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Timing of pregnancy, postpartum risk of virologic failure and loss to follow-up among HIV-positive women

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Objectives: We assessed the association between the timing of pregnancy with the risk of postpartum virologic failure and loss from HIV care in South Africa.

Design: This is a retrospective cohort study of 6306 HIV-positive women aged 15–49 at antiretroviral therapy (ART) initiation, initiated on ART between January 2004 and December 2013 in Johannesburg, South Africa.

Methods: The incidence of virologic failure (two consecutive viral load measurements of >1000 copies/ml) and loss to follow-up (>3 months late for a visit) during 24 months postpartum were assessed using Cox proportional hazards modelling.

Results: The rate of postpartum virologic failure was higher following an incident pregnancy on ART [adjusted hazard ratio 1.8, 95% confidence interval (CI): 1.1–2.7] than among women who initiated ART during pregnancy. This difference was sustained among women with $CD4^+$ cell count less than 350 cells/μl at delivery (adjusted hazard ratio 1.8, 95% CI: 1.1–3.0). Predictors of postpartum virologic failure were being viremic, longer time on ART, being 25 or less years old and low $CD4^+$ cell count and anaemia at delivery, as well as initiating ART on stavudine-containing or abacavir-containing regimen. There was no difference postpartum loss to follow-up rates between the incident pregnancies group (hazard ratio 0.9, 95% CI: 0.7–1.1) and those who initiated ART in pregnancy.

Conclusion: The risk of virologic failure remains high among postpartum women, particularly those who conceive on ART. The results highlight the need to provide adequate support for HIV-positive women with fertility intention after ART initiation and to strengthen monitoring and retention efforts for postpartum women to sustain the benefits of ART.

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Introduction

HIV among women of childbearing age remains an important contributor to maternal and child morbidity and mortality [1]. The risk remains high as the HIV prevalence among women attending antenatal care (ANC) in the South African public health sector has remained steady around 30% in the past 10 years [2–4]. In 2015, the amended South African guidelines for the prevention of mother-to-child transmission (PMTCT) of

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HIV made provisions to initiate all HIV-positive pregnant and breastfeeding women on lifelong antiretroviral therapy (ART) upon HIV diagnosis [5]. Although this policy further increased the ART coverage in this population, long-term ART success will depend on their ability to attain sustained virologic suppression.

The PMTCT programmes play a critical role in the diagnosis and ART initiation of HIV-positive women. However, the programme's strong focus on protecting the baby frames the ART experience of many HIV-positive women [6–9]. As a result, the motivation of women initiated on ART in the context of PMTCT to adhere to ART and remained in HIV care wanes gradually after delivery [10–12]. Although this is well documented among women who initiate ART during pregnancy (prevalent pregnancies at ART initiation), far less has been written about women who conceive while receiving ART (incident pregnancies). The 2013 South African national ANC survey showed that the majority (73.5%) of primiparous women who tested HIV-positive in ANC had prior knowledge of their HIV status but the proportion with prior ART exposure is unclear [2]. Certainly, as South Africa scales up the 'treat-all' strategy, many more HIV-positive women will be receiving ART at conception [13,14].

To date, few studies have quantified the postpartum risk of virologic failure because of viral load data limitations in most resource-limited settings. Furthermore, the question of whether initiating ART before a pregnancy improves postpartum retention and virologic outcomes has not been sufficiently explored. Understanding predictors of postpartum virologic failure and loss from HIV care among treatment experienced women who conceive on ART is necessary to inform interventions to improve postpartum retention in care and ART adherence among women with fertility intentions after ART initiation.

In this article, we aim to assess whether the timing of ART initiation in relation to pregnancy start has some bearing on the risk of virologic failure and the risk of becoming lost to follow-up (LTFU) in the first 2 years postpartum.

Methods

Study population

We conducted a cohort study using prospectively collected, anonymized medical records of HIV-infected adult women (18–49 years old at ART initiation) initiated on a standard first-line ART regimen according to South African guidelines between 1 January 2004 and 31 December 2013, at three nongovernmental organizations (NGO) and seven public ART clinics that receive technical support from right to care, a nonprofit organization in Johannesburg, South Africa. The first South African ART guidelines in 2004 made provisions for one first-line regimen including stavudine (d4T), lamivudine (3TC), efavirenz (EFV) or nevirapine (NVP) in the case of contraindications to EFV [15]. In 2010, the standard first-line regimens were updated to substitute d4T with tenofovir (TDF) as the first option for new patients, include zidovudine (ZDV) as part of first-line ART in which TDF was contraindicated and use emtricitabine (FTC) as an alternative for 3TC [16]. In 2013, abacavir (ABC) was added as an option in cases of contraindications to TDF, ZDV and d4T in first-line ART [17].

Clinical data from the ART clinics were captured on site and stored in an electronic patient-management system, TherapyEdge-HIV (Advanced Biologic Laboratories, SA, Luxembourg). Additional clinical and laboratory data were obtained from electronic records held by the National Health Laboratory Services. Data were fully anonymized for analysis. The final analytic data set included only women who had at least one recorded viral load measurement during the period of observation.

The primary exposure event was having a first (ever) pregnancy lasting at least 7 months and ending before 31 December 2013 that resulted in a live birth. Unexposed women (no recorded pregnancy) were matched to exposed women on age at ART initiation, year of ART initiation and time on ART at delivery. Time on ART for exposed women was measured from ART initiation to the date of delivery. The observation period for unexposed women (pseudo-postpartum period) began at the delivery date of their matched exposed woman.

The data set was closed on 31 December 2015, allowing for 24 months of postpartum (or equivalent period on ART for the unexposed) follow-up. Up to two unexposed women were matched to each exposed woman. Ethics approval for the data review was obtained from the Human Research Ethics Committee of the University of Witwatersrand (M140201) as well as Boston University Institutional Review Board (H-29768).

Analytic variables

The secondary exposure variable was created by further categorizing exposed women by when, in relation to the pregnancy start date, ART was initiated as unexposed women (no recorded pregnancy), women conceived while receiving ART (incident pregnancy) and women who initiated ART during pregnancy (prevalent pregnancy).

The primary outcome was virologic failure (defined as having two consecutive viral load measurements >1000 copies/ml, and the first failing viral load occurring

at least 3 months after the date of delivery) in the first 24 months postpartum or pseudo-postpartum for unexposed women (six). The secondary outcome was postpartum LTFU from HIV care, defined as being at least 3 months late for a scheduled visit during the observation period.

Potential confounders included were demographic variables as well as clinical and laboratory variables measured closest to the date of delivery either in the last trimester of the pregnancy or no more than 3 months after delivery or baseline for the unexposed, including BMI, $CD4^+$ cell counts, ART regimen and haemoglobin (Hb). BMI was categorized as underweight ($BMI < 18.5$), normal ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$) and obese ($BMI \geq 30$). Anaemia was defined as an Hb value below 11.5 g/dl. $CD4^+$ (measured in cells/μl) was categorized as less than199, 200–350 and more than 350 cells/μl. Viral suppression was defined as having a viral load measurement less than 50 copies/ml.

Follow-up time

Person-time accrued from the date of delivery (considered as baseline time point) for postpartum women or their matched baseline date for unexposed women. Women were followed until the outcome of interest, the last date seen at the clinic during the first 2 years after the baseline date (for those who died, were LTFU or transferred out) or 31 December 2015, whichever came first.

Statistical analysis

Baseline characteristics were described using medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables stratified by pregnancy status. Computed incidence of virologic failure or LTFU was expressed as rates per 100 person-years. Cox proportional hazard models were used to explore predictors of postpartum virologic failure and LTFU separately. We then conducted a Cox regression stratified by timing of the first pregnancy to examine whether predictors of postpartum virologic failure or LTFU among women who conceive on ART differ from those of women who initiate ART during pregnancy. Variables associated with virologic failure or LTFU in crude Cox proportional hazards models ($P < 0.10$) in the postpartum period were included in multivariate models. Also included were variables that changed the hazard ratio for the exposure of interest by more than10% and are known not to be on the causal pathway or colliders. Schoenfeld residuals were used to test for adherence to the proportional hazard assumption. Kaplan–Meier curves were used to compare progression to first virologic failure or LTFU event in the postpartum period among women with high baseline $CD4^+$ (>350 cells/μl) to women with low baseline $CD4^+$ (≤350 cells/μl), stratified by timing of pregnancy. Data analysis was conducted using STATA version 14 (StataCorp, College Station, Texas, USA).

Results

Baseline demographic characteristics of study sample

The data set included 7953 women. From these, 1128 (14.2%) with missing scheduled visits after delivery and 519 (6.5%) with missing postpartum viral load measurements were excluded from the final analytic data set. Among the excluded women, 278 of 1647 (16.9%) were transferred within the first 3 months after delivery, and 44 of 1647 (2.7%) women died within 90 days of delivery.

Table 1 presents the demographic and clinical characteristics of the study sample consisting of 6306 women, 2403 (38.1%) were unexposed, 1953 (31.0%) had an incident pregnancy on ART and 1950 (30.9%) had a prevalent pregnancy at ART initiation. The overall median age at the start of observation was 31.2 years (IQR: 27.7–35.0). The prevalent pregnancy group was slightly younger at delivery (median 29.7 years, IQR: 26.4–33.6) compared with the incident pregnancy group (median 32.3, IQR: 28.9–35.6). Furthermore, the proportion of school attenders with at least a grade 12 level of education was markedly higher among women with an incident pregnancy (67.9%) than women with a prevalent pregnancy (50.3%). Unemployment rates were similar across exposure categories with an average rate of 61.9%.

Baseline clinical characteristics of study sample

Overall, 30.2% of women initiated ART on a combination of 3TC/FTC, TDF and EFV or NVP, only 9.7% were initiated on a regimen of ZDV, 3TC and EFV/NVP, and 59.8% were initiated on d4T, 3TC and EFV/NVP. Although the majority (93.6%) of women with prevalent pregnancy and 80.2% of unexposed women remained on their first regimen throughout the pregnancy, only 53.7% of women with incident pregnancies were still on their first regimen with 11.2% permanently switched to second-line ART at delivery. Overall, 39.8% of postpartum (exposed) women had detectable viral RNA (>50 copies/ml) at delivery. Anaemia at delivery was most common in the prevalent pregnancy group (29.6, 26.3 and 50.5% among unexposed women, incident pregnancy and prevalent pregnancy, respectively). Overall, 47.0% had baseline $CD4^+$ at least 350 cells/μl, 43.1% among unexposed women, 61.9% among the incident pregnancy group and 38.0% among prevalent pregnancy group.

Predictors of virologic failure 24 months postpartum

Table 2 and Fig. 1 show rates and predictors of virologic failure in the study sample. Study patients were followed up for an average of 1.6 years (SD 0.6). Overall, 510 (8.1%) women experienced virologic failure in the 10 091.5 person-years of observation [incidence rate 5.1/100 person-years, 95% confidence interval (CI):

Table 1. Demographic and baseline clinical characteristics of the study sample.

	Women with no recorded pregnancy *n* (col %) *N* = 2403	Women with incident pregnancy *n* (col %) *N* = 1953	Women with prevalent pregnancy *n* (col %) *N* = 1950	Total *n* (col %) *N* = 6306
Average follow-up time, mean years (SD)	1.6 (0.6)	1.7 (0.5)	1.5 (0.6)	1.6 (0.6)
Race				
Black	2334 (98.3)	1917 (98.6)	1896 (98.6)	6147 (98.5)
Other	41 (1.7)	28 (1.4)	27 (1.4)	96 (1.5)
Age at delivery/baseline				
Under 25	289 (12.0)	120 (6.1)	323 (16.6)	732 (11.6)
25–29.9	669 (27.8)	518 (26.5)	689 (35.3)	1876 (29.7)
30–39.9	1327 (55.2)	1223 (62.6)	867 (44.5)	3417 (54.2)
40–49.9	118 (4.9)	91 (4.7)	71 (3.6)	280 (4.4)
Highest level of education at ART initiation				
Primary school	213 (9.2)	143 (7.6)	121 (6.4)	477 (7.9)
Some secondary school	528 (22.8)	260 (13.8)	525 (27.9)	1313 (21.6)
Grade 12 completed	971 (42.0)	801 (42.7)	627 (33.4)	2399 (39.5)
Postmatric	48 (2.1)	53 (2.8)	27 (1.4)	128 (2.1)
No schooling	552 (23.9)	621 (33.1)	580 (30.9)	1753 (28.9)
Employment status at ART initiation				
Employed	838 (36.8)	680 (36.1)	770 (41.9)	2288 (38.1)
Unemployed	1441 (63.2)	1203 (63.9)	1069 (58.1)	3713 (61.9)
ART site				
Clinic in hospital complex	1055 (43.9)	1037 (53.1)	510 (26.2)	2602 (41.3)
Local primary care clinic	949 (39.5)	438 (22.4)	593 (30.4)	1980 (31.4)
NGO-run clinic	398 (16.6)	478 (24.5)	847 (43.4)	1723 (27.3)
Initial first-line ART regimen				
3TC/FTC + TDF + EFV/NVP	753 (31.3)	309 (15.8)	843 (43.2)	1905 (30.2)
ZDV + 3TC + EFV/NVP	146 (6.1)	112 (5.7)	355 (18.2)	613 (9.7)
d4T + 3TC + EFV/NVP	1491 (62.0)	1530 (78.3)	751 (38.5)	3772 (59.8)
3TC + ABC + EFV/NVP	13 (0.5)	2 (0.1)	1 (0.1)	16 (0.3)
ART regimen changes by the time of delivery (or equivalent matched time)				
First-line regimen preserved	1927 (80.2)	1049 (53.7)	1826 (93.6)	4802 (76.2)
First-line drug substitution	346 (14.4)	619 (31.7)	50 (2.6)	1015 (16.1)
Switched to second-line ART	56 (2.3)	219 (11.2)	15 (0.8)	290 (4.6)
Treatment interrupted	74 (3.1)	66 (3.4)	59 (3.0)	199 (3.2)
Among those who interrupted ART				
Overall length of treatment interruption, median months (IQR)	12.7 (6.6–21.2)	5.8 (3.9–11.4)	5.7 (2.7–14.1)	8.0 (4.1–16.2)
Period of ART interruption in pregnancy, median months (IQR)	4.6 (1.4–9.0)	0.6 (0–4.5)	0 (0–0.5)	1.0 (0–5.0)
Period of interruption after delivery, median months (IQR)	6.3 (2.4–13.6)	4.7 (3.0–7.3)	6.3 (2.0–14.8)	5.4 (2.4–12.8)
New regimen after treatment interruption				
3TC/FTC + TDF + EFV/NVP	32 (43.2)	18 (27.7)	25 (42.4)	75 (37.9)
ZDV + 3TC + EFV/NVP	3 (4.1)	9 (13.9)	6 (10.2)	18 (9.1)
d4T + 3TC + EFV/NVP	25 (33.8)	19 (29.2)	22 (37.3)	66 (33.3)
Second-line (three ARVs with LPVr/ATVr)	6 (8.1)	16 (24.6)	5 (8.5)	27 (13.6)
Other	8 (10.8)	3 (4.6)	1 (1.7)	12 (6.1)
Time on ART before delivery (or equivalent matched time)				
3 months or less	563 (23.4)	0	1390 (71.3)	1953 (31.0)
4–6 months	432 (18.0)	0	440 (22.6)	872 (13.8)
7–12 months	428 (17.8)	163 (8.3)	120 (6.2)	711 (11.3)
13–24 months	527 (21.9)	862 (44.1)	0	1389 (22.0)
25 months or longer	453 (18.9)	928 (47.5)	0	1381 (21.9)
BMI up to 3 months before or after delivery (or equivalent matched time)				
Underweight	135 (7.5)	21 (1.2)	19 (1.1)	175 (3.3)
Normal	876 (48.7)	570 (31.7)	553 (31.6)	1999 (37.4)
Overweight	499 (27.8)	719 (39.9)	697 (39.8)	1915 (35.8)
Obese	288 (16.0)	490 (27.2)	483 (27.6)	1261 (23.6)
Anaemic up to 3 months before or after delivery (or equivalent matched time)				
No	1103 (70.4)	1075 (73.7)	777 (49.5)	2955 (64.3)
Yes	463 (29.6)	383 (26.3)	794 (50.5)	1640 (35.7)
$CD4^+$ cell count up to 3 months before or after delivery (or equivalent matched time)				
Under 200	464 (25.3)	148 (9.9)	462 (28.2)	1074 (21.6)
200–349	579 (31.6)	420 (28.2)	555 (33.9)	1554 (31.3)
350 or higher	789 (43.1)	923 (61.9)	622 (38.0)	2334 (47.0)
Unsuppressed viral load (≥50 copies/ml) up to 3 months before or after delivery (or equivalent matched time)				
No	1149 (63.1)	1054 (64.6)	913 (55.7)	3116 (61.2)
Yes	672 (36.9)	577 (35.4)	726 (44.3)	1975 (38.8)
Viral load ≥400 copies/ml up to 3 months before or after delivery (or equivalent matched time)				
No	1464 (80.4)	1359 (83.3)	1226 (74.8)	4049 (79.5)
Yes	357 (19.6)	272 (16.7)	413 (25.2)	1042 (20.5)

Baseline/equivalent matched time: end of first pregnancy for exposed and equivalent time on ART for matched nonexposed women. 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; LPVr, lopinavir; NGO, nongovernmental organizations; NVP, nevirapine; IQR, interquartile range; TDF, tenofovir; ZDV, zidovudine.

Table 2. Predictors of virologic failure 24 months postpartum among HIV-positive women receiving antiretroviral therapy in Johannesburg, South Africa.

	Virologic failure	Person-years	Rate per100 PY (95% CI)	Total sample		Women with incident pregnancy	Women with prevalent pregnancy
				Crude HR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Total sample	510 (8.1)	10 091.5	5.1 (4.6–5.5)				
Timing of pregnancy							
No recorded pregnancy	198 (8.2)	3870.1	5.1 (4.5–5.9)	1	1		
Incident pregnancy	188 (9.6)	3284.9	5.7 (5.0–6.6)	1.1 (0.9–1.4)	1.3 (1.0–1.8)		
Prevalent pregnancy	124 (6.4)	2936.4	4.2 (3.5–5.0)	0.8 (0.7–1.0)	0.7 (0.5–1.0)		
Age at baseline							
Under 25	73 (10.0)	1085.6	6.7 (5.3–8.5)	1	1	1	1
25–29.9	166 (8.8)	2947.8	5.6 (4.8–6.6)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.9 (0.5–1.7)	0.6 (0.3–1.3)
30–39.9	257 (7.5)	5583.2	4.6 (4.1–5.2)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.6 (0.4–1.1)	0.9 (0.5–1.7)
40–49.9	14 (5.0)	473.2	3.0 (1.8–5.0)	0.4 (0.2–0.8)	0.3 (0.1–0.7)	0.2 (0.1–0.8)	0.4 (0.1–1.7)
Highest level of education at ART initiation							
Primary school	43 (9.0)	744.2	5.8 (4.3–7.8)	1			
Some secondary school	96 (7.3)	1974.3	4.9 (4.0–5.9)	0.8 (0.6–1.2)			
Grade 12 completed	203 (8.5)	3875.3	5.2 (4.6–6.0)	0.9 (0.7–1.3)			
Postmatric	11 (8.6)	210.5	5.2 (2.9–9.4)	0.9 (0.5–1.8)			
No schooling or unknown	141 (8.0)	2908.2	4.8 (4.1–5.7)	0.8 (0.6–1.2)			
Employment status at ART initiation							
Employed	160 (7.0)	3777.8	4.2 (3.6–4.9)	1	1	1	1
Unemployed	333 (9.0)	5847.9	5.7 (5.1–6.3)	1.3 (1.1–1.6)	1.2 (0.9–1.5)	1.0 (0.7–1.4)	1.2 (0.8–1.9)
ART site							
Clinic in hospital complex	219 (8.4)	4258.7	5.1 (4.5–5.9)	1			
Local primary care clinic	167 (8.4)	3012.6	5.5 (4.8–6.5)	1.1 (0.9–1.3)			
NGO-run clinic	124 (7.2)	2819.2	4.4 (3.7–5.2)	0.9 (0.7–1.1)			
First ever ART regimen							
TDF + 3TC/FTC + EFV/NVP	130 (6.8)	2845.0	4.6 (3.8–5.4)	1	1	1	1
ZDV + 3TC + EFV/NVP	44 (7.2)	1001.8	4.4 (3.3–5.9)	1.0 (0.7–1.3)	1.0 (0.7–1.6)	0.9 (0.3–3.0)	1.2 (0.6–2.3)
d4T + 3TC + EFV/NVP	332 (8.8)	6221.6	5.3 (4.8–5.9)	1.2 (0.9–1.4)	0.7 (0.4–1.2)	2.3 (1.2–4.4)	0.2 (0.1–0.8)
ABC + 3TC + EFV/NVP	4 (25.0)	23.1	17.3 (6.5–46.1)	3.8 (1.4–10.3)	0.9 (0.2–3.5)	5.5 (1.1–27.0)	–
ART regimen changes by delivery/baseline							
First-line regimen preserved	377 (8.0)	7600.6	5.0 (5.9–5.5)	1	1	1	1
First-line drug substitution	74 (7.3)	1730.9	4.3 (3.4–5.4)	0.9 (0.7–1.1)	0.8 (0.6–1.2)	1.0 (0.7–1.5)	0.6 (0.1–2.5)
Switched to second-line ART	27 (9.3)	446.4	6.0 (4.1–8.8)	1.2 (0.8–1.8)	0.8 (0.5–1.3)	1.0 (0.6–1.7)	
Treatment interrupted	32 (16.1)	313.6	10.2 (7.2–14.4)	2.1 (1.4–2.9)	1.1 (0.7–1.9)	1.2 (0.5–2.6)	0.7 (0.2–2.9)
Time on ART before delivery/baseline							
3 months or less	136 (7.0)	2973.5	4.6 (3.9–5.4)	1	1		1
4–6 months	61 (7.0)	1333.2	4.6 (3.6–5.9)	1.0 (0.8–1.3)	1.6 (1.1–2.3)		1.8 (1.0–3.1)
7–12 months	59 (8.3)	1160.5	5.1 (3.9–6.6)	1.0 (0.7–1.4)	1.4 (0.9–2.2)	1	3.0 (1.4–6.2)
13–24 months	147 (10.6)	2300.8	6.4 (5.4–7.5)	1.1 (0.8–1.5)	2.0 (1.3–3.1)	1.8 (1.0–3.5)	
25 months or longer	107 (7.7)	2323.5	4.6 (3.8–5.6)	1.4 (1.1–1.8)	1.7 (1.1–2.9)	1.5 (0.7–2.9)	
BMI (up to 3 months before or after baseline)							
Underweight	15 (8.6)	265.9	5.6 (3.4–9.4)	1.1 (0.6–1.8)			
Normal	171 (8.6)	3190.3	5.4 (4.6–6.2)	1			
Overweight	138 (7.2)	3076.3	4.5 (3.8–5.3)	0.8 (0.7–1.1)			
Obese	104 (8.2)	2017.9	5.2 (4.3–6.2)	1.0 (0.8–1.2)			
Anaemic (up to 3 months before or after delivery/baseline)							
No	227 (7.7)	4867.3	4.7 (4.1–5.3)	1	1	1	1
Yes	160 (9.8)	2537.3	6.3 (5.4–7.4)	1.4 (1.1–1.7)	1.2 (0.9–1.5)	1.6 (1.1–2.3)	1.0 (0.7–1.6)
$CD4^+$ cell count (up to 3 months before or after delivery/baseline)							
Under 200	149 (13.9)	1637.7	9.1 (7.7–10.7)	1	1	1	1
200–349	153 (9.8)	2447.0	6.3 (5.3–7.3)	0.7 (0.5–0.9)	0.6 (0.4–0.9)	1.1 (0.7–1.7)	0.8 (0.5–1.4)
350 or higher	129 (5.5)	3740.7	3.4 (2.9–4.1)	0.4 (0.3–0.5)	0.2 (0.1–0.4)	0.4 (0.3–0.7)	0.5 (0.3–0.9)
$CD4^+$ recovery from date of ART initiation to date of delivery							
Decline/no change	105 (9.5)	1684.0	6.2 (5.1–7.5)	1	1	1	1
<99 cell/μl increase	85 (12.0)	1098.3	7.7 (6.3–9.6)	1.2 (0.9–1.7)	1.5 (1.1–2.1)	1.1 (0.5–2.1)	1.6 (0.8–3.0)
100–200 cell/ μl increase	95 (8.8)	1698.3	5.6 (4.6–6.8)	0.9 (0.7–1.2)	1.2 (0.8–1.7)	0.7 (0.4–1.4)	1.3 (0.6–2.6)
>200 cell/μl increase	146 (7.0)	3344.6	4.4 (3.7–5.1)	0.7 (0.5–0.9)	1.3 (0.9–2.0)	1.0 (05–2.0)	1.4 (0.6–3.4)
Unsuppressed viral load (≥50 copies/ml) up to 3 months before or after delivery (or equivalent matched time)							
No	97 (3.1)	5080.1	1.9 (1.6–2.3)	1	1	1	1
Yes	333 (16.9)	2908.6	11.4 (10.2–12.7)	6.0 (4.8–7.5)	42.4 (20.2–89.0)	6.1 (4.2–8.9)	74.4 (11.6–477.5)

3TC, lamivudine; ABC, abacavir; aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; HR, hazard ratio; NGO, nongovernmental organizations; NVP, nevirapine; PY, person-years; TDF, tenofovir; ZDV, zidovudine.

4.6–5.5]. Among exposed (postpartum) women, 9.4% experienced a virologic failure compared with 8.2% in the unexposed group. The crude incidence rate of failure was highest among the incident pregnancy group (5.7/100 person-years, 95% CI: 5.0–6.6) and lower among the prevalent pregnancy group (4.2/100 person-years, 95% CI: 3.5–5.0). Although only 16.9% of women with unsuppressed baseline viral load went on to fail in the postpartum period, they were 42.4 times more likely to fail (95% CI: 20.2–89.0) compared with those who were suppressed at delivery.

After adjusting for baseline demographics and baseline viral suppression, women in the incident pregnancy

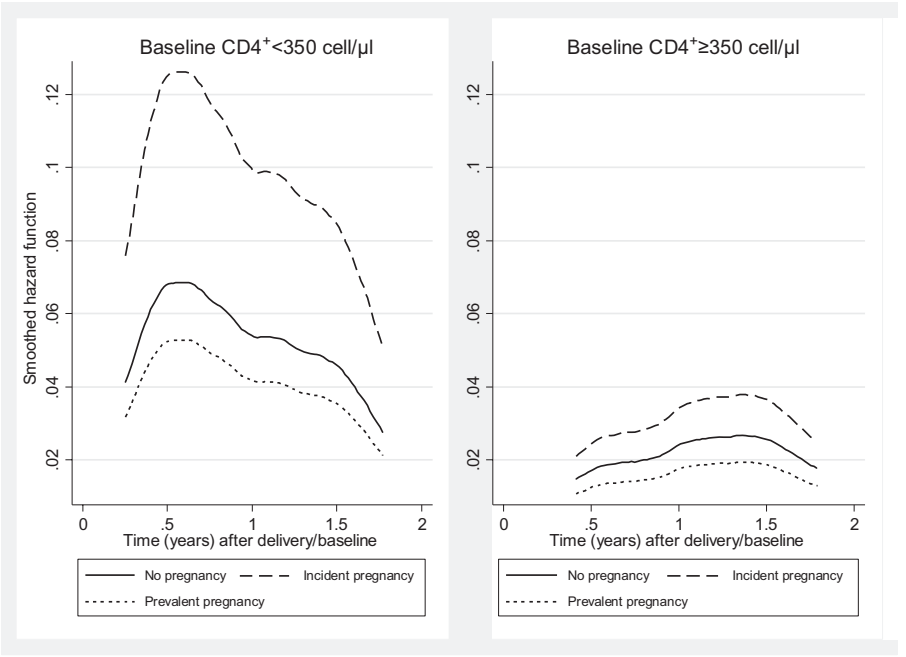

Fig. 1. Instantaneous probability of virologic failure during the first 24 months postpartum among HIV-positive women on antiretroviral therapy in Johannesburg, South Africa.

group were at higher risk of virologic failure compared with unexposed women [adjusted hazard ratio (aHR) 1.3, 95% CI: 1.0–1.8] and to those with a prevalent pregnancy at ART initiation (aHR 1.8, 95% CI: 1.1–2.7), particularly among those with baseline $CD4^+$ cell count less than 350 cells/µl. The hazard for virologic failure was highest in the first 12 months postpartum and decreased with time (aHR 1.8, 95% CI: 1.1–3.0) (Fig. 1). Overall, the risk of failure decreased with older age but increased with longer duration on ART before delivery/baseline.

When the model was stratified by pregnancy group (incident vs. prevalent pregnancy), we found that, although baseline $CD4^+$ cell count and time on ART remained important predictors across pregnancy groups, age was only influential among women in the incident pregnancy group. Although not statistically significant, women who conceived on ART and delivered after receiving ART for longer than 12 months (13–24 months, aHR 1.8, 95% CI: 1.0–3.5) were more likely to experience a failure compared with those who initiated ART less than 12 months before delivery. Furthermore, women who initiated ART on regimens that included d4T (aHR 2.3, 95% CI: 1.2–4.4) or ABC (aHR 5.5, 95% CI: 1.1–27.0) were more likely to fail compared with patients who were receiving TDF-based regimens. Increased risk of postpartum virologic failure was also associated with being anaemic at baseline (aHR 1.6, 95% CI: 1.1–2.3).

In the prevalent pregnancy group, longer antenatal ART duration also increased the risk of postpartum virologic failure (aHR 3.0, 95% CI: 1.4–6.2 for those with $\geq$7 months of antenatal ART compared with $\leq$3 months). Similarly, to the incident pregnancy group, among the prevalent pregnancy group, low $CD4^+$ cell count at delivery predicted postpartum virologic failure (aHR 0.5, 95% CI: 0.3–0.9 for those with baseline $CD4^+ \geq 350$ cells/µl compared with $CD4^+ < 200$ cell/µl).

Predictors of being loss to follow-up by 24 months postpartum

Table 3 presents rates and predictors of becoming LTFU by 24 months postpartum. When the LTFU analysis was restricted to women with at least one viral load measure on record, 1482 (23.5%) had become LTFU at a rate of 14.7/100 person-years (95% CI: 14.0–15.5) compared with 29.3% at a rate of 19.4/100 person-years (95% CI: 18.6–20.3) when all 6825 women with at least one scheduled visit after delivery were included. To ensure comparability between the sample in the virologic failure model, all further LTFU regression analyses were conducted on the restricted sample of 6306 representing 10 077.4 person-years (mean 1.5 years, SD 0.7) of observation time. The proportion of LTFU was lower among women with incident pregnancies (19.5% compared with 27.7% in the prevalent pregnancy group). Women in the prevalent pregnancy group had a slightly higher risk of becoming LTFU compared with unexposed women (aHR 1.2, 95% CI: 1.0–1.5) and a similar risk as women who conceived on ART (aHR 0.9, 95% CI: 0.7–1.1). The hazard of becoming LTFU increased sharply in the first 12 postpartum months and remained relatively stable until about 18 months postpartum (Fig. 2).

Table 3. Predictors of being lost to follow-up at 24 months postpartum among HIV-positive women receiving antiretroviral therapy in Johannesburg, South Africa.

	LTFU	Person-years	Rate per 100 PY (95% CI)	Total sample		Women with incident pregnancy	Women with prevalent pregnancy
				Crude HR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Total sample	1482 (23.5)	10077.4	14.7 (14.0–15.5)				
Timing of pregnancy							
No recorded pregnancy	561 (23.3)	3873.6	14.5 (13.3–15.7)	1	1		
Incident pregnancy	380 (19.5)	3281.5	11.6 (10.5–12.8)	0.8 (0.7–0.9)	1.0 (0.8–1.3)		
Prevalent pregnancy	541 (27.7)	2922.3	18.5 (17.0–20.1)	1.3 (1.2–1.5)	1.2 (1.0–1.5)		
Age at baseline							
Under 25	216 (29.5)	1073.7	20.1 (17.6–23.0)	1	1	1	1
25–29.9	462 (24.6)	2945.1	15.7 (14.3–17.2)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	1.3 (0.7–2.3)	0.8 (0.6–1.2)
30–39.9	741 (21.7)	5591.9	13.3 (12.3–14.2)	0.6 (0.6–0.7)	0.7 (0.6–0.9)	1.1 (0.6–1.8)	0.7 (0.5–1.0)
40–49.9	63 (22.5)	464.9	13.6 (10.6–17.3)	0.7 (0.5–0.9)	0.9 (0.6–1.3)	1.0 (0.4–2.2)	0.9 (0.5–1.6)
Highest level of education at ART initiation							
Primary school	115 (24.1)	750.7	15.3 (12.8–18.4)	1	1	1	1
Some secondary school	414 (31.5)	2006.4	20.6 (18.7–22.7)	1.4 (1.1–1.7)	1.5 (1.1–2.1)	1.5 (0.8–2.9)	1.6 (1.0–2.7)
Grade 12 completed	497 (20.7)	3884.2	12.8 (11.7–14.0)	0.8 (0.7–1.0)	0.9 (0.7–1.2)	0.8 (0.5–1.4)	0.8 (0.5–1.4)
Postmatric	25 (19.5)	208.7	12.0 (8.1–17.7)	0.8 (0.5–1.2)	1.1 (0.6–2.0)	1.0 (0.4–2.5)	1.2 (0.4–3.2)
No schooling or unknown	372 (21.2)	2855.9	13.0 (11.8–14.4)	0.8 (0.7–1.0)	1.5 (1.1–2.0)	1.4 (0.8–2.4)	1.5 (0.9–2.6)
Employment status at ART initiation							
Employed	491 (21.5)	3784.9	13.0 (11.9–14.2)	1	1	1	1
Unemployed	894 (24.1)	5829.3	15.3 (14.4–16.4)	1.2 (1.1–1.3)	1.2 (1.0–1.4)	1.1 (0.8–1.5)	1.2 (1.0–1.6)
ART site							
Clinic in hospital complex	546 (21)	4232.1	12.9 (11.9–14.0)	1	1	1	1
Local primary care clinic	595 (30.1)	3030.6	19.6 (18.1–21.3)	1.6 (1.4–1.7)	1.3 (1.1–1.5)	1.5 (1.1–2.1)	1.1 (0.7–1.7)
NGO-run clinic	341 (19.8)	2813.7	12.1 (10.9–13.5)	0.9 (0.8–1.1)	0.6 (0.5–0.7)	0.6 (0.4–1.0)	0.8 (0.4–1.5)
First ever ART regimen							
3TC/FTC + TDF + EFV/NVP	634 (33.3)	2882.8	22.0 (20.3–23.8)	1	1	1	1
ZDV + 3TC + EFV/NVP	173 (28.2)	977.8	17.7 (15.2–20.5)	0.8 (0.7–0.9)	0.9 (0.7–1.1)	1.2 (0.6–2.4)	1.3 (0.9–1.9)
d4T + 3TC + EFV/NVP	672 (17.8)	6192.0	10.9 (10.1–11.7)	0.5 (0.4–0.5)	1.1 (0.8–1.6)	1.4 (0.6–3.1)	1.7 (0.9–3.1)
3TC + ABC + EFV/NVP	3 (18.8)	24.8	12.1 (3.9–37.5)	0.5 (0.2–1.7)	1.1 (0.7–1.7)		68.3 (6.9–673.2)
ART regimen changes by delivery/baseline							
First-line regimen preserved	1126 (25.3)	6973.8	16.1 (15.2–17.1)	1	1	1	1
First-line drug substitution	132 (17.6)	1263.8	10.4 (8.8–12.4)	0.6 (0.5–0.8)	0.9 (0.7–1.1)	0.8 (0.6–1.1)	0.7 (0.3–1.5)
Switched to second-line ART	180 (19.8)	1514.6	11.9 (10.2–13.8)	0.7 (0.6–0.8)	1.1 (0.8–1.6)	1.1 (0.7–1.7)	0.3 (0.04–2.2)
Treatment Interrupted	44 (22.1)	325.2	13.5 (10.1–18.2)	0.8 (0.6–1.1)	1.1 (0.7–1.7)	1.2 (0.6–2.4)	2.0 (0.9–4.3)
Time on ART before delivery/baseline							
3 months or less	553 (28.3)	2943.8	18.8 (17.3–20.4)	1	1		1
4–6 months	228 (26.1)	1341.4	17.0 (14.9–19.4)	0.9 (0.8–1.1)	1.0 (0.8–1.2)		0.8 (0.6–1.1)
7–12 months	155 (21.8)	1150.6	13.5 (11.5–15.8)	0.7 (0.6–0.8)	0.8 (0.6–1.1)	1	0.4 (0.2–0.7)
13–24 months	269 (19.4)	2317.1	11.6 (10.3–13.1)	0.6 (0.5–0.7)	0.8 (0.5–1.2)	0.9 (0.6–1.4)	
25 months or longer	277 (20.1)	2324.5	11.9 (10.6–13.4)	0.6 (0.5–0.7)	0.7 (0.4–1.2)	0.9 (0.6–1.5)	
BMI (up to 3 months before or after baseline)							
Underweight	39 (22.3)	264.9	14.7 (10.8–20.2)	1.0 (0.7–1.4)			
Normal	464 (23.2)	3175.4	14.6 (13.3–16.0)	1			
Overweight	457 (23.9)	3063.6	14.9 (13.6–16.3)	1.0 (0.9–1.2)			
Obese	324 (25.7)	2031.5	15.9 (14.3–17.8)	1.1 (0.9–1.3)			
Anaemic (up to 3 months before or after delivery/baseline)							
No	611 (20.7)	4843.7	12.6 (11.7–13.7)	1	1	1	1
Yes	420 (25.6)	2554.1	16.4 (14.9–18.1)	1.3 (1.2–1.5)	1.1 (1.0–1.3)	1.1 (0.8–1.5)	1.1 (0.9–1.4)
$CD4^+$ cell count (up to 3 months before or after delivery/baseline)							
Under 200	278 (25.9)	1665.0	16.7 (14.8–18.8)	1	1	1	1
200–349	372 (23.9)	2455.5	15.1 (13.7–16.8)	0.9 (0.8–1.1)	0.9 (0.7–1.1)	0.9 (0.6–1.4)	0.8 (0.6–1.1)
350 or higher	514 (22.0)	3703.5	13.9 (12.7–15.1)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.7 (0.5–1.1)	1.1 (0.8–1.5)
Unsuppressed viral load (≥50 copies/ml) up to 3 months before or after delivery (or equivalent matched time)							
No	685 (22.0)	4972.1	13.8 (12.8–14.8)	1	1	1	1
Yes	505 (25.6)	3059.5	16.5 (15.2–18.0)	1.2 (1.1–1.4)	1.5 (1.1–2.1)	1.6 (1.2–2.1)	0.9 (0.7–1.2)

3TC, lamivudine; ABC, abacavir; aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; HR, hazard ratio; LTFU, loss to follow-up; NGO, nongovernmental organizations; NVP, nevirapine; PY, person-years; TDF, tenofovir; ZDV, zidovudine.

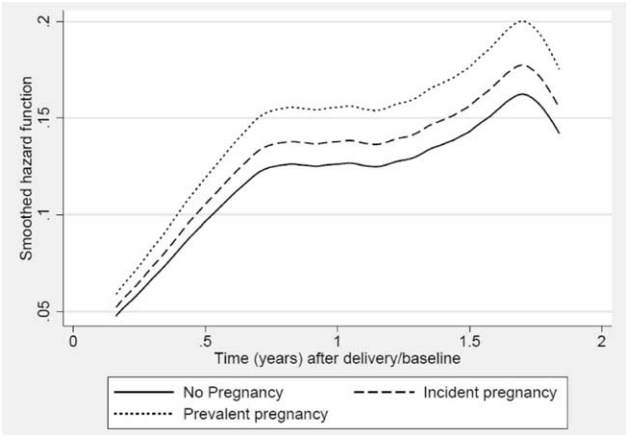

Fig. 2. Instantaneous probability of becoming loss to follow-up during the first 24 months postpartum among HIV-positive women on antiretroviral therapy in Johannesburg, South Africa.

Women in the incident pregnancy group who received HIV care from an NGO clinic had a lower risk of becoming LTFU (aHR 0.6, 95% CI: 0.4–1.0) compared with those from hospital-based clinics, whereas those who were treated at a local primary care clinic were more likely to become LTFU (aHR 1.5, 95% CI: 1.1–2.1). However, having a baseline $CD4^+$ cell count at least 350 cells/μl was associated with a slightly lower risk of becoming LTFU (hazard ratio 0.7, 95% CI: 0.5–1.1) compared with those with $CD4^+$ less than 200 cells/μl at delivery. In addition, women who were unsuppressed at delivery were 60% more likely to become LTFU (95% CI: 1.2–2.1). In this group, the risk of postpartum LTFU was not associated with age, education, employment status or length of time on ART.

Among women in the prevalent pregnancy group, those who attended some secondary school were more likely to be lost compared with those who only attended primary school (aHR 1.6, 95 CI: 1.0–2.7), and being unemployed marginally increased the risk of becoming LTFU (aHR 1.2, 95% CI: 1.0–1.6). Notably, having received at least 7 months of antenatal ART compared with 3 or less months was associated with a lower risk of becoming LTFU (aHR 0.4, 95% CI: 0.2–0.7). $CD4^+$ cell count and viral suppression at delivery did not predict LTFU in this group.

Discussion

In this article, we show that South African women who conceive while receiving ART are more likely to experience a virologic failure postpartum compared with nonpregnant women and those who initiate ART in pregnancy. Women who initiate ART in pregnancy have a slightly higher risk of becoming lost from care after delivery compared with nonpregnant women. However, there was no difference in the risk of becoming LTFU by 24 months when compared with the incident pregnancy group.

Similar to findings from other sub-Saharan African settings, we found that 39.8% of postpartum women had detectable viral RNA at delivery, and 9.4% experienced a virologic failure in the postpartum period [18–20]. Viral suppression rates decrease gradually from nonpregnant state to postpartum period [18]. Although the PMTCT programme coverage in South Africa has been successful in nearly eliminating MTCT, postpartum virologic suppression is the key for further reductions of postpartum transmission rates [20].

Predictors of postpartum virologic failure among women who conceived on ART included having a $CD4^+$ less than 350 cells/μl at delivery, longer periods on ART before delivery and possible prior experience with adverse drug reaction (initiating ART on regimens including ABC or d4T). Low $CD4^+$ cell count at delivery points to declining health during pregnancy and perhaps even at conception [21–23]. Westreich *et al.* showed an increased risk of virologic failure in pregnancy among women who conceived on ART, suggesting persistently poorer viral control during pregnancy as well as postpartum [24,25]. The incident pregnancy group was more likely to have had prior ART adherence challenges as demonstrated by the higher proportion switched to second-line ART by the time of delivery compared with the prevalent pregnancy group. This higher risk of failure may also be because of experiences of drug toxicities and treatment fatigue as a consequence of being on ART for longer. Longer period of continuous viral suppression have been associated with lower risk of virologic failure [26,27]. Treatment-experienced women with a longer period of good adherence may be better prepared to handle adherence challenges postpartum. However, women who are already prone to nonadherence may struggle even more postpartum.

In contrast, a similar analysis among HIV-positive women in the United Kingdom found that women who initiated ART in pregnancy were more likely to experience viral rebound at 3 months postpartum compared with those who conceived on ART [27]. The difference may be in improved monitoring of patients on ART before and during pregnancy. Our findings highlight the need to strengthen adherence counselling and viral load monitoring during pregnancy to help identify women in need of additional adherence support postpartum.

The overall proportion of women who became LTFU by 24 months postpartum is considerably lower than previously reported figures in South African settings [28,29]. Over 20% of the original sample was excluded

because of missing postpartum viral load data. This may have biased the analysis towards women who are more inclined to enter and remain in postpartum care at the selected clinics. Our results also potentially underestimate rates of programmatic losses from care and virologic failure, which does not bode well for the postpartum risk of MTCT [30]. This is problematic as the data set only covered the pre-Option B+ and 'treat-all' policy era (pre-2015), when only women with low $CD4^+$ cell count were initiated on lifelong ART for their own health. Healthier women initiated on lifelong ART under the Option B+ programme and the 'treat-all' policy may be even less inclined to adhere and remain in care in the postpartum period [31–34].

Although there was no difference in the risk of becoming LTFU between the incident and prevalent pregnancy groups, the difference in predictors of LTFU could be attributed to the phase of ART experience. The incident pregnancy group most likely consisting of 'survivors' of the initial wave of losses after ART initiation and the prevalent pregnancy group are in the early stages of their ART experience. Losses among treatment-experienced women could be related to health system factors such as patient management approaches or monitoring data quality. It is possible that women with low $CD4^+$ cell count and those who were unsuppressed at delivery were sicker, and the referrals to higher level healthcare facilities or even deaths were poorly recorded. In addition, our analysis is limited by the fact that the data consisted of routinely collected medical records with unevenly distributed proportions of missing information. Therefore, further research is needed to understand the differences in LTFU across types of sites to further elaborate on possible retention/data system strengthening interventions for the PMTCT programme.

Losses among the prevalent pregnancy group are associated with personal factors (education, unemployment) that impact on engagement with HIV care both during and after pregnancy. However, women who initiated antenatal ART in the first trimester of pregnancy were more likely to be retained compared with women who initiated in the last trimester or at delivery. This highlights an additional benefit of early ART initiation during pregnancy. Longer ART exposure also ensures that women receive repeat counselling and acquire a better understanding of the risks associated with disengaging from care.

In conclusion, the results highlight the need to strengthen adherence-monitoring efforts during pregnancy to identify women, particularly treatment-experienced women, who will require further support in the postpartum phase of the PMTCT programme. Monitoring and evaluation data must account for transfers across health facilities to better inform retention and follow-up strategies, and for accurate determinations of LTFU rates among postpartum women. Finally, increasing the demand for early ANC and ART initiation among treatment-naive HIV-positive women will also have a positive impact on postpartum LTFU which will, in turn, contribute to the goals of reducing transmission risks and promoting the health of new mothers.

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Authors' contributions: D.O. and T.S. conceptualized the analysis, analysed the data and drafted the article. A.B., L.L. and M.P.F. assisted in the analysis and contributed to the interpretation of the results as well as the article preparations.

Conflicts of interest

There are no conflicts of interest.

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