit the patient from adhering to the study medication or complying with the study visits or procedures.

According to the Brazilian guidelines for management of HIV in infants born from mothers with HIV, children were not breastfed but rather received formula milk, provided by the Brazilian Ministry of Health [9].

Drug Regimen

DTG/3TC was provided as a single-pill fixed-dose combination with 50 mg/300 mg in unlabeled bottles with fill count of 30 tablets (1 tablet once a day).

Main Assessments

Participants were evaluated at study inclusion (baseline), every 4 weeks, and at delivery. In addition, the infants were assessed at birth, 4 weeks, and 6 weeks.

At baseline, all participants had their demographic information recorded, including education level, smoking habits, alcohol consumption, and recreational drug use. A brief clinical assessment was also conducted, measuring their weight, height, sitting blood pressure, and pulse. The researchers also documented the participants' HIV infection status, $CD4^+$ cell count and CD4 percentage, HIV transmission risk behavior assessment, and HIV RNA plasma. The data collected were registered on standardized case report forms.

During the other evaluated periods, the clinical assessments that were previously conducted were performed in addition to the evaluation of adverse events (AEs). AEs for mothers included miscarriages, preterm births, stillbirths, weight changes, and other. AEs for infants included neonatal deaths, small for gestational age, preterm births, and other. Neonatal assessments were conducted through surface examinations to detect congenital anomalies, and gestational age at delivery was determined using the best available estimates based on the dates of the last normal menstrual period and ultrasound measurements.

At delivery, neonatal length, weight, head circumference, and Apgar scores were measured. The viral load at delivery (mothers), frequency of AEs (for mothers and infants), and viral load for infants at delivery, 4 weeks, and 6 weeks were also evaluated. Plasma HIV-1 RNA viral load was assessed by real-

time polymerase chain reaction, with a lower detection limit of 40 copies/mL (Abbott *m*2000 Real Time System, Abbott Park, Illinois).

To evaluate the adherence to ART among the study population, we used pill count and the AIDS Clinical Trials Group adherence questionnaire, at every visit. For analysis purposes we considered the adherence during the last 4 days and the number of missed pills in the last 4 weeks.

Ethical Procedures

The study was approved by the institutional review board (Comitê de Ética em Pesquisa da Maternidade Climério de Oliveira, approval number: 4.481.052). All study participants signed an informed consent prior to inclusion in the study.

Study Outcomes

The primary outcome was to determine the proportion of women and infants who had an undetectable level of HIV-1 RNA at the time of delivery. This was measured by assessing the proportion of individuals in the intention to treat–exposed population with plasma HIV-1 RNA <50 copies/mL at the time of delivery. To accomplish this, the Snapshot algorithm was used. Infants were tested at birth, and after 4 and 6 weeks, to assess perinatal transmission.

Secondary outcomes included the proportion of women who changed therapy by delivery, as well as the frequency of AEs regardless of their association with the drugs.

Statistical Analyses

Descriptive statistics were used to evaluate the primary and secondary outcomes. All analyses were performed using IBM SPSS software, version 21.

RESULTS

Participants

From January 2019 to March 2021, a total of 20 pregnant women with HIV were enrolled from 1 center. Table 1 presents demographic characteristics of these women. Most of the volunteers (55%) were racially mixed, married or in a stable union (65%), and had completed 8–12 years of schooling (65%). Half of the patients in the study reported that they had consumed alcohol in the past, while 30% reported alcohol consumption during pregnancy. Most of the women in the study (60%) reported that they had never smoked, and 75% had not used recreational drugs. However, 15% reported current marijuana use. The mean age of the women was 25.4 years, and they had a mean gestational age of 18 weeks plus 5 days at baseline. Their mean weight gain until delivery was 6.3 kg. Table 1 summarizes the characteristics of study participants.

Participants had a mean 2.8 previous pregnancies (Supplementary Material). Six women reported only 1 (current) pregnancy, 5 had 2 pregnancies, 6 had 3 pregnancies, 2 had 4 pregnancies, and 1 had 9 pregnancies (in this case, in the 8 previous pregnancies the outcomes were miscarriages). Previous miscarriages were reported by 10 participants: 8 women had 1 miscarriage, 1 woman reported 2 episodes, and 1 woman had 8 miscarriages.

Table 1. Sociodemographic and Clinical Characteristics of Women Included in the Study

Characteristic	No. (%)
Race	
White	1 (5.0)
Black	8 (40.0)
Mixed	11 (55.0)
Marital status	
Married/cohabitation	13 (65.0)
Single	7 (35.0)
Education level, y	
<8	5 (25.0)
8–12	13 (65.0)
>12	2 (10.0)
Serological status of the current partner	
With HIV	5 (25.0)
Without HIV	8 (40.0)
Unknown	7 (35.0)
Previous miscarriages	
None	10 (50.0)
1	8 (40.0)
2	1 (5.0)
8	1 (5.0)
Alcohol consumption	
No	4 (20.0)
During pregnancy	6 (30.0)
Previous	10 (50.0)
Recreational drugs	
Never	15 (75.0)
Current	3 (15.0)
Previous	2 (10.0)
Smoking	
Never	12 (60.0)
Current	4 (20.0)
Previous	4 (20.0)
Age, y, mean ± SD	25.4 ± 5.4
Weight at baseline, kg, mean ± SD	78.8 ± 14.0
Weight at delivery, kg, mean ± SD	85.1 ± 14.3
Gestational age at baseline, wk, mean ± SD	18.7 ± 4.0
Gestational age at delivery, wk, mean ± SD	38.8 ± 1.0

Data are presented as No. (%) unless otherwise indicated. No drug resistance mutation was detected at baseline.

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.

Efficacy

At baseline, the mean (± standard deviation) CD4 cell count was 401.6 cells/μL (±113.6), and at delivery it was 690.2 cells/μL (±266.5), a gain of 289 cells/μL. The mean time to an undetectable viral load (<50 copies/mL) was 40.4 days and no cases of perinatal transmission occurred (Table 2).

Table 2. Summary of Efficacy Results of Pregnant Women Using a Dolutegravir/Lamivudine Antiretroviral Therapy Regimen

Characteristics	Baseline	Delivery	Difference
CD4 count, cells/μL, mean ± SD	401.6 ± 113.6	690.2 ± 266.5	289
HIV plasma VL, copies/mL, median (min–max)	9514 (1049–118 455)	0	0
Time to undetectable VL (<50 copies/mL), d, mean ± SD	…	40.4 ± 23.7	…
Cases of perinatal transmission, No.	…	0	0

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation; VL, viral load.

Table 3. Characteristics of Infants at Birth

Characteristics	No. (%)
Mode of delivery	
Natural birth	6 (30.0)
Cesarean delivery	14 (70.0)
Weight at birth, g, mean ± SD	3158 ± 364
Length at birth, cm, mean ± SD	48 ± 2.3
Apgar score at 1 min, mean ± SD	8.6 ± 0.6
Apgar score at 5 min, mean ± SD	9.4 ± 5.9

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: SD, standard deviation.

Characteristics of Infants

Table 3 shows the characteristics of infants at birth. Most of the infants were delivered through cesarean delivery (70%), with an average weight of 3158 g and length of 48 cm.

The mean Apgar score was 8.6 and 9.4 at 1 and 5 minutes, respectively, after birth. Cesarean delivery was preferred by 14 (70%) women, because it could be scheduled in advance, making secure a bed in public maternities, a main concern for those choosing a vaginal delivery. Only 1 cesarean delivery had an obstetric indication (arterial hypertension). Infants were not breastfed and they received formula milk. In addition, they also received oral zidovudine for 28 days [9].

Safety Results

There were no discontinuations of DTG/3TC. AEs, such as urinary tract infection and toxoplasmosis, were not related to the treatment (Supplementary Material). Table 4 summarizes the frequency of AEs for mothers and infants.

Adherence to Treatment

The proportion of participants reporting not missing a dose in the last 4 days was 90%, 95%, and 89% at weeks 4, 8, and 12, respectively. All participants reported 100% adherence at weeks 16, 20, and 24.

DISCUSSION

All pregnant women followed in the study had an undetectable viral load at delivery, and all infants had an undetectable viral load at birth. Other studies have shown that a treatment regimen of DTG/3TC is as effective and safe as a 3-drug regimen in both antiretroviral-naive and -experienced adults with HIV [10, 11]. This simplified regimen reduces the number of drugs an individual is exposed to, aiming to decrease the risk of AEs and long-term toxicity.

An effective 2-drug regimen, when used during pregnancy, also reduces the number of medications to which a fetus is exposed in utero. However, current guidelines do not recommend initiating a 2-drug regimen in either antiretroviral-naive or experienced pregnant women, primarily due to a paucity of data [19]. Therefore, this study provides important information on the safety and effectiveness of using DTG/3TC in antiretroviral-naive pregnant women with HIV. Our findings are supported by the VESTED study, which showed that women who began treatment early in pregnancy experienced superior responses with DTG (defined as having a viral load of <50 copies/mL) [20].

The rate of cesarean deliveries was 70%. However, all but 1 of these procedures were elective, not due to obstetric reasons nor to prevent transmission risk. Instead, they were for patients' convenience, since scheduling an appointment guaranteed a place in the maternity hospital. This is comparable to the rate of cesarean delivery in the general population in Brazil. According to data from the HIV and AIDS epidemiological bulletin, in 33.9% of cases, information about the procedure was missing. However, considering only the cases with known information, elective or emergency cesarean was the main delivery route (62.6%) in 2022, and the reasons are like those observed in our study [4].

The prevalence of smoking and alcohol and marijuana use was higher than that observed in the general population. However, in a previous study, we detected an overall prevalence of 16.8% of use of alcohol and/or marijuana among pregnant women diagnosed with HIV in Salvador [21]. In addition, another report detected use of drugs as the main risk for HIV infection among female adolescents in Brazil [22].

The safety of initiating DTG/3TC during pregnancy was assessed as a secondary outcome. No treatment discontinuations or switches were observed. AEs observed were not thought to be related to the treatment, and the high rates of reported adherence reinforce the tolerability of 3TC/DTG regimen during pregnancy.

The use of DTG during early pregnancy/conception was initially controversial due to reports on an association with increased risk of NTDs in the TSEPAMO study [18]. However, some studies have already shown that there is no increased risk, as in the cohort carried out from a Brazilian ART database with 1427 women, in which 48% of the women were exposed to DTG and there were no cases of NTDs (0 [95% confidence

Table 4. Frequency of Adverse Events for Mothers and Infants

Adverse Event	No. (%)
Mothers	
Urinary tract infection	2 (10.0)
Trichomoniasis	1 (5.0)
Vaginal discharge	2 (10.0)
Toxoplasmosis	1 (5.0)[a]
Sleepiness	1 (5.0)
Headache	3 (15.0)
Genital itching	2 (10.0)
Anemia	1 (5.0)
Abscess in armpit	1 (5.0)
Gestational arterial hypertension	2 (10.0)
Infants	
Oral candidiasis	4 (20)
Cough/runny nose	4 (20)
Bronchiolitis	2 (10)
Scabies	1 (10)
Diarrhea and fever	1 (10)
Boiling water burn	1 (10)

[a]Premature birth at 36.2 weeks' gestational age.

interval, 0,10]) [23]. A cohort study conducted in the United States also carried out treatment with DTG in early pregnancy in which the results also did not show an increased risk of DTG [24]. Furthermore, the update of the TSEPAMO study as well as the results of a birth surveillance study in Eswatini showed similar rates of NTDs in children exposed to DTG periconception [25, 26].

Late diagnosis of HIV in pregnant women can lead to delayed initiation of ART, which is linked with a 7-fold higher risk of perinatal transmission of HIV from mother to infant. The use of INIs provides a faster decline in viral load and is especially useful for treatment of late-presenting pregnant women, increasing the likelihood of achievement of undetectable viral load up to delivery [27, 28]. Although the present study did not include late-presenting pregnant women, the short time to viral suppression suggests that the 2-drug regimen of 3TC/DTG may result in a similar rapid decline in viral load to that seen in a conventional 3-drug regimen.

It is essential to ensure that pregnant women, and women in childbirth, with HIV receive high-quality prenatal care. According to data from the Brazilian Ministry of Health bulletin, the percentage of women who receive prenatal care has remained at around 90% throughout the period analyzed [4]. However, in 2022, only 66.8% of cases reported the use of ART during prenatal care. Antiretroviral drugs such as DTG can cause a rapid decline in viral load, regardless of gestational age. Hence, the updated World Health Organization treatment guidelines in 2019 recommended first- and second-line DTG-containing regimens for pregnant women, offering more opportunities for viral load suppression [20].

This study has some limitations. This is a proof-of concept study with a small sample size performed in a single center in Brazil. Thus, the results may not be representative of all pregnant women with HIV. However, the high safety and efficacy demonstrated in this pilot trial of antiretroviral-naive pregnant women indicates that the use of this strategy in pregnant women with HIV should be investigated further.

CONCLUSIONS

Eliminating perinatal HIV transmission remains a key global health priority. Safe, effective, and well-tolerated antiretroviral drugs during pregnancy are crucial to achieve this goal. In this small study of antiretroviral-naive pregnant women, the use of DTG/3TC showed favorable efficacy and safety profiles, with all women achieving an undetectable viral load at delivery, with no case of perinatal HIV transmission and no treatment-related AEs.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2022 UNAIDS estimates. **2022**. Available at: https://www.unaids.org/en/resources/documents/2023/2023_unaids_data. Accessed 14 July 2024.
2. Yang L, Cambou MC, Nielsen-Saines K. The end is in sight: current strategies for the elimination of HIV vertical transmission. Curr HIV/AIDS Rep **2023**; 20: 121–30.
3. Chevalier JM, Hansen MA, Coskun E, et al. Cost-effectiveness of intervention combinations towards the elimination of vertical transmission of HIV in limited-resource settings: a mathematical modelling study. Lancet Glob Health **2024**; 12:e457–66.
4. Ministério da Saúde, Brasil. Boletim epidemiológico—HIV e AIDS 2023 [in Portuguese]. **2023**. Available at: www.gov.br/aids/pt-br/central-de-conteudo/boletins-epidemiologicos/2023/hiv-ai….
5. Malaba TR, Nakatudde I, Kintu K, et al. 72 weeks post-partum follow-up of dolutegravir versus efavirenz initiated in late pregnancy (DolPHIN-2): an open-label, randomised controlled study. Lancet HIV **2022**; 9:e534–43.
6. Ministério da Saúde, Brasil. Atenção integral às pessoas com infecções sexualmente transmissíveis (IST). Protocolo clínico e diretrizes ter [in Portuguese]. **2015**. Available at: PCDT_HIV_Modulo_1_2024.indd.
7. Mohan H, Nguyen J, MacKenzie B, et al. Folate deficiency increases the incidence of dolutegravir-associated foetal defects in a mouse pregnancy model. EBioMedicine **2023**; 95:104762.
8. Francois K, Van Onacker JD, Jordan MR, et al. First case report of a perinatally HIV-infected infant with HIV resistance to dolutegravir associated with tenofovir/lamivudine/dolutegravir use in mothers. AIDS **2023**; 37:2097–9.
9. Ministério da Saúde, Brasil. Protocolo clínico e diretrizes terapêuticas para prevenção da transmissão vertical de hiv, sífilis e hepatites virais [in Portuguese]. **2022**. Available at: https://bvsms.saude.gov.br/bvs/publicacoes/protocolo_clinico_hiv_sifilis_hepatites.pdf. Accessed 10 May 2024.

10. Punekar YS, Parks D, Joshi M, et al. Effectiveness and safety of dolutegravir two-drug regimens in virologically suppressed people living with HIV: a systematic literature review and meta-analysis of real-world evidence. HIV Med **2021**; 22: 423–33.
11. Gibas KM, Kelly SG, Arribas JR, et al. Two-drug regimens for HIV treatment. Lancet HIV **2022**; 9:e868–83.
12. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS **2010**; 24: 1667–78.
13. Nduka CU, Stranges S, Kimani PK, Sarki AM, Uthman OA. Is there sufficient evidence for a causal association between antiretroviral therapy and diabetes in HIV-infected patients? A meta-analysis. Diabetes Metab Res Rev **2017**; 33. doi: 10.1002/dmrr.2902.
14. Lin SP, Wu CY, Wang CB, Li TC, Ko NY, Shi ZY. Risk of diabetes mellitus in HIV-infected patients receiving highly active antiretroviral therapy: a nationwide population-based study. Medicine (Baltimore) **2018**; 97:e12268.
15. Pinto DSM, da Silva MJLV. Cardiovascular disease in the setting of human immunodeficiency virus infection. Curr Cardiol Rev **2018**; 14:25–41.
16. Ahmad AN, Ahmad SN, Ahmad N. HIV infection and bone abnormalities. Open Orthop J **2017**; 11:777–84.
17. Revuelta-Herrero JL, Chamorro-de-Vega E, Rodríguez-González CG, Alonso R, Herranz-Alonso A, Sanjurjo-Sáez M. Effectiveness, safety, and costs of a treatment switch to dolutegravir plus rilpivirine dual therapy in treatment-experienced HIV patients. Ann Pharmacother **2018**; 52:11–8.
18. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med **2018**; 379:979–81.
19. World Health Organization (WHO). Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030. Geneva, Switzerland: WHO; **2022**.
20. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet **2021**; 397:1276–92.
21. Vargas L, Bastos F, Guimarães A, et al. Seroprevalence and factors associated with human immunodeficiency virus, human T lymphotropic virus and hepatitis B/C infections in parturient women of Salvador—Bahia, Brazil. Braz J Infect Dis **2020**; 24:279–87.
22. Bassols AM, Boni Rd, Pechansky F. Alcohol, drugs, and risky sexual behavior are related to HIV infection in female adolescents. Braz J Psychiatry **2010**; 32:361–8.
23. Kourtis AP, Zhu W, Lampe MA, Huang YA, Hoover KW. Dolutegravir and pregnancy outcomes including neural tube defects in the USA during 2008-20: a national cohort study. Lancet HIV **2023**; 10:e588–96.
24. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med **2019**; 381:827–40.
25. Gill MM, Khumalo P, Chouraya C, et al. Strengthening the evidence: similar rates of neural tube defects among deliveries regardless of maternal HIV status and dolutegravir exposure in hospital birth surveillance in Eswatini. Open Forum Infect Dis **2023**; 10:ofad441.
26. Kintu K, Malaba TR, Nakibuka J, et al. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. Lancet HIV **2020**; 7:e332–9.
27. João EC, Morrison RL, Shapiro DE, et al. Raltegravir versus efavirenz in antiretroviral-naive pregnant women living with HIV (NICHD P1081): an open-label, randomised, controlled, phase 4 trial. Lancet HIV **2020**; 7:e322–31.
28. Pereira GFM, Kim A, Jalil EM, et al. Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study. Lancet HIV **2021**; 8:e33–41.