

Effects of preterm birth, maternal ART and breastfeeding on 24-month infant HIV-free survival in a randomized trial

Sufia Dadabhai^{a,u,*}, Victoria B. Chou^{b,*}, Mauricio Pinilla^c,
Lameck Chinula^{d,e}, Maxensia Owor^f, Avy Violari^g, Dhayendre
Moodley^h, Lynda Stranix-Chibanda^{i,j}, Taguma Allen Matubu^k,
Gift Tafadzwa Chareka^l, Gerhard Theron^k, Aarti Avinash Kinikar^l,
Mwangelwa Mubiana-Mbewe^m, Lee Fairlieⁿ, Raziya Bobat^o,
Blandina Theophil Mmbaga^p, Patricia M. Flynn^q, Taha E. Taha^a,
Katie S. McCarthy^r, Renee Browning^s, Lynne M. Mofenson^t,
Sean S. Brummel^c, Mary Glenn Fowler^b, for the IMPAACT PROMISE
1077BF/FF team

See related paper on page 1430

Background: IMPAACT 1077BF/FF (PROMISE) compared the safety/efficacy of two HIV antiretroviral therapy (ART) regimens to zidovudine (ZDV) alone during pregnancy for HIV prevention. PROMISE found an increased risk of preterm delivery (<37 weeks) with antepartum triple ART (TDF/FTC/LPV+r or ZDV/3TC/LPV+r) compared with ZDV alone. We assessed the impact of preterm birth, breastfeeding, and antepartum ART regimen on 24-month infant survival.

Methods: We compared HIV-free and overall survival at 24 months for liveborn infants by gestational age, time-varying breastfeeding status, and antepartum ART arm at 14 sites in Africa and India. Kaplan–Meier survival probabilities and Cox proportional hazards ratios were estimated.

^aDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, ^bDepartment of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, ^cCenter for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, ^dDivision of Global Women's Health, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, ^eUniversity of North Carolina Project Malawi, Tiziwe Centre, Lilongwe, Malawi, ^fMU-JHU Research Collaboration; Upper Mulago Hill Road, Kampala, Uganda, ^gPerinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Soweto, ^hCentre for the AIDS Programme of Research in South Africa and School of Clinical Medicine, University of KwaZulu Natal, Congella, South Africa, ⁱChild, Adolescent and Women's Health Department, Faculty of Medicine and Health Sciences, University of Zimbabwe, Avondale, ^jUniversity of Zimbabwe Clinical Trials Research Centre, Belgravia, Harare, Zimbabwe, ^kDepartment of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, ^lB.J. Government Medical College, Department of Paediatrics, Pune, India, ^mCentre for Infectious Disease Research in Zambia, George CRS, Lusaka, Zambia, ⁿWits RHI, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, ^oDepartment of Paediatrics and Child Health, University of KwaZulu-Natal, Durban, South Africa, ^pKilimanjaro Christian Medical Centre, Kilimanjaro Clinical Research Institute and Kilimanjaro Christian Medical University College/Kilimanjaro CRS, Moshi, Tanzania, ^qSt. Jude Children's Research Hospital, Memphis, TN, ^rFHI 360, Durham, NC, ^sNational Institute of Allergy and Infectious Diseases/NIH, Rockville, MD, ^tElizabeth Glaser Pediatric AIDS Foundation, Washington DC, USA, and ^uKamuzu University of Health Sciences-Johns Hopkins Research Project, Blantyre, Malawi.

Correspondence to Sufia Dadabhai, MHS, PhD, Johns Hopkins University Bloomberg School of Public Health, Blantyre, Malawi, P.O. Box 1131, Blantyre, Malawi.

Tel: +265 882130694; e-mail: sufia@jhu.edu

* S. Dadabhai and V.B. Chou are co-first authors.

Received: 13 September 2023; revised: 30 January 2024; accepted: 12 February 2024.

DOI:10.1097/QAD.0000000000003878

Results: Three thousand four hundred and eighty-two live-born infants [568 (16.3%) preterm and 2914 (83.7%) term] were included. Preterm birth was significantly associated with lower HIV-free survival [0.85; 95% confidence interval (CI) 0.82–0.88] and lower overall survival (0.89; 95% CI 0.86–0.91) versus term birth (0.96; 95% CI 0.95–0.96). Very preterm birth (<34 weeks) was associated with low HIV-free survival (0.65; 95% CI 0.54–0.73) and low overall survival (0.66; 95% CI 0.56–0.74). Risk of HIV infection or death at 24 months was higher with TDF-ART than ZDV-ART (adjusted hazard ratio 2.37; 95% CI 1.21–4.64). Breastfeeding initiated near birth decreased risk of infection or death at 24 months (adjusted hazard ratio 0.05; 95% CI 0.03–0.08) compared with not breastfeeding.

Conclusion: Preterm birth and antepartum TDF-ART were associated with lower 24-month HIV-free survival compared with term birth and ZDV-ART. Any breastfeeding strongly promoted HIV-free survival, especially if initiated close to birth. Reducing preterm birth and promoting infant feeding with breastmilk among HIV/antiretroviral drug-exposed infants remain global health priorities.

Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

AIDS 2024, **38**:1304–1313

Keywords: antiretroviral drug exposures, breastfeeding, HIV-exposed children, infant survival, preterm birth

Introduction

Globally, women of reproductive age living with HIV must have access to well tolerated, effective combination antiretroviral therapy (ART) to protect their health and prevent vertical and breastfeeding transmission. The IMPAACT network's Promoting Maternal and Infant Survival Everywhere (PROMISE/1077) study (NCT01061151) was a multicountry, randomized, open-label, perinatal trial comparing the relative safety and efficacy of proven antiretroviral interventions for the prevention of vertical HIV transmission. PROMISE showed that perinatal HIV transmission can be reduced to less than 1% when antiretroviral drugs are used in three-drug combinations, during pregnancy [1], and during breastfeeding [2].

PROMISE also demonstrated that women receiving an antepartum zidovudine (ZDV)-based regimen (zidovudine/lamivudine/lopinavir-ritonavir: ZDV/3TC/LPV+r) or a tenofovir-based regimen (tenofovir disoproxil fumarate/emtricitabine/lopinavir-ritonavir: TDF/FTC/LPV+r) had a significantly higher risk of preterm delivery (<37 weeks gestational age) compared with women taking antenatal ZDV alone from enrolment through delivery, plus single-dose nevirapine (NVP) at labour onset, and a 14-day TDF/FTC 'tail' (referred to 'ZDV alone'). In the ZDV-ART and TDF-ART arms, 19.7 and 18.5% of babies were born preterm, respectively, compared with the ZDV alone arm (13.5%) [3], during the study period, when women were randomized equally to the three ARV arms. Other randomised trials, observational studies, and systematic reviews have also shown an increased risk of preterm birth with use of ART during pregnancy, compared with no ART or to single drug regimens, which are no longer used by any

country but were standard of care at many sites during PROMISE [4–8].

The protease inhibitor-based regimens used as first-line ART in the United States and globally at the time of PROMISE are now infrequently used among adults, including pregnant women, with a shift over time to EFV-based ART and recently to DTG-based ART. Nonetheless, PROMISE results have enduring relevance because they demonstrate an increased risk of adverse pregnancy outcomes among infants exposed to TDF-based ART, compared with ZDV-based ART. Current WHO [9] and US ART guidelines [10] still include protease inhibitor-based ART as an alternative adult regimen under certain circumstances, and as part of first-line treatment for infants. Similarly, the recent VESTED trial [11] (IMPAACT 2010) and Botswana cohort registry study [12] showed that DTG/TDF/FTC ART, while critical for reducing drug resistance and virologic failure, remains associated with adverse pregnancy outcomes. Underlying mechanisms for this concerning finding across multiple studies and settings remain unclear.

Each year, globally, 15 million babies (11%) are born preterm; 1 million die before age 5 [13]. Preterm birth can also have significant long-term consequences for child development and quality of life, particularly among very early preterm births [14]. Risks associated with preterm birth may be long-term, with modestly increased mortality persisting into adulthood [15]. In sub-Saharan Africa, with 28% of the global burden of preterm births [13], care for pregnant women with HIV becomes complex, as both untreated HIV infection and some ART regimens increase risk for preterm birth [5,8,16,17].

In this planned secondary analysis, we assessed the impact of preterm and very preterm, antenatal antiretroviral drugs and type of infant feeding on 24-month overall and HIV-free survival outcomes among liveborn infants from PROMISE.

Methods

Study design and participants

Pregnant women living with HIV at 14 weeks' gestation or greater were recruited because they did not meet local criteria for HIV treatment at the time of enrolment. Mothers and their liveborn infants were enrolled from 14 study sites in seven countries across East and Southern Africa and India. Although extended breastfeeding was the norm in most resource-limited settings where PROMISE took place, formula and clean water were accessible to a small group of women in the trial and thus formula-fed infants were also included in analyses. PROMISE was approved by all local and collaborating institutional review boards, and all participants provided written informed consent. Information about the methods, including eligibility criteria, randomization, and study visit procedures, has been described [1,2]. The study protocol is available: <https://www.impaactnetwork.org/studies/1077bf> and <https://www.impaactnetwork.org/studies/1077ff>. This article addresses protocol objective 2.222 and the analyses and corresponding subgroups are presented in the statistical analysis section.

Randomization

Maternal antepartum regimens included three arms: oral ZDV alone, consisting of ZDV taken twice-daily during pregnancy; single dose NVP and double dose TDF/FTC at the onset of labour; followed by a 1 week (7–14 days) course of TDF/FTC to reduce the risk of NVP resistance; oral ZDV-ART, consisting of ZDV/3TC/LPV+r twice-daily during pregnancy and labour/delivery and through the first week postdelivery; and oral TDF-ART, consisting of TDF/FTC/LPV+r (TDF/FTC once daily and LPV+r twice daily), and through the first week postdelivery.

During period 1 of PROMISE, when limited safety data were available about TDF during pregnancy, women who were hepatitis B virus (HBV)-negative were randomised 1 : 1 to ZDV alone or ZDV-ART; women co-infected with HBV were randomized 1 : 1 : 1 to one of three regimens: ZDV alone, ZDV-ART or TDF-ART. During period 2 (October 2012 through October 2014), after sufficient safety data were available, all new PROMISE enrollees were randomized 1 : 1 : 1 to one of the three regimens.

Infants in all trial groups received weight-based NVP prophylaxis from birth through 6 weeks. Breastfeeding mother–infant pairs who qualified underwent two subsequent randomizations, during breastfeeding: to either continued daily infant NVP or maternal ART

(TDF-ART) through cessation of breastfeeding; and after the breastfeeding-associated transmission risk ended: to continue ART or stop maternal ART. Women and infants received prophylaxis with trimethoprim–sulfamethoxazole per study-site country guidelines. Women who met country-specific treatment guidelines and infants confirmed to have HIV began ART immediately, and were not included PROMISE. This analysis also included women who presented close to delivery (late presenters). The overall PROMISE schema is presented in Supplemental Figure 1, <http://links.lww.com/QAD/D139>.

In mid-2015, results of the adult 'START' trial [18] demonstrated significant benefits to receiving immediate ART regardless of CD4⁺ cell count at diagnosis, versus delayed treatment. In July 2015, the PROMISE team recommended that all maternal PROMISE participants transition to ART, ending randomization. Analyses done by ART randomization arm are thus limited to data before 07 July 2015.

Procedures

The mothers' visit schedule has been previously described. Infant visits occurred postnatal weeks 1, 6, 10, and 14; then monthly until 6 months; and quarterly thereafter. Gestational age was assessed at two timepoints. At screening, gestational age was estimated based on a specified hierarchy of available data including last menstrual period (LMP) and standard obstetric examination assessments. For both facility-based and home-based deliveries, gestational age was also assessed during a newborn clinical examination using the New Ballard score [19], either at birth or within approximately 2 days of birth for home deliveries (maximum 8 days).

Outcomes

The primary outcomes of the antepartum component of the PROMISE trial were HIV transmission at 1 week after birth as well as maternal and infant safety including prematurity and other adverse pregnancy outcomes. This current analysis focused on 24-month HIV-free survival and overall survival in infants based upon gestational age and maternal antiretroviral strategy. Infants were followed for at least 24 months.

Research sites reported serious adverse events, including infant death, within 72 h of site awareness (or as soon as possible thereafter) through the online DAIDS adverse event reporting system (DAERS). An independent Data and Safety Monitoring Board (DSMB) reviewed the PROMISE study every 6 months.

Statistical analysis

In this analysis, two 24-month outcomes are presented: infant overall survival and HIV-free survival at 24 months. Overall survival was defined by date of reported infant death, whereas HIV-free survival was defined as date of first event being either infant death or confirmed HIV

infection. Confirmation of HIV infection was based on a second sample taken at a different time point than the first positive HIV nucleic acid test (NAT) test, and discrepant HIV infection results were adjudicated by the Infant Endpoint Review Committee.

For both overall survival and HIV-free survival, time zero was defined as the date of birth and censoring of follow-up was applied at the earlier of the date the infant was last seen or at 104 weeks. Multiple births are included in the baseline summaries but were only counted once in the analysis, using the earliest censoring date or event date. No additional censoring was applied at subsequent PROMISE randomizations and gestational age based on the New Ballard score, at birth or approximately 2–8 days after birth, was used in all analyses.

Three comparisons were made: by gestational age, by ART arm, and by breastfeeding status. Gestational age at birth was categorized in two ways: preterm infants (born <37 weeks) were compared with those born full-term (born $\geq$ 37 weeks) and very preterm infants (born <34 weeks) were compared with those not very preterm (born $\geq$ 34 weeks). ART arms were compared using the appropriate contemporaneously randomized periods. Comparisons of ZDV alone to ZDV-ART included women randomized during period 1 and period 2; comparisons to TDF-ART only included period 2 [1]. This analysis focused on assessing the impact of the antepartum regimens and therefore, comparisons did not consider the postpartum ART regimen, which was determined by a second randomization step. Breastfeeding (yes/no) was summarized as a time-dependent covariate. Cessation of breastfeeding was defined as completely stopping all infant exposure to breastmilk for greater than or equal to 28 days based on maternal report. The ART arm and breastfeeding comparisons included mothers randomized in pregnancy. Analyses comparing outcomes by gestational age at birth included the same women randomized in pregnancy plus Late Presenters who transitioned into the study's postpartum component.

The Kaplan–Meier method and Greenwood's formula for standard error were used to calculate infant survival probability estimates and 95% CIs at 104 weeks of age for the ART arm and gestational age comparisons. Cox proportional hazards regression with breastfeeding was used to calculate hazard ratios and 95% CIs. We analysed breastfeeding with and without adjustment for study arm.

Supplemental competing risk analyses were also performed for the comparisons by antenatal maternal ART regimen. Foetal losses were treated as a competing risk and included spontaneous abortions (foetal loss at <20 weeks gestational age) and stillbirths ($\geq$ 20 weeks). Results did not significantly alter the conclusions in this article, and are provided as Supplemental materials, Tables 1.1–1.8, <http://links.lww.com/QAD/D139>.

SAS version 9.4 and R version 3.2.2 were used for analyses. Missing data were assumed to be missing completely at random and analyses were based on a complete case analysis. *P* values <0.05 were considered to be statistically significant, and no adjustments for multiple comparisons were made.

Role of the funding source

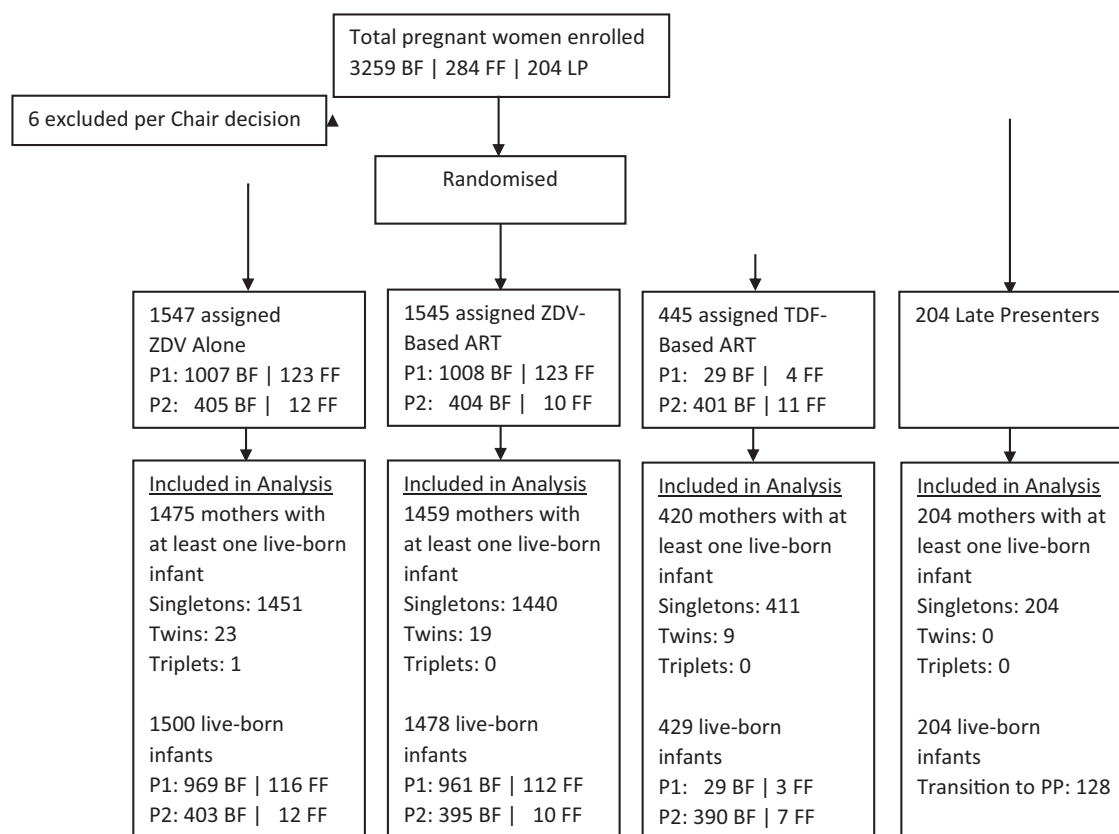
Following the initial decision to approve and fund the study, decisions around data collection, analysis, interpretation were made independent of funding decisions. One co-author from the sponsoring agency is included on the manuscript given her subject matter expertise. One funding source (NIAID) sponsored the independent DSMB. Finally, a science review body from NIH reviewed and approved protocol amendments prior to implementation, with no influence on, or from, the funding office.

Results

This secondary analysis included mother–infant pairs (3558 mothers and 3611 infants) enrolled in the PROMISE 1077BF/FF trial between 2011 and 2015 who were followed through 2017 (Fig. 1). Maternal participants were predominantly African (97%), with a median age of 26 years (Q1–Q3 22–30) and a median BMI of 26 kg/m² (Q1–Q3 23–30). Antepartum component mothers enrolled at a median of 26 gestational weeks (Q1–Q3 21–31); Late presenters enrolled at a median of 38 gestational weeks (Q1–Q3 38–40). Most mothers were categorized as WHO clinical stage I (asymptomatic), and the median CD4⁺ cell count was 531 (Q1–Q3 436–667) (Table 1).

After excluding 76 mother–infant late presenter pairs who did not transition to the postpartum component, we included 3535 live-born infants in the analyses. These infants were born to mothers enrolled in antepartum component, or as late presenters and who later enrolled in the postpartum component: 51% were male individuals, 97% African, 82% had normal birthweight ($\geq$ 2500 g), 17% had low birthweight (1500 to <2500 g), and 1% very low birthweight (<1500 g). Median gestational age at delivery was 39 weeks; 83% of infants were born full-term and 17% were preterm (14% born $\geq$ 34 to <37 weeks and 3% born <34 weeks). APGAR assessments recorded at 1 and 5 min after birth were generally in the high range (7–10) for 93 and 99% of infants, respectively (Table 2). Overall, 91% (*n* = 3188) of women delivered in a facility, attended by trained healthcare staff, and 7% (239) in the home. Among women with premature births, 86% (489) delivered in a health facility, and 12% (68) in the home.

For the preterm birth analyses, there were 3482 live-born infants (after selecting only one infant per mother in the



BF: Breastfeeding protocol; FF: Formula-feeding protocol; PP: Postpartum component; P1: Period 1; P2: Period 2

Fig. 1. Consort diagram for the PROMISE 24-month infant/child survival analyses. This diagram summarizes the number of pregnant women enrolled in the trial ($n = 3747$) and subset of mothers ($n = 3558$) and infants ($n = 3611$) included in the 24-month survival analyses. BF, breastfeeding protocol; FF, formula-feeding protocol; P1, period 1; P2, period 2; PP, postpartum component.

case of multiple births), whose mothers intended to breastfeed: 2914 full-term (83.7%) and 568 preterm (16.3%). Among the 2914 full-term infants included in the preterm birth analysis, there were 64 deaths (2.2%) and 53 HIV infections (1.8%). Among the 568 preterm infants, there were 62 (10.9%) deaths, 49 during the neonatal period (first 28 days of life) and 13 deaths after. Among preterm infants, there were 18 (3.2%) HIV infections, 9 within 28 days, 8 on day 28 or after; 1 infection was followed by death within 28 days.

Preterm birth less than 37 weeks was associated with decreased 24-month HIV-free survival compared with full-term birth [survival probability of 0.85 (95% CI 0.82–0.88) and 0.96 (95% CI 0.95–0.96), respectively]. The difference in 24-month HIV-free survival was more pronounced for infants born very preterm compared with infants born after 34 weeks [survival probability of 0.65 (95% CI 0.54–0.73) and 0.95 (95% CI 0.94–0.96), respectively] (Fig. 2). Similar differences were seen when comparing the overall survival of infants born preterm (0.89; 95% CI 0.86–0.91) to infants born full-term (0.97; 95% CI 0.97–0.98), to infants born very preterm (0.66; 95% CI 0.56–0.74) to infants born after 34 weeks (0.97; 95% CI 0.96–0.98).

For periods 1 and 2, combined and comparing infants exposed to either antepartum ZDV alone or maternal ZDV-ART, there were no differences in 24-month HIV-free survival (i.e. HIV infection or infant death as the outcome) and no difference in infant survival (overall) between infants whose mothers received antenatal ZDV alone compared with those who received antenatal ZDV-ART (Tables 3 and 4, top). In period 2, with 1:1:1 randomization for the three exposure arms, infants with antenatal TDF-ART exposure had a greater risk of HIV infection or death by 24 months compared with ZDV-ART, when adjusted for breastfeeding (adjusted hazard ratio 2.37, 95% CI 1.21–4.64). However, HIV-free survival with TDF-ART exposure was not significantly different from antenatal ZDV alone (adjusted hazard ratio 1.66, 95% CI 0.89–3.11) (Tables 3 and 4, bottom).

Among infants in these analyses whose mothers intended to breastfeed, 81.0% were still breastfeeding at 26 weeks and over half (59.3%) were still breastfeeding at 52 weeks of age. By 78 weeks of age, most (86.6%) were no longer breastfeeding.

For periods 1 and 2, time-varying breastfeeding was protective against risk of HIV infection or death by

Table 1. Baseline characteristics for women randomized during pregnancy and late presenters.

		Periods 1 and 2		Period 2 only			
		ZDV alone (N = 1547)	ZDV-based ART (N = 1545)	ZDV alone (N = 417)	ZDV-based ART (N = 414)	TDF-based ART (N = 412)	Late presenter (N = 204)
Age (years)	Min-Max	18–49	18–44	18–46	18–43	18–40	18–43
	Median (Q1–Q3)	26 (22–30)	26 (23–30)	25 (22–29)	26 (23–30)	26 (22–30)	26 (23–31)
	18 to <30	1148 (74%)	1130 (73%)	322 (77%)	298 (72%)	303 (74%)	146 (72%)
	30 to <40	384 (25%)	391 (25%)	93 (22%)	108 (26%)	108 (26%)	54 (26%)
Race	≥40	15 (1%)	24 (2%)	2 (0%)	8 (2%)	1 (0%)	4 (2%)
	Black African	1499 (97%)	1498 (97%)	416 (100%)	413 (100%)	411 (100%)	184 (90%)
	Indian	47 (3%)	46 (3%)	1 (0%)	1 (0%)	1 (0%)	19 (9%)
	Other	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Country	India	46 (3%)	46 (3%)	1 (0%)	1 (0%)	0 (0%)	19 (9%)
	Malawi	489 (32%)	493 (32%)	139 (33%)	139 (34%)	141 (34%)	31 (15%)
	South Africa	513 (33%)	510 (33%)	70 (17%)	68 (16%)	67 (16%)	27 (13%)
	Tanzania	23 (1%)	24 (2%)	11 (3%)	12 (3%)	10 (2%)	0 (0%)
	Uganda	207 (13%)	205 (13%)	83 (20%)	83 (20%)	82 (20%)	9 (4%)
	Zambia	32 (2%)	31 (2%)	18 (4%)	19 (5%)	18 (4%)	2 (1%)
	Zimbabwe	237 (15%)	236 (15%)	95 (23%)	92 (22%)	94 (23%)	116 (57%)
	N	1545	1535	416	407	409	202
Height (cm)	Min-Max	117–179	120–185	117–178	134–185	139–180	140–188
	Median	158	158	158	158	158	160
	(Q1–Q3)	(153–162)	(153–162)	(152–162)	(152–163)	(153–162)	(155–164)
	N	1547	1545	417	414	412	200
Weight (kg)	Min-Max	36–128	35–140	43–122	37–119	43–136	42–106
	Median (Q1–Q3)	64 (58–74)	65 (58–74)	63 (57–71)	64 (58–73)	64 (58–75)	61 (53–69)
GA at entry (weeks)	N	1547	1544	417	413	412	203
	Min-Max	14–42	13–43	14–39	14–41	14–39	30–44
BMI (kg/m ²)	Median (Q1–Q3)	26 (21–30)	25 (21–30)	26 (21–31)	26 (21–31)	26 (22–31)	38 (38–40)
	N	1545	1535	416	407	409	198
	Min-Max	15–52	14–55	18–47	16–43	19–52	17–40
	Median (Q1–Q3)	26 (23–30)	26 (23–30)	26 (23–29)	26 (23–29)	26 (24–30)	24 (22–27)
WHO clinical stage	Stage I	1493 (97%)	1506 (98%)	404 (97%)	403 (97%)	405 (98%)	165 (98%)
	Stage II	50 (3%)	34 (2%)	13 (3%)	11 (3%)	7 (2%)	4 (2%)
	Missing	3	3	0	0	0	35
	Stage III	1 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Viral load (copies/ml)	N	1540	1542	415	414	412	196
	Min-Max	20–1 433 155	20–750 000	20–1 433 155	20–569 511	20–2 361 568	40–3 976 393
CD4 ⁺ cell count (cells/μl)	Median	6409	8002	6122	6939	8536	12 140
	(Q1–Q3)	(1451–22 720)	(1854–28 767)	(1400–24 133)	(1510–26 664)	(1886–29 030)	(2408–39 139)
	<400	213 (14%)	146 (9%)	54 (13%)	48 (12%)	42 (10%)	21 (11%)
	400 to <1000	117 (8%)	132 (9%)	35 (8%)	29 (7%)	26 (6%)	7 (4%)
	1000 to <10 000	579 (38%)	574 (37%)	153 (37%)	164 (40%)	150 (36%)	63 (32%)
	10 000 to <100 000	532 (35%)	570 (37%)	145 (35%)	145 (35%)	162 (39%)	80 (41%)
	100 000 to <200 000	60 (4%)	71 (5%)	14 (3%)	14 (3%)	22 (5%)	14 (7%)
	≥200 000	39 (3%)	49 (3%)	14 (3%)	14 (3%)	10 (2%)	11 (6%)
	Missing	7	3	2	0	0	8
	N	1547	1545	417	414	412	195
	Min-Max	350–2033	351–1842	350–1493	351–1821	350–1277	71–1498
	Median	534	526	530	541	543	522
	(Q1–Q3)	(435–678)	(439–651)	(431–687)	(452–666)	(432–689)	(347–737)
	<350	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	49 (25%)
	350 to <400	224 (14%)	215 (14%)	61 (15%)	44 (11%)	51 (12%)	13 (7%)
	400 to <450	238 (15%)	227 (15%)	71 (17%)	57 (14%)	76 (18%)	15 (8%)
	450 to <500	181 (12%)	213 (14%)	45 (11%)	51 (12%)	40 (10%)	10 (5%)
	≥500	904 (58%)	890 (58%)	240 (58%)	262 (63%)	245 (59%)	108 (55%)
	Missing	0	0	0	0	0	9

Age is at randomization. Weight, BMI, WHO clinical stage, and viral load are last measurements before randomization. CD4⁺ cell count is from screening for antepartum component mothers and from study entry for late presenter mothers.

Table 2. Baseline characteristics for live-born infants^a of women randomized during pregnancy and late presenters.

		Periods 1 and 2		Period 2 only			Late presenter (N = 204)
		ZDV alone (N = 1500)	ZDV-based ART (N = 1478)	ZDV alone (N = 415)	ZDV-based ART (N = 405)	TDF-based ART (N = 397)	
Sex	Male	797 (53%)	701 (47%)	229 (55%)	191 (47%)	223 (56%)	100 (49%)
	Female	702 (47%)	777 (53%)	186 (45%)	214 (53%)	174 (44%)	104 (51%)
	Missing	1	0	0	0	0	0
Gestational age (weeks)	N	1500	1478	415	405	397	204
	<34	42 (3%)	47 (3%)	13 (3%)	8 (2%)	25 (6%)	1 (0%)
	34 to <37	162 (11%)	249 (17%)	46 (11%)	62 (15%)	51 (13%)	21 (10%)
Country	≥37	1296 (86%)	1182 (80%)	356 (86%)	335 (83%)	321 (81%)	182 (89%)
	India	44 (3%)	44 (3%)	1 (0%)	1 (0%)	0 (0%)	19 (9%)
	Malawi	472 (31%)	470 (32%)	138 (33%)	135 (33%)	140 (35%)	31 (15%)
	South Africa	490 (33%)	476 (32%)	70 (17%)	66 (16%)	59 (15%)	27 (13%)
	Tanzania	24 (2%)	24 (2%)	12 (3%)	12 (3%)	10 (3%)	0 (0%)
	Uganda	203 (14%)	199 (13%)	81 (20%)	80 (20%)	80 (20%)	9 (4%)
Birth weight (g)	Zimbabwe	33 (2%)	31 (2%)	19 (5%)	19 (5%)	18 (5%)	2 (1%)
	N	234 (16%)	234 (16%)	94 (23%)	92 (23%)	90 (23%)	116 (57%)
	<1500	1449	1422	389	380	373	204
APGAR score at 1 min	1500 to <2500	14 (1%)	20 (1%)	1 (0%)	2 (1%)	11 (3%)	0 (0%)
	≥2500	170 (12%)	310 (22%)	38 (10%)	73 (19%)	56 (15%)	34 (17%)
	Missing	1265 (87%)	1092 (77%)	350 (90%)	305 (80%)	306 (82%)	170 (83%)
APGAR score at 5 min	N	51	56	26	25	24	0
	0–3	1362	1293	356	328	328	175
	4–6	15 (1%)	14 (1%)	4 (1%)	5 (2%)	6 (2%)	0 (0%)
Household running water	7–10	72 (5%)	74 (6%)	19 (5%)	12 (4%)	21 (6%)	12 (7%)
	Missing	1275 (94%)	1205 (93%)	333 (94%)	311 (95%)	301 (92%)	163 (93%)
	N	138	185	59	77	69	29
	0–3	1354	1291	355	328	327	175
	4–6	4 (0%)	4 (0%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)
	7–10	11 (1%)	11 (1%)	2 (1%)	4 (1%)	7 (2%)	2 (1%)
	Missing	1339 (99%)	1276 (99%)	350 (99%)	324 (99%)	319 (98%)	173 (99%)
	N	146	187	60	77	70	29
	Yes	597 (44%)	613 (46%)	127 (33%)	120 (31%)	106 (29%)	70 (38%)
	No	754 (56%)	730 (54%)	261 (67%)	264 (69%)	258 (71%)	116 (62%)
	Unknown	149	135	27	21	33	18

Gestational age is at birth. Weight and length measurements are from the week 0 visit (0–5 days old). APGAR scores are at the time specified, after birth. Infants born to mothers on the TDF-ART arm in period 1 were excluded.

^aAll infants from multiple pregnancies were included in baseline summaries.

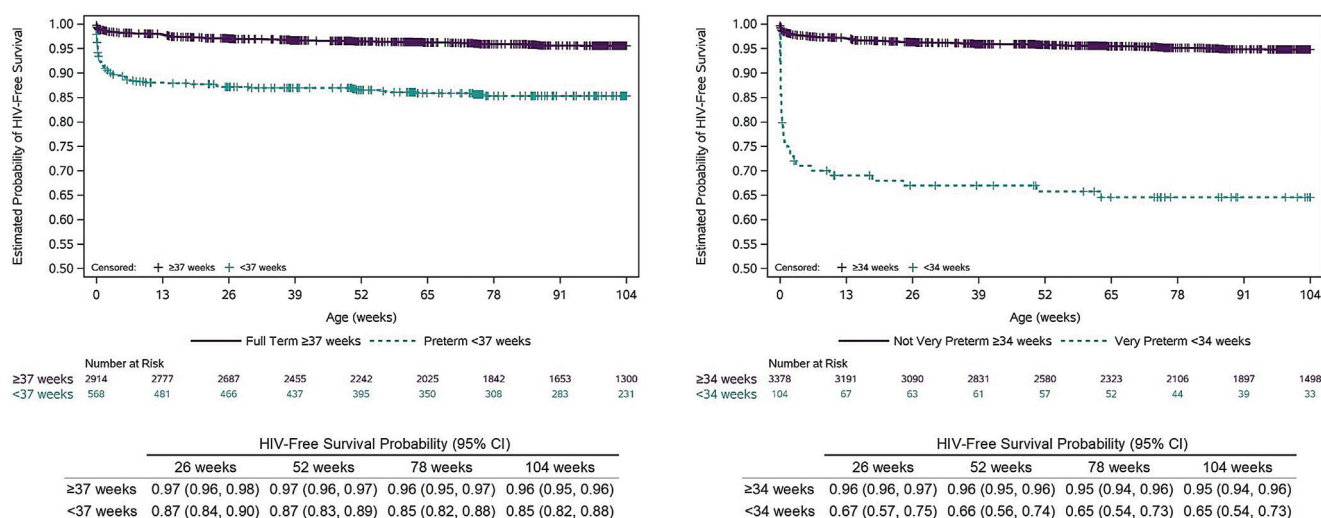


Fig. 2. Twenty-four-month HIV-free survival among PROMISE infants, by gestational age at birth. Kaplan–Meier estimated survival probabilities for time to infant HIV infection or death through 104 weeks of age, by gestational age at birth (full-term, ≥37 weeks; preterm, <37 weeks; and very preterm, <34 weeks).

Table 3. Hazard ratios for HIV-free survival (no HIV infection or death) at 24 months by breastfeeding status and maternal antepartum regimen.

Periods 1 and 2	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
BF vs. not BF	0.14 (0.09–0.21)	<0.001	0.14 (0.09–0.20)	<0.001
ZDV-ART vs. ZDV alone	0.85 (0.61–1.20)	0.36	0.83 (0.59–1.16)	0.27
Period 2 only	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
BF vs. not BF	0.05 (0.03–0.09)	<0.001	0.05 (0.03–0.08)	<0.001
ZDV-ART vs. ZDV alone	0.80 (0.38–1.66)	0.55	0.70 (0.34–1.46)	0.34
TDF-ART vs. ZDV alone	1.59 (0.85–2.97)	0.15	1.66 (0.89–3.11)	0.11
TDF-ART vs. ZDV-ART	1.98 (1.02–3.88)	0.0450	2.37 (1.21–4.64)	0.0122

24 months (adjusted hazard ratio 0.14, 95% CI 0.09–0.20), when adjusted for maternal antenatal ART arm. Similar results were observed for period 2 only (adjusted hazard ratio 0.05, 95% CI 0.03–0.08) (Tables 3 and 4 and Supplemental Figures 2a/2b, <http://links.lww.com/QAD/D139>).

Discussion

In this secondary analysis of longer term survival of preterm versus term breastfed infants, we found that the probability of 24-month HIV-free and overall survival was significantly lower for infants born preterm, especially those born very preterm, compared with infants born later in gestation. Infants born preterm (<37 weeks), and very preterm (<34 weeks), had lower overall survival and HIV-free survival probabilities at 24 months than infants born at least 37 and at least 34 weeks gestational age, respectively (all $P < 0.001$), with survival curves that separated early in life.

Infants born to mothers randomized to TDF-ART had a more than two-fold increased risk of HIV infection or death at 24 months compared with those exposed to maternal ZDV-ART; whereas HIV-free survival with TDF-ART was not significantly different from ZDV alone. No other differences were observed by maternal antiretroviral/ART regimen. These findings may point to an

effect of maternal ART on longer term child outcomes, mediated through the association of antepartum ART and preterm birth, as documented in PROMISE antepartum results [1] and other studies [6,20–22].

Early breastfeeding was strongly associated with decreased risk of HIV or death. The general infant/child survival literature confirms the benefits of breastfeeding, but the relationship is more complex among infants who might be too sick to breastfeed and thus would not obtain the benefits of breastfeeding for nutrition and the immune system.

Prior studies [1,3,5,20,23] and systematic reviews [7,8,24] have shown an association between antepartum ART and adverse perinatal outcomes including preterm birth, compared with no ART and when comparing different maternal regimens. Preterm birth is associated with elevated risk for morbidity and mortality among newborns, infants, and children [25,26]. Conclusions drawn from prior observational cohort studies and randomized trials are difficult to compare because of substantial heterogeneity in design and comparator groups [24]. Nonetheless, our findings are consistent with reports from a hospital-based retrospective study [4] and a randomized trial in Botswana [17] that found high preterm rates among pregnant women taking a protease inhibitor-containing ART regimen. However, unlike our current analysis, they did not detect any difference in

Table 4. Hazard ratios for overall survival (no death) at 24 months by breastfeeding status and maternal antepartum regimen.

Periods 1 and 2	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
BF vs. not BF	0.05 (0.03–0.08)	<0.001	0.05 (0.03–0.08)	<0.001
ZDV-ART vs. ZDV alone	0.81 (0.52–1.24)	0.33	0.76 (0.49–1.17)	0.21
Period 2 only	Unadjusted hazard ratio (95% CI)	P value	Adjusted hazard ratio (95% CI)	P value
BF vs. not BF	0.02 (0.01–0.04)	<0.001	0.02 (0.01–0.04)	<0.001
ZDV-ART vs. ZDV alone	0.54 (0.20–1.46)	0.23	0.45 (0.17–1.23)	0.12
TDF-ART vs. ZDV alone	1.77 (0.84–3.71)	0.13	1.87 (0.89–3.93)	0.0992
TDF-ART vs. ZDV-ART	3.27 (1.31–8.19)	0.0114	4.13 (1.64–10.37)	0.0026

Graphical representation of Tables 3 and 4 are provided as supplemental materials, Figures 1a and 1b, <http://links.lww.com/QAD/D139>. BF, breastfed; TDF-ART, oral tenofovir/emtricitabine/lopinavir-ritonavir twice-daily during pregnancy and labour/delivery and through the first week postdelivery; ZDV alone, oral Zidovudine twice-daily during pregnancy and labour/delivery with single dose nevirapine at delivery and followed by a 2-week course of tenofovir/emtricitabine to reduce the risk of nevirapine resistance; ZDV-ART, oral zidovudine/lamivudine/lopinavir-ritonavir twice-daily during pregnancy and labour/delivery through the first week postdelivery.

mortality at 6 months of age [6]. The mechanisms linking ART to preterm delivery, and potential impact on subsequent longer term survival, have not yet been determined, but the timing of maternal ART initiation relative to body changes during pregnancy [21], inflammatory pathways [22], and hormonal or placental changes [27] have been hypothesized.

Our study had some limitations. Assessment of gestational age based on a clinical newborn examination to determine the new Ballard score is not as accurate as using early antenatal ultrasound. However, at the time of the PROMISE trial, antenatal ultrasound was not widely available in international resource-limited study settings. Our estimates may be biased if incorrect gestational dating and misclassification were widespread, but a secondary analysis of PROMISE data found that the association between ART use and preterm birth persisted despite some misclassification [3]. Additionally, bias by gestational age was not likely to be different by randomized study arm. Our findings may be generalizable only to low-resource international environments where HIV burden is high and less relevant in countries with lower HIV prevalence and preterm burden, or in well resourced countries with more intensive interventions to prevent severe sequelae of preterm birth. Women enrolled in PROMISE were also a selected sample who were generally asymptomatic with high CD4⁺ cell counts and are not representative of all mothers with HIV because of the study eligibility criteria. Another limitation of the study is that the ART regimens, including protease inhibitors, which were first-line at the time of PROMISE, are currently used only as alternative adult regimens for special circumstances. In 2021, the WHO recommended [9] dolutegravir (DTG)-based ART as first-line treatment, including for pregnant women, based in part on results of the VESTED trial [11]. In VESTED, the rates of preterm delivery were lower for the DTG-ART regimens (6.0% in DTG-FTC-TAF and 9.4% in DTG-FTC-TDF) when compared with the EFV-TDF/FTC ART regimen (12.0%). Future ART regimens may further reduce the risk of preterm birth among women living with HIV compared with women without HIV.

A major strength of the PROMISE trial was its large sample size and ability to compare infant safety/survival outcomes through 24 months after birth for triple antiretroviral drug regimens versus mono-drug regimens. PROMISE also benefited from the rigor of a randomized design, and robust numbers for precision comparisons across subgroups. Maternal and infant baseline characteristics in this analysis were well balanced. Data for the multisite study were collected from diverse countries representing global regions hardest hit by and still battling the HIV epidemic. The competing risk analysis for foetal loss was an additional strength, as this is infrequently performed in other trials. The extended follow-up

allowed us to explore the association between preterm birth risk and later survival. Additionally, while observational studies may be unable to capture the timing of initiation and duration of antepartum ART, PROMISE captured these data, with high retention (>90%) during pregnancy, labour/delivery, and 24 months of infant follow-up.

Our findings highlight the importance of longer term follow-up of mothers living with HIV and their HIV/ART-exposed children as new ART regimens become available. This will allow for monitoring of potential late sequelae with use of new ART regimens. Although many studies focus only on infants born very preterm at less than 32 or 34 weeks' gestation, our findings suggest that preventing preterm births less than 37 weeks is likewise important in terms of improving HIV-free survival. Innovative screening approaches are needed to identify early warning signals of increased risk of preterm delivery that can be utilized in international settings. For example, machine learning could help identify predictive markers of preterm birth or other adverse pregnancy outcomes among women living with HIV. Likewise, further research is needed to delineate the biological mechanisms leading to preterm delivery among women living with HIV on ART to inform future HIV drug development. Reducing the risk of preterm birth and continued support for breastfeeding should yield substantial gains in the survival of HIV-exposed uninfected infants worldwide.

Acknowledgements

The authors gratefully acknowledge the mothers and children who participated in the PROMISE 1077BF/FF study at the 14 research sites in Eastern Africa, Southern Africa, and India; the dedicated site investigators and staff; colleagues at the Statistical and Data Analysis Center/Center for Biostatistics in AIDS Research (SDAC/CBAR); and the Frontier Science & Technology Research Foundation team.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding 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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Study products were provided as a donation by AbbVie (Abbott), Gilead Sciences, Boehringer Ingelheim, and GlaxoSmithKline.

Disclaimer: Parts of this manuscript were presented at the 2021 virtual CROI, abstract 587, 6–10 March 2021. The content of this manuscript is the responsibility of the authors and does not necessarily represent the official views of sponsors or donors.

Conflicts of interest

There are no conflicts of interest.

References

1. Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, *et al.*, IMPAACT 1077BF/1077FF PROMISE Study Team. **Benefits and risks of antiretroviral therapy for perinatal HIV prevention.** *N Engl J Med* 2016; **375**:1726–1737.
2. Flynn PM, Taha TE, Cababasay M, Fowler MG, Mofenson LM, Owor M, *et al.*, PROMISE Study Team. **Prevention of HIV-1 transmission through breastfeeding: efficacy and safety of maternal antiretroviral therapy versus infant nevirapine prophylaxis for duration of breastfeeding in HIV-1-infected women with high CD4 cell count (IMPAACT PROMISE): a randomized, open-label, clinical trial.** *J Acquir Immune Defic Syndr* 2018; **77**:383–392.
3. Venkatesh KK, Farhad M, Fenton T, Moodley D, Naik S, Nakabiito C, *et al.* **Association between HIV antiretroviral therapy and preterm birth based on antenatal ultrasound gestational age determination: a comparative analysis.** *AIDS* 2019; **33**:2403–2413.
4. Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogbu A, Lockman S, *et al.* **Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana.** *J Infect Dis* 2012; **206**:1695–1705.
5. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. **Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or still-birth?** *J Infect Dis* 2006; **193**:1195–1201.
6. Powis KM, Kitch D, Ogbu A, Hughes MD, Lockman S, Leidner J, *et al.* **Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy.** *J Infect Dis* 2011; **204**:506–514.
7. Saleska JL, Turner AN, Maierhofer C, Clark J, Kwiek JJ. **Use of antiretroviral therapy during pregnancy and adverse birth outcomes among women living with HIV-1 in low- and middle-income countries: a systematic review.** *J Acquir Immune Defic Syndr* 2018; **79**:1–9.
8. Tshivuila-Matala COO, Honeyman S, Nesbitt C, Kirtley S, Kennedy SH, Hemelaar J. **Adverse perinatal outcomes associated with antiretroviral therapy regimens: systematic review and network meta-analysis.** *AIDS* 2020; **34**:1643–1656.
9. WHO. In: Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva; 2021.
10. Panel on Antiretroviral Guidelines for Adults and Adolescents. **Guidelines for the use of antiretroviral agents in adults and adolescents with HIV.** Department of Health and Human Services; 2023.
11. Lockman S, Brummel SS, Ziemba L, Stranix-Chibanda L, McCarthy K, Coletti A, *et al.*, IMPAACT 2010/VESTED Study Team and Investigators. **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.
12. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex 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.
13. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, *et al.* **Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis.** *Lancet Glob Health* 2019; **7**:e37–e46.
14. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. **Neurologic and developmental disability after extremely preterm birth. EPICure Study Group.** *N Engl J Med* 2000; **343**:378–384.
15. Crump C. **Preterm birth and mortality in adulthood: a systematic review.** *J Perinatol* 2020; **40**:833–843.
16. Eke AC, Olagunju A, Best BM, Mirochnick M, Momper JD, Abrams E, *et al.* **Innovative approaches for pharmacology studies in pregnant and lactating women: a viewpoint and lessons from HIV.** *Clin Pharmacokinet* 2020; **59**:1185–1194.
17. Shapiro RL, Kitch D, Ogbu A, Hughes MD, Lockman S, Powis K, *et al.* **HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana.** *AIDS* 2013; **27**:1911–1920.
18. Group ISS, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, *et al.* **Initiation of antiretroviral therapy in early asymptomatic HIV infection.** *N Engl J Med* 2015; **373**:795–807.
19. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. **New Ballard Score, expanded to include extremely premature infants.** *J Pediatr* 1991; **119**:417–423.
20. Piske M, Qiu AQ, Maan EJ, Sauve LJ, Forbes JC, Alimenti A, *et al.*, CIHR Team Grant on Cellular Aging and HIV Comorbidities in Women and Children. **Preterm birth and antiretroviral exposure in infants HIV-exposed uninfected.** *Pediatr Infect Dis J* 2021; **40**:245–250.
21. Short CE, Douglas M, Smith JH, Taylor GP. **Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission.** *HIV Med* 2014; **15**:233–238.
22. Short CE, Taylor GP. **Antiretroviral therapy and preterm birth in HIV-infected women.** *Expert Rev Anti Infect Ther* 2014; **12**:293–306.
23. Townsend C, Schulte J, Thorne C, Dominguez KI, Tookey PA, Cortina-Borja M, *et al.*, Pediatric Spectrum of HIV Disease Consortium, the European Collaborative Study and the National Study of HIV in Pregnancy and Childhood. **Antiretroviral therapy and preterm delivery—a pooled analysis of data from the United States and Europe.** *BJOG* 2010; **117**:1399–1410.
24. Brocklehurst P, French R. **The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis.** *Br J Obstet Gynaecol* 1998; **105**:836–848.
25. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, *et al.*, CHERG Small-for-Gestational-Age-Preterm Birth Working Group. **Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis.** *Lancet* 2013; **382**:417–425.
26. Walani SR. **Global burden of preterm birth.** *Int J Gynaecol Obstet* 2020; **150**:31–33.
27. Obimbo MM, Zhou Y, McMaster MT, Cohen CR, Qureshi Z, Ong'ech J, *et al.* **Placental structure in preterm birth among HIV-positive versus HIV-negative women in Kenya.** *J Acquir Immune Defic Syndr* 2019; **80**:94–102.