Subsequent Pregnancies in the IMPAACT 2010/VESTED Trial: High Rate of Adverse Outcomes in Women Living With HIV

Lee Fairlie, MBChB, MMed, FCPaeds (SA),[a] Sean Brummel, PhD,[b] Lauren Ziemba, MS,[b] Anne Coletti, MS,[c] Lameck Chinula, MBBS, MMed, FCOG,[d] Roger Shapiro, MD, MPH,[b] Jeffrey Stringer, MD,[e] Grace Malonga, MPH, MS Biostatistician,[b] Renee Browning, RN, MSN,[f] Nahida Chakhtoura, MD, MsGH,[g] Blandina Theophil Mmbaga, MD, Mmed, PhD,[h] Tsungai P. Mhembere, MB, ChB, FRCOG, FECSACOG,[i] Ayotunde Omoz-Oarhe, MD,[j] Beatrice Nagaddya, EM, RM, RN, BSM,[k] Megeshinee Naidoo, MBChB,[l] Risa M. Hoffman, MD, MPH,[m] and Shahin Lockman, MD, MSc,[b,j,n] for the IMPAACT 2010/VESTED Study Team

Introduction: Women with HIV (WHIV) have higher risks of adverse pregnancy outcomes, particularly in the absence of antiretroviral treatment (ART), and timing of ART may impact risk.

Methods: In the International Maternal Pediatric Adolescent AIDS Clinical Trials 2010/VESTED study, 643 pregnant WHIV in 9 countries were randomized in a 1:1:1 ratio to initiate ART: dolutegravir (DTG)+emtricitabine (FTC)/tenofovir alafenamide (TAF), DTG+FTC/tenofovir disoproxil fumarate (TDF), or efavirenz (EFV)/FTC/TDF. We describe adverse pregnancy outcomes in women with a subsequent pregnancy during 50 weeks of postpartum follow-up: spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), preterm delivery (<37 weeks), and small for gestational age.

Results: Of 643 women, 19 (3%) had 20 subsequent pregnancies while receiving ART at conception: DTG/FTC/TAF (3), DTG/FTC/TDF (2), EFV/FTC or lamivudine (3TC)/TDF (12), EFV/abacavir/3 TC (1), and no ART (1). Four spontaneous abortions, 3 stillbirths, and 1 induced abortion occurred. Three (25%) of 12 liveborn infants were preterm (24, 26, and 36 weeks of gestation). Only 12 subsequent pregnancies (60%) resulted in live birth, and at least 1 adverse pregnancy outcome occurred in 11 of 19 (58%) (induced abortion excluded). Of 7 women who experienced spontaneous abortion/stillbirth in the subsequent pregnancy, 4 experienced a stillbirth and 1 a neonatal death as outcomes of their earlier index pregnancy. No congenital anomalies were reported.

Conclusions: Adverse pregnancy outcomes were common in this cohort of WHIV who conceived on ART shortly after an index pregnancy, 35% ended in stillbirth or spontaneous abortion. The majority of fetal losses occurred in women with recent prior

Received for publication November 7, 2023; accepted March 19, 2024.

From the [a]Faculty of Health Sciences, Wits RHI, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [b]Harvard TH Chan School of Public Health, Boston, MA; [c]FHI 360, Durham, NC; [d]University of North Carolina Project–Malawi, Lilongwe, Malawi; [e]University of North Carolina at Chapel Hill, Chapel Hill, NC; [f]National Institute of Allergy and Infectious Diseases, Bethesda, MD; [g]National Institute of Child Health and Human Development, Bethesda, MD; [h]Kilimanjaro Christian Medical Centre and Kilimanjaro Christian Medical University College, Moshi, Tanzania; [i]University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC), Harare, Zimbabwe; [j]Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana; [k]Baylor College of Medicine Children's Foundation-Uganda, Kampala, Uganda; [l]Centre for the Aids Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa; [m]Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California; and [n]Brigham and Women's Hospital, Boston, MA.

This study was funded and sponsored by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network. Overall support for the IMPAACT Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC), and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. S.L. received support from K24 AI131928.

Conference on Retroviruses and Opportunistic Infections February 12–16, 2022, Abstract 680, Virtual.

S.B. and L.Z. received NIH funding and ViiV Healthcare funding, both paid to their institution. R.M.H. serves on the editorial board for Elsevier's Clinical Key, a clinical resource for clinicians.

L.F., S.L., S.B., L.Z., R.S., and J.S. conceived of the study. L.F. developed the first and subsequent drafts, with input from all coauthors. All coauthors reviewed and approved the manuscript.

Ethics approvals were obtained from all relevant regulatory bodies in countries where participants were participating in the IMPAACT 2010 study. Participants provided written informed consent for study participation.

ClinicalTrials.gov number: NCT03048422.

Correspondence to: Lee Fairlie, MBChB, MMed, FCPaeds (SA), Wits, RHI Shandukani, 7 Esselen Street, Hillbrow, Johannesburg 2001, South Africa (e-mail: lfairlie@wrhi.ac.za).

pregnancy loss. Data from larger cohorts of WHIV conceiving on ART and surveillance are needed to elucidate rates and predictors of adverse pregnancy outcome.

Key Words: women living with HIV, conception on antiretroviral therapy, pregnancy outcomes, high rates adverse outcomes, prior pregnancy loss, interpregnancy interval

(*J Acquir Immune Defic Syndr* 2024;97:150–155)

INTRODUCTION

Adverse pregnancy outcomes are more common in pregnant cisgender women living with HIV (WHIV) compared with HIV-negative pregnant women, including preterm and very preterm delivery, stillbirth, low birth weight (LBW), and small for gestational age (SGA).[1–4] Adverse pregnancy outcomes are less frequent in WHIV receiving ART compared with those not receiving ART; however, they remain higher compared with HIV-negative women.[5,6] The benefits of maternal ART in improving maternal health and reducing vertical transmission are beyond question.[7] The timing of antiretroviral therapy (ART) may also have an impact: a meta-analysis by Uthman et al,[1] reports an increased risk of prematurity (pooled RR 1.20, 95% CI: 1.01 to 1.44), very preterm birth (RR 1.53, 1·22–1.92), or LBW infants (RR 1.30, 1.04–1.62) when ART is initiated preconception, compared with initiating ART after conception. The PROMISE study, which was one of the largest studies evaluating the prevention of vertical transmission and maternal health on ART, reported increased risk of LBW, spontaneous abortion, stillbirth, and neonatal death in subsequent pregnancies (following the index pregnancy) in which women conceived on ART.[8] Potential mechanisms for adverse outcomes include abnormal placental morphology with low placental weight and abnormal placental cord insertion and vascular malformation causing placental insufficiency.[9,10] Studies of the effects of ART from conception are difficult to do, and observational pregnancy studies are susceptible to biases, including immortal time bias.[11]

History of prior fetal loss is associated with higher risk of miscarriage or stillbirth.[12,13] Short interpregnancy interval may also be an important factor in adverse pregnancy outcomes, although data are conflicting.[10–12] Studies specifically evaluating the interaction between ART and short pregnancy intervals are scarce.

As HIV treatment programs strengthen globally, most WHIV conceive on ART, yet as new ART regimens and formulations become available, they are understudied in pregnancy. It is important to identify the safest and most effective ART regimens in pregnancy in the context of newer ART regimens used by WHIV. In this study, we evaluated subsequent pregnancy outcomes in women conceiving on ART while participating in the International Maternal Pediatric Adolescent HIV/AIDS Clinical Trial Network (IMPAACT) 2010/VESTED randomized pregnancy ART study, during the 50-week postpartum follow-up period following the index pregnancy.

METHODS

Study Participants and Procedures

IMPAACT 2010 (VESTED) enrolled 643 pregnant WHIV (PWHIV) from January 2018 to February 2019 in 9 countries, predominantly in sub-Saharan Africa. The last study visit was February 2, 2021, database locked February 15, 2021. Women were randomized in a 1:1:1 ratio to start one of the following ART regimens between 14 and 28 weeks of gestation: dolutegravir (DTG)+emtricitabine (FTC)/tenofovir alafenamide (TAF); DTG+FTC/tenofovir disoproxil fumarate (TDF); or efavirenz (EFV)/FTC/TDF. Women and their infants were followed until 50 weeks postpartum. The primary results of the study have been described.[14,15] We conducted a preplanned exploratory analysis of outcomes among women who had subsequent pregnancies while taking part in IMPAACT 2010 (ie, pregnancies which occurred after the index IMPAACT 2010 study pregnancy, when women were enrolled). The subsequent pregnancy was followed up until pregnancy outcome, even if this period extended beyond 50 weeks after completion of the index pregnancy.

Because of a protocol amendment based on recommendations at the time to mitigate potential risk of neural tube defects in infants whose mothers conceived on DTG (based on preliminary findings from the Tsepamo study),[16] women on DTG-based ART who did not wish to take effective contraception following delivery were switched from DTG to another antiretroviral (usually EFV) at the discretion of the site investigator during the 50 weeks of postpartum follow-up.[17]

Analysis

We describe the following adverse pregnancy outcomes in women who became pregnant during postpartum follow-up (subsequent pregnancy): spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), preterm delivery in liveborn babies (<37 weeks), and small for gestational age (SGA; <10th centile). A composite adverse pregnancy outcome was defined as the occurrence of any of these individual adverse pregnancy outcomes. A severe adverse pregnancy outcome was defined as the occurrence of either spontaneous abortion (<20 weeks) or stillbirth (≥20 weeks). Induced abortions were described but excluded from analysis of outcomes. Gestational age at delivery was determined using the American College of Obstetricians and Gynecologists algorithm.[18] Infants were classified as SGA based on methods from the INTERGROWTH-21st project, using birthweight, sex, and gestational age at delivery.[19] Data were analyzed using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

Nineteen (3%) of 643 women had 20 subsequent pregnancies on study (1 woman had 2 pregnancies). Baseline characteristics of WHIV with subsequent pregnancies are described in Table 1. At 50 weeks after index delivery, VL was <50 copies/mL in 17 participants and 18 had

TABLE 1. Baseline Characteristics of Women at Randomization and ARVs at the Start of First Subsequent Pregnancy by Randomized Treatment Group

Treatment Group	DTG+FTC/TAF (N = 7)	DTG+FTC/TDF (N = 5)	EFV/FTC/TDF (N = 7)	Total (N = 19)
Baseline characteristics at randomization (during initial pregnancy)				
Age (yr)				
Median (Q1–Q3)	25.9 (23.0–29.6)	20.9 (20.5–26.4)	25.2 (24.0–32.5)	25.4 (23.0–29.6)
Weight (kg)				
Median (Q1–Q3)	67.8 (60.5–96.1)	73.6 (62.6–77.1)	62.1 (51.2–62.6)	62.6 (60.3–77.1)
BMI (kg/cm^2)				
Median (Q1–Q3)	27.5 (22.4–32.5)	28.0 (27.8–28.0)	24.8 (21.1–26.2)	27.0 (22.4–28.0)
Hepatitis B surface antigen				
Positive (missing = 1, %)	0 (0.0)	0 (0.0)	1 (14.3)	1 (5.6)
WHO clinical stage, %				
Stage 1	7 (100.0)	5 (100.0)	7 (100.0)	19 (100.0)
HIV-1 RNA (copies/mL, %)				
Median (Q1–Q3)	451.0 (20.0–1587.0)	784.0 (372.0–2604.0)	2610.0 (112.0–11,418.0)	1201.0 (87.0–6647.0)
HIV-1 RNA <50	2 (33.3)	1 (20.0)	1 (14.3)	4 (22.2)
HIV-1 RNA <200	3 (50.0)	1 (20.0)	2 (28.6)	6 (33.3)
HIV-1 RNA <1000 (missing = 1)	4 (66.7)	3 (60.0)	2 (28.6)	9 (50.0)
CD4 (cells/mm^3)				
Median (Q1–Q3)	815 (390–833)	536 (412–875)	385 (137–589)	551 (307–831)
50–349, %	1 (16.7)	1 (20.0)	3 (42.9)	5 (27.8)
350–499, %	1 (16.7)	1 (20.0)	1 (14.3)	3 (16.7)
500–750, %	0 (0.0)	1 (20.0)	3 (42.9)	4 (22.2)
>750 (missing = 1)	4 (66.7)	2 (40.0)	0 (0.0)	6 (33.3)
Start of subsequent pregnancy				
ARV at conception, N (%)				
DTG+FTC/TAF	3 (42.9)	0 (0.0)	0 (0.0)	3 (15.8)
DTG+FTC/TDF	0 (0.0)	2 (40.0)	0 (0.0)	2 (10.5)
EFV/FTC/TDF	3 (42.9)	3 (60.0)	5 (71.4)	11 (57.9)
Non-study ART	0 (0.0)	0 (0.0)	2 (28.6)	2 (10.5)
Not on ART	1 (14.3)	0 (0.0)	0 (0.0)	1 (5.3)

a VL <200 cps/mL. This was the closest approximation to VL during the subsequent pregnancy available. One participant was not on ART at conception and the remaining 18 women were receiving the following ART regimens at conception: DTG+FTC/TAF (3), DTG+FTC/TDF (2), EFV/FTC or lamivudine (3TC)/TDF (12 women with 13 pregnancies, as 1 woman had 2 pregnancies), and EFV/abacavir (ABC)/3TC (1). The median (Q1–Q3) interpregnancy interval was 6 (5,6) months (the maximum interpregnancy interval 11 months). Outcomes of the 20 subsequent pregnancies were 1 (5%) induced abortion (excluded from outcome analysis), 4 (20%) spontaneous abortions, 3 (15%) stillbirths, and 3 (25%) preterm infants (at 24, 26, and 36 weeks of gestation). Excluding the induced abortion, only 12 of 19 subsequent pregnancies (63%) resulted in live birth, and at least 1 adverse pregnancy outcome occurred in 11 (58%) subsequent pregnancies. Adverse pregnancy outcomes occurred in 8 of 12 pregnancies (67%) with EFV/FTC/TDF at conception and 1 of 4 pregnancies with DTG-ART at conception (Fig. 1, Table 2).

Of the 7 women who experienced spontaneous abortion or stillbirth in the subsequent pregnancy, 4 had experienced a stillbirth and 1 a neonatal death as outcomes of the earlier index pregnancy (Table 3).

DISCUSSION

In this planned exploratory analysis of the IMPAACT 2010 study, we found high rates of adverse pregnancy outcomes in women who conceived on ART subsequent to their index pregnancy on study. Just over one-third (36%) of pregnancies ended in either stillbirth or spontaneous abortion, and the majority of pregnancies ended with at least 1 adverse outcome. This is consistent with several other studies showing higher risk of low birthweight, prematurity, spontaneous abortion, stillbirth, and neonatal death with ART from conception.[2,8,20] A recently published study using health care claims data reported increased pregnancy loss (spontaneous/induced abortion) in WHIV compared with HIV-negative women.[21] In the PROMISE study, 13% of 837 subsequent pregnancies resulted in spontaneous abortion, 3% in stillbirth, and 1% neonatal death, with 72% live births recorded (the remainder experienced ectopic pregnancy or induced abortion).[8] Stringer et al[22] show high risk for adverse pregnancy outcomes in women conceiving on ART, with 53% of deliveries occurring <37 weeks (median gestational age 35 weeks 5 days), 4% stillbirths, 20% spontaneous abortion, but no difference between protease inhibitor–based and NNRTI-based ART. Of note, observational studies that

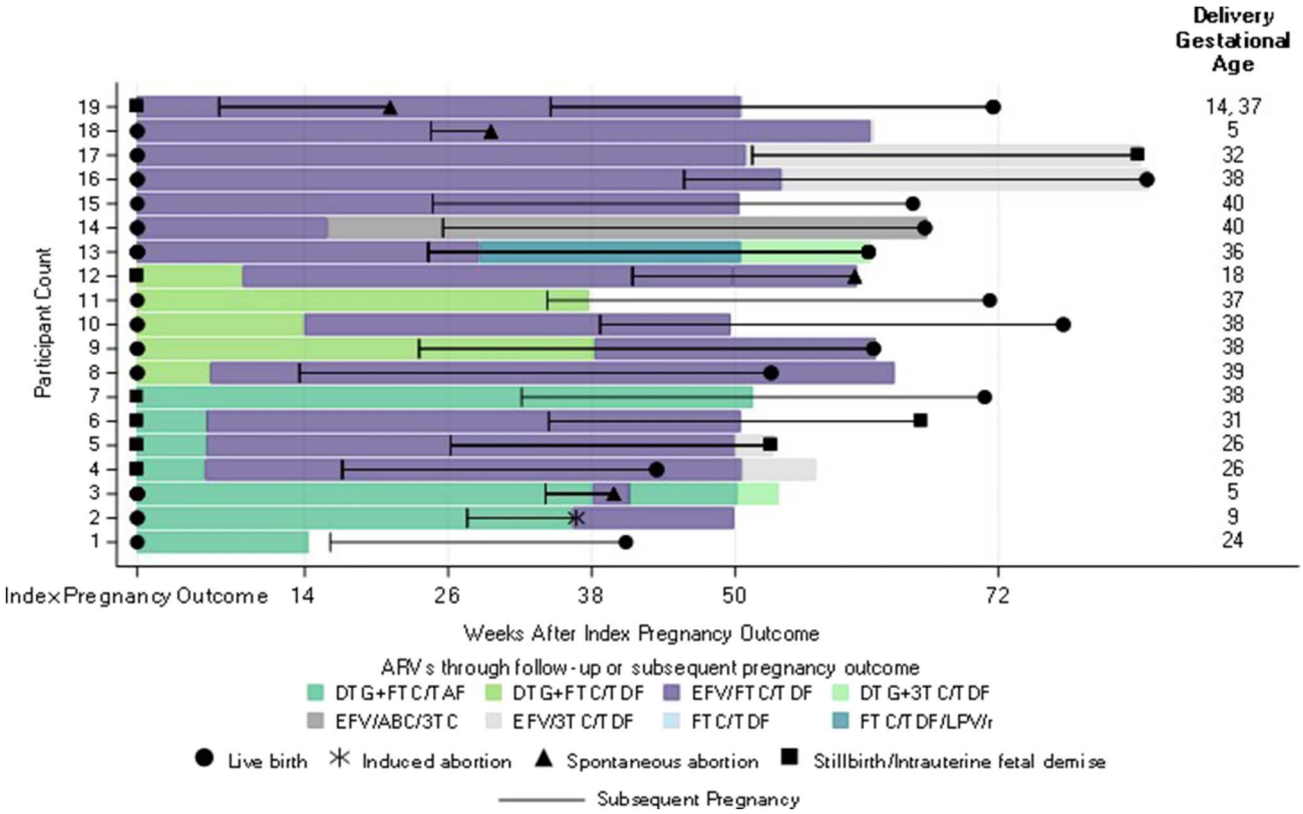

FIGURE 1. ART regimen from completion of index pregnancy, through time of conception and subsequent pregnancy in the IMPAACT 2010 study. This figure shows the time between the index pregnancy outcome on the IMPAACT 2010 study and the outcome of the subsequent pregnancy, including the regimen that each participant was receiving at index pregnancy and subsequent pregnancy.

evaluate the impact of timing of ART exposure during pregnancy on pregnancy outcomes need to be interpreted with caution because of their susceptibility to biases, including immortal time bias.[11] It is also important to note that untreated WHIV experience significantly higher rates of adverse pregnancy outcomes than women without HIV, with rates of preterm delivery, stillbirth, and LBW twice as high in the pre-ART era, compared with the ART era[3,5,6,20,23,24]; uninterrupted ART from before conception and throughout pregnancy is clearly recommended to optimize maternal and child health.[25] In addition, "background" rates of spontaneous abortion range from 12% to 15% among women who are followed prospectively from before conception, particularly in the context of early and/or frequent pregnancy testing (as is the case in studies such as PROMISE and our analysis).[7,8]

The reasons for potentially higher rates of adverse pregnancy outcomes with at least some ART regimens from conception are uncertain, although some studies have shown that lopinavir/ritonavir (LPV/r) may be associated with abnormal placental vascularisation.[10,26] Another possible

TABLE 2. Adverse Pregnancy Outcomes in Subsequent Pregnancies, by ART Regimen at the Time of Conception

	ARV Treatment at Start of Pregnancy Events/N (%)				
Outcome	**DTG+FTC/TAF (N = 2)**	**DTG+FTC/TDF (N = 2)**	**EFV/FTC/TDF (N = 12)**	**Nonstudy ART Treatment or No ART (N = 3)**	**Total (N = 19)**
Stillbirth or spontaneous abortion	1/2 (50)	0/2 (0)	5/12 (41.7)	1/3 (33)	7/19 (36.8)
Preterm delivery (<37 weeks)	0/1 (0)	0/2 (0)	2/7 (28.6)	1/2 (50)	3/12 (25)
Small for gestational age (<10th percentile)	0/0 (NA)	0/1 (0)	1/4 (25)	0/1 (0)	1/6 (16.7)
Composite adverse outcome*	1/2 (50)	0/2 (0)	8/12 (66.7)	2/3 (66.7)	11/19 (57.9)

One pregnancy resulting in induced abortion was excluded from all analyses. One participant had 2 subsequent pregnancies, and both are included in summaries above.
*Composite adverse pregnancy outcome was defined as experiencing at least 1 of the following: spontaneous abortion, stillbirth/intrauterine fetal demise, preterm delivery, and infant SGA.

TABLE 3. Outcomes of Subsequent Pregnancies, by Outcome of Prior (Index) Pregnancy

Pregnancy Outcome		Treatment Group			
		DTG+FTC/TAF (N = 6)	DTG+FTC/TDF (N = 5)	EFV/FTC/TDF (N = 7)	Total (N = 18)
Index IMPAACT 2010 pregnancy	Subsequent IMPAACT 2010 pregnancy	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Severe pregnancy outcomes index pregnancy	Severe pregnancy outcome	2/4 (50.0)	1/3 (33.3)	2/4 (50.0)	5/11 (45.5)
	No severe pregnancy outcome	2/4 (50.0)	2/3 (66.7)	2/4 (50.0)	6/11 (54.5)
No severe pregnancy outcomes index pregnancy	Severe pregnancy outcome	1/2 (50.0)	0/2 (0.0)	1/3 (33.3)	2/7 (28.6)
	No severe pregnancy outcome	1/2 (50.0)	2/2 (100.0)	2/3 (66.7)	5/7 (71.4)

Severe pregnancy outcome was defined as experiencing a stillbirth, spontaneous abortion, or neonatal death for index pregnancy outcome and experiencing a stillbirth or spontaneous abortion for the subsequent pregnancy.

mechanism could be insufficient pregnancy weight gain. IMPAACT 2010 previously reported that overall pregnancy outcomes were better in women receiving DTG/FTC/TAF than those receiving DTG/FTC/TDF or EFV/FTC/TDF,[14] and that poor pregnancy weight gain (most frequent in women receiving EFV/FTC/TDF and least frequent with DTG/FTC/TAF) was associated with a higher risk of adverse pregnancy outcome (HR: 1.4, 95% CI: 1.04 to 2.00 compared with normal weight gain).[27] Efavirenz and TDF in combination are known to suppress weight gain, particularly in those who are slow CYP2B6 metabolizers.[28–30] Tenofovir disoproxil fumarate may restrict weight gain independently, with potential mechanisms including reduced appetite, nausea, vomiting, and other gastrointestinal side effects.[28,30]

Prior fetal loss is a risk factor for subsequent fetal loss, regardless of interpregnancy interval.[12,13] Our current analysis showed that 71% of women who experienced fetal loss in a subsequent pregnancy had experienced either stillbirth (n = 4) or neonatal death (n = 1) in their recent index pregnancy. In our analysis, interpregnancy interval was median 6 months.[5,7] Shorter interpregnancy interval following fetal loss might also be associated with worse subsequent pregnancy outcome, although data on this topic are conflicting and a 2017 systematic review and meta-analysis including data from more than 1 million women in 16 studies, reports that in women who experienced miscarriage, overall risks of repeat miscarriage and preterm birth were not increased with a subsequent interpregnancy interval of ≤6 months compared with a longer interpregnancy interval, and the interpregnancy interval had no impact on stillbirth, preeclampsia, or LBW.[31]However, minimal data on optimal interpregnancy interval are available for WHIV.[32] The WHO recommends at least 24-month interpregnancy interval in women who have had a live birth and at least 6 months in women who have experienced a miscarriage, based on a 2005 technical consultation.[33]

Our study is limited by small sample size and enrollment of most participants in 1 continent (Africa). Pooled data from clinical trials and studies in diverse populations, in which women conceive on different antiretrovirals and are followed up longitudinally would help close this knowledge gap. Surveillance projects such as the Antiretroviral Pregnancy Registry (US-based global),[34] Tsepamo (Botswana),[23] UBOMI BUHLE (South Africa)[35,36] may also contribute data evaluating risks of subsequent pregnancies on ART, where women have been included in the registry in a prior pregnancy or have conceived on ART and are followed up through the pregnancy to delivery/outcome (although many surveillance systems and registries do not capture spontaneous abortion). Cohorts that are able to compare the impact of different interpregnancy intervals by maternal HIV status would also be helpful.

CONCLUSIONS

Adverse pregnancy outcomes occurred in more than one-third of WHIV who conceived on ART shortly after an index pregnancy. Most of the women with spontaneous abortion or stillbirth had experienced a recent prior pregnancy loss. Prior fetal loss (and interpregnancy interval) should be considered in analyses of incident pregnancies where possible. ART before and throughout pregnancy is essential in preserving maternal health and preventing onward vertical HIV transmission. Antenatal and peripartum care should be optimized, with identification of the safest maternal ART regimens, interventions to address modifiable risk factors, and clinical management of high-risk pregnancies.

ACKNOWLEDGMENTS

The authors are gratefully thank and acknowledge the participants enrolled in this study. The authors acknowledge the hard work of each of the clinical research sites.

REFERENCES

1. Uthman OA, Nachega JB, Anderson J, et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *Lancet HIV*. 2017;4:e21–e30.
2. Caniglia EC, Abrams J, Diseko M, et al. Seasonality of adverse birth outcomes in women with and without HIV in a representative birth outcomes surveillance study in Botswana. *BMJ Open*. 2021;11:e045882.
3. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375:1726–1737.
4. Tukei VJ, Hoffman HJ, Greenberg L, et al. Adverse pregnancy outcomes among HIV-positive women in the era of universal antiretroviral therapy remain elevated compared with HIV-negative women. *Pediatr Infect Dis J*. 2021;40:821–826.

5. Portwood C, Sexton H, Kumarendran M, et al. Adverse perinatal outcomes associated with antiretroviral therapy in women living with HIV: a systematic review and meta-analysis. *Front Med (Lausanne)*. 2022;9:924593.
6. Wedi CO, Kirtley S, Hopewell S, et al. Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis. *Lancet HIV*. 2016;3:e33–e48.
7. Hoffman RM, Brummel SS, Britto P, et al. Adverse pregnancy outcomes among women who conceive on antiretroviral therapy. *Clin Infect Dis*. 2019;68:273–279.
8. Theron G, Brummel S, Fairlie L, et al. Pregnancy outcomes of women conceiving on antiretroviral therapy (ART) compared to those commenced on ART during pregnancy. *Clin Infect Dis*. 2021;73:e312–e320.
9. Yampolsky M, Shlakhter O, Deng D, et al. Exploring the impact of HIV infection and antiretroviral therapy on placenta morphology. *Placenta*. 2021;104:102–109.
10. Ikumi NM, Malaba TR, Pillay K, et al. Differential impact of antiretroviral therapy initiated before or during pregnancy on placenta pathology in HIV-positive women. *AIDS*. 2021;35:717–726.
11. Daniel S, Koren G, Lunenfeld E, et al. Immortal time bias in drug safety cohort studies: spontaneous abortion following nonsteroidal antiinflammatory drug exposure. *Am J Obstet Gynecol*. 2015;212:307.e1–307.e3076.
12. Lamont K, Scott NW, Jones GT, et al. Risk of recurrent stillbirth: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2015;350:h3080.
13. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, et al. Recurrent miscarriage: evidence to accelerate action. *Lancet (London, England)*. 2021;397:1675–1682.
14. 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;397:1276–1292.
15. Chinula L, Ziemba L, Brummel S, et al. Efficacy and safety of three antiretroviral therapy regimens started in pregnancy up to 50 weeks post partum: a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet HIV*. 2023;10:e363–e374.
16. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381:827–840.
17. World Health Organization. *Potential Safety Issue Affecting Women Living with HIV Using Dolutegravir at the Time of Conception*. Geneva, Switzerland: World Health Organization; 2018.
18. American College of Obstetricians and Gynaecologists. *Methods for Estimating the Due Date. Committee Opinion*; 2017. Available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co700.pdf?dmc=1&ts=20180614T1445563792. Accessed August 10, 2023.
19. Intergrowth-21st. *Standards and Tools*; 2023. Available at: https://intergrowth21.tghn.org/standards-tools/. Accessed August 10, 2023.
20. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis*. 2012;206:1695–1705.
21. Kourtis AP, Zhu W, Lampe MA, et al. Dolutegravir and pregnancy outcomes including neural tube defects in the USA during 2008-20: a national cohort study. *Lancet HIV*. 2023;10:e588–e596.
22. Stringer EM, Kendall MA, Lockman S, et al. Pregnancy outcomes among HIV-infected women who conceived on antiretroviral therapy. *PloS One*. 2018;13:e0199555.
23. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *Lancet Glob Health*. 2018;6:e804–e810.
24. Eke AC, Mirochnick M, Lockman S. Antiretroviral therapy and adverse pregnancy outcomes in people living with HIV. *N Engl J Med*. 2023;388:344–356.
25. Hoffman RM, Angelidou KN, Brummel SS, et al. Maternal health outcomes among HIV-infected breastfeeding women with high CD4 counts: results of a treatment strategy trial. *HIV Clin Trials*. 2018;19:209–224.
26. Vieira VA, Fairlie L. Effects of preconception antiretroviral therapy in placenta development and pregnancy outcomes. *AIDS (London, England)*. 2021;35:1139–1141.
27. Hoffman Risa, Ziemba Lauren, Chinula Lameck, et al., eds. *Antepartum Weight Gain and Adverse Pregnancy Outcomes: A Mediation Analysis*. Denver, CO: CROI; 2023.
28. Joseph NT, Satten GA, Williams RE, et al. The effect of antiretroviral therapy for the treatment of human immunodeficiency virus (HIV)-1 in pregnancy on gestational weight gain. *Clin Infect Dis*. 2022;75:665–672.
29. Leonard MA, Cindi Z, Bradford Y, et al. Efavirenz pharmacogenetics and weight gain following switch to integrase inhibitor-containing regimens. *Clin Infect Dis*. 2021;73:e2153–e2163.
30. Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? *AIDS (London, England)*. 2021;35(suppl 2):S189–S195.
31. Kangatharan C, Labram S, Bhattacharya S. Interpregnancy interval following miscarriage and adverse pregnancy outcomes: systematic review and meta-analysis. *Hum Reprod Update*. 2017;23:221–231.
32. van Eijk AM, De Cock KM, Ayisi JG, et al. Pregnancy interval and delivery outcome among HIV-seropositive and HIV-seronegative women in Kisumu, Kenya. *Trop Med Int Health*. 2004;9:15–24.
33. World Health Organization. *Report of a WHO Technical Consultation on Birth Spacing Geneva, Switzerland*. Geneva, Switzerland: World Health Organization; 2005.
34. Antiretroviral Pregnancy Registry Steering Committee. *Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2024*. Morrisville, NC: Registry Coordinating Center; www.APRegistry.com (2024).
35. Mehta U, Kalk E, Fairlie L, et al. Why South Africa urgently needs to support the development of pregnancy exposure registries. *S Afr Med J*. 2019;109:294–295.
36. Ubomi Buhle Pregnancy Exposure Registry. *Ubomi Buhle Website*; 2022. Available at: ubomibuhle.org.za. Accessed August 10, 2023.