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Predictors and Timing to Viral Suppression in HIV-Infected Pregnant Women in the University of Zimbabwe Birth Cohort Study During the Era of Lifelong Antiretroviral Therapy (Option B+ Treatment Strategy)

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Background: Achieving and maintaining viral suppression (VS) in people living with HIV/AIDS on antiretroviral therapy (ART) remains a crucial clinical goal, more so in pregnancy to prevent mother-to-child-transmission (MTCT). There is a need to understand VS kinetics and barriers to achieving it in order to meet the target of eliminating HIV-MTCT by 2030.

Methods: HIV-infected pregnant women ≥ 20 weeks of gestation with different durations of Tenofovir/Lamivudine/Efavirenz exposures seeking antenatal care services at four primary health centres in high-density residential areas in Harare, Zimbabwe were enrolled in the University of Zimbabwe Birth Cohort Study. Plasma viral load (VL) was quantified by reverse transcriptase–polymerase chain reaction. Demographic, clinical, socio-economic and HIV- and ART-related factors were tested in multivariable logistic regression analyses as potential predictors for VS and undetectable VL.

Results: From March 2016 to June 2019, 608 HIV-infected pregnant women were enrolled. 63 (10.4%) were self-reported-ART-naïve; 324 (53.3%) and 221 (36.3%) initiated ART pre- and post-conception, respectively. Time from ART initiation to VS (VL $\leq 1,000$ copies/ml) in 95% of the women was 126 days. Overall lack of VS (VL $> 1,000$ copies/ml) was observed in 133 (21.9%) women being 76.2, 27.4 and 7.7% in self-reported-ART-naïve, post-conception and pre-conception groups, respectively. Undetectable VL (≤ 50 copies/ml) was observed in 371 (61.2%) and low-level viremia (51–1,000 copies/ml) in 102 (16.8%) women.

In multivariable models for all participants regardless of ART exposure, being on ART was the strongest predictor for both VS and undetectable VL (odds ratio 95% confidence interval, OR (CI): 8.9(4.2–19.5) and 8.1(3.2–24.4), respectively). For women on ART, duration of ART use >126 days was the strongest predictor with OR (CI): 6.7(3.3–14.0) for VS and 8.5(5.6–13.1) for undetectable VL. Other relevant predictors for favourable virological outcomes were older maternal age, HIV-status disclosure, absence of ART side effects and self-reported depression. Having a spouse/intimate partner on ART predicted a 4 times higher likelihood for VS.

Discussion: Lack of VS was frequently observed in this Harare cohort of pregnant women, mainly due to new HIV diagnosis, hence not being on ART and suboptimal duration of ART exposure. Since VS for 95% of women needed about 4 months of ART exposure, eliminating HIV-MTCT will require timely screening and commencing women together with their spouses/intimate partners on ART before pregnancy or early after conception.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT04087239.

Keywords: antenatal plasma HIV RNA load, pre-/post-conception ART initiation, lack of viral suppression, undetectable HIV plasma viral load, days to viral suppression after ART initiation, option B plus era in a resource limited setting, low level viremia

INTRODUCTION

Current treatment guidelines for human immunodeficiency virus (HIV) infection in pregnant women recommend lifelong antiretroviral therapy (ART) immediately following HIV diagnosis irrespective of any clinical staging or assessment of cluster of differentiation-4 positive (CD4$^+$) T-lymphocytes (Option B+ treatment strategy) [1]. The effectiveness, success or failure of ART can be assessed mainly virologically by measuring viral particle genetic material/ribonucleic acid (RNA) or viral load (VL) in the blood [2]. In an effort to curb the pandemic, the joint United Nations Programme on HIV/AIDS (UNAIDS) set a global 90–90–90 goal, targeting 90% of people living with HIV/AIDS (PLWHA) to know their HIV status, 90% of the diagnosed to initiate ART and 90% of those on ART to achieve viral suppression (VS) by year 2020 [3]. However, there are different cut-offs of HIV RNA levels defining VS or undetectable VL. The World Health Organisation (WHO) 2021 guidelines define undetectable VL as viral RNA levels below the detection limit of an ultra-sensitive assay, currently pegged at ≤50 copies/ml [4]. Low-level viremia (LLV), i.e. VL of 51–1,000 copies/ml, can predict future virological failure [4]. Lack of VS, according to the same guidelines, is the inability of a treatment plan to achieve and/or maintain VL below 1,000 copies/ml after at least 6 months of continuous ART use [4]. However, this

threshold is in stark contrast to the European and American HIV guidelines that define lack of VS as VL>200 copies/ml [5, 6], with some contemporary low resource setting studies now defining it as VL>400 copies/ml [7].

The public health benefits of ART use are realised if VS is attained and maintained, and this has been associated with lower mortality, near to normal life expectancy and improved general health of PLWHA [8, 9]. Monitoring the effectiveness of ART is important to identify adherence challenges and guides decisions on whether ART regimens should be switched to a second-line regimen. However, access to this essential service remains a challenge in resource-limited settings [10], more so in pregnant women, where VL monitoring is critical to reduce the mother-to-child transmission (MTCT) of HIV [11, 12].

Initiating ART early in pregnancy generally outweighs the potential adverse neonatal outcomes and recommended regimens include dual nucleoside reverse transcriptase inhibitors (NRTIs) combination such as Tenofovir disoproxilfumarate plus either Lamivudine or Emtricitabine or an integrase strand transfer inhibitor like Dolutegravir [13, 14]. Mechanisms of reducing MTCT include lowering maternal HIV RNA levels as NRTIs have high transplacental passage that inhibits viral replication in the foetus [15]. Suppression of maternal VL to undetectable levels should be achieved as rapidly as possible to reduce the risk of HIV-MTCT [16], yet pregnancy as a condition is associated with poor VS [17, 18].

Achieving VS by time of delivery remains critical for pregnant women in both low- and high-income countries since failure to achieve VS puts the unborn babies at high risk of MTCT of HIV [16]. In Zimbabwe, there has been a huge scaling up of prevention of MTCT (PMTCT) initiatives, from a couple of sites during the piloting stages in 1999 to the current 1,560 health facilities offering these services [19]. According to

Zimbabwean national guidelines, all HIV-infected women should be on lifelong ART (1). Since 2013, the standard of care for all Zimbabwean HIV-infected pregnant women for PMTCT has been TENOLAM-E (Tenofovir, Lamivudine and Efavirenz), a combination of (non)-nucleoside reverse transcriptase inhibitors (NNRTIs). However, since 2018, Dolutegravir has been slowly replacing Efavirenz as a fixed dose combination resulting in Tenofovir/Lamivudine/Dolutegravir (TENOLAM-D) now the preferred first-line therapy. Zidovudine is still occasionally offered as an alternative treatment regimen in some PLWHA on second line or salvage regimens in those who develop renal issues with Tenofovir.

Despite these remarkable preventive measures in place, the HIV burden, although in a downward trajectory, remains unacceptably high, at approximately 33,000 new cases every year with annual incidence and prevalence rates of 0.60 and 16%, respectively, among adult female urbanites of the 24- to 35-year age group (20). In addition, up to 54% of Zimbabwean women of child-bearing age living with HIV/AIDS desire to get pregnant in the future (21). Previous Zimbabwean studies on maternal VS lacked more critical data, including potentially modifiable factors such maternal demographics, socio-economic status and family/household/spouse/intimate partner factors, and HIV- and ART-related factors (10). Thus, there is a paucity of comprehensive local data regarding HIV suppression and frequencies of LLV in pregnant women during this era of lifelong ART.

To achieve the UNAIDS 95–95–95-set target of ending the HIV epidemic by 2030, there is therefore a need to understand VS kinetics and barriers/facilitators with the aim to craft more effective public health policies to improve mother–infant care. This study aimed to determine rates and predictors of undetectable VL and VS in HIV-infected pregnant women accessing antenatal care services at 4 City of Harare primary health facilities in high-density residential areas.

MATERIALS AND METHODS

We aimed to

1. Determine the proportion of pregnant women at least 20 weeks gestational age with undetectable baseline HIV RNA load ≤50 copies/ml, LLV (VL of 51–1,000 copies/ml) and lacking VS; VL > 1,000 copies/ml.
2. Estimate the average time to plasma VS (VL ≤ 1,000 copies/ml) from the time of ART initiation in ≥95% of the pregnant women.
3. Determine facilitators of undetectable VL (≤50 copies/ml) and barriers to VS; VL > 1,000 copies/ml including clinical characteristics, laboratory markers, ART/HIV infection-related factors, socio-demographic parameters and intimate partner/spouse factors.

Design of University of Zimbabwe Birth Cohort Study (UZBCS)

The aims and methodology of the University of Zimbabwe Birth Cohort Study (UZBCS) have been previously described (22).

Briefly, the UZBCS is a prospective cohort study investigating the role of maternal comorbidities, including co-infections with persistent viruses such as HIV, cytomegalovirus, hepatitis B virus and other infectious diseases like syphilis, non-communicable diseases, including maternal nutritional status on pregnancy outcomes, infant mortality, growth and development, immunity and general health.

The study population was HIV-infected and HIV-uninfected pregnant women seeking antenatal care services at four municipal primary health centres in high-density residential areas in Harare. Following a pre-study site feasibility assessment in September 2015, out of the 12 polyclinics, Kuwadzana, Dzivaresekwa (Rujeko), Glenview and Budiriro in South West of Harare city centre were selected based on the higher volumes of maternal and child health services, frequency of HIV sero-positivity and lack of competing research activities targeting the same population. The catchment areas of the selected four polyclinics have relatively stable communities that do not frequently change their accommodation. By design, ~50% of the expecting women in the UZBCS were HIV-infected as previously described (22).

Inclusion and Exclusion Criteria

Inclusion criteria were pregnant women ≥15 years of age, at least 20 weeks of gestation at enrolment and planning to deliver at any of the 4 study sites.

Exclusion criteria were the presence of severe mental health disorders, rendering the women incapacitated to provide informed consent or comply with study procedures as assessed by the study clinicians.

Study Procedures

The study midwife administered a structured questionnaire to all pregnant women at enrolment aiming at a comprehensive clinical and socio-demographics characterisation. Socio-economic information comprising employment status, family monthly income, money set aside for food and general household food security were assessed. Furthermore, questions addressing maternal lifestyle such as alcohol use, concurrent medications, presence of comorbidities, awareness of spouse/intimate partner's HIV status, HIV status disclosure and stock unavailability of ART at health centres, including missed ART doses were asked.

Maternal Physical Examination

At enrolment, the study midwife performed a full physical examination, blood pressure checks, assessment of oedema and anthropometry of body mass index and mid upper arm circumference to assess nutritional status as previously described (22). WHO clinical staging was done to assess immune status.

Blood Collection and Analysis

Ten millilitres of maternal venous blood was collected in EDTA tubes at enrolment. The whole blood EDTA samples were aliquoted for subsequent measurements of CD4$^+$ T-lymphocyte counts within a maximum of 6 h after acquisition. Plasma was processed and stored at −80°C for later HIV RNA testing.

Maternal HIV diagnosis was done from an aliquot of whole-blood EDTA using qualitative rapid immunochromatographic assays, SD Bioline HIV-1/2 3.0 (Standard Diagnostics Inc., Kyonggi-do, South Korea) and Abbott's Determine® HIV-1/2. Western Blot was the tiebreaker for any indeterminate test results.

Absolute CD4+ T-lymphocyte counts in whole-blood EDTA samples were enumerated within a maximum of 6 hours after sample acquisition using a Partec Cyflow counter (Cyflow, Partec, Munster, Germany).

HIV RNA was extracted from 1 ml maternal baseline frozen plasma and quantified using an automated TaqMan Roche Amplicor 1.5 Monitor Test (Cobas AmpliPrep/Cobas TaqMan, Roche Diagnostics, Branchburg NJ), according to the manufacturer's instructions. The detection limit was 20 HIV RNA copies/ml. However, we used a VL of 50 copies/ml as the end point for measuring the efficacy of ART since correlation and concordance at this threshold are comparable between different VL assays (23).

Data Management and Statistical Analysis

Data were entered and managed using Research Electronic Data Capture (REDCap v 8.0, © 2020); http://www.redcap.uzchs.ac.zw/redcap/. Quality assurance on the accuracy of data entry included independent double entries and verification in case of discrepancies.

For continuous variables, normalcy testing was performed using the Shapiro–Wilk test, which revealed a non-normal distribution of all parameters. Descriptive summary statistics were calculated for predictor and outcome variables of interest using frequencies and percentages for categorical variables. Medians and interquartile ranges, minimum and maximum values were used for continuous variables. A p-value <0.05 was considered significant.

Parameters from groups of HIV-infected self-reported ART naïve, women who initiated ART before or during pregnancy (i.e. the pre-conception and post-conception ART initiation groups, respectively) were compared using the Kruskal–Wallis test, Mann–Whitney U test or Fisher's exact test where appropriate. Multivariable logistic regression analyses were performed to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for factors associated with undetectable VL (≤50 copies/ml) and lack of VS, defined as VL >1,000 copies/ml. We used automated variable elimination to obtain simplified models with fewer parameters but high predictive power. Variable elimination was performed for maximising the Akaike information criterion which considers both the model fit and the number of parameters (i.e. the Akaike information criterion increases with a better model fit but decreases according to the number of predictors) (24). For the analysis, missing values for the relevant variables were excluded. To clearly distinguish effects of being on ART and being ART-naïve, the ART defaulters were excluded from group comparisons and the predictive models. The following potential predictors of VS and undetectable VL, all assessed at the time of enrolment, were tested: whether the pregnancy was planned, self-reported depression, mid upper arm circumference, median maternal age, level of education, employment status,

ethnicity, gravida, number of days since HIV diagnosis, whether women were currently living with spouses/intimate partners under the same roof, any experience(s) of domestic violence during pregnancy, disclosure of HIV status to anyone and food security. For those on ART, we included the additional predictors of access to constant supply of ART, presence of any ART-related side effects, ART duration and if an ART dose was ever missed. Estimation of the number of days on ART where 95% of the women were VS was done using the receiver operator characteristic (ROC) curve. Statistical analyses were performed in RStudio, version 1.4.1717.

Consent to Participate

UZBCS complied with the ethical principles of the Declaration of Helsinki (updated 2013) and was conducted in compliance with the international council for harmonisation of Good Clinical and Laboratory Practice guidelines and local regulatory requirements. Literacy is nearly universal in Zimbabwe (25), and all potential participants were able to read and comprehend the informed consent form. All study participants provided written informed consent.

RESULTS

Demographic Characteristics of the Study Population

From March 2016 to June 2019, 608 HIV-infected pregnant women were enrolled into UZBCS. A total of 324 (53.3%) and 221 (36.3%) of the participants initiated ART pre- and post-conception, respectively, whilst 63 (10.4%) were self-reported ART-naïve (**Table 1**). Within the post-conception group, 2 (0.9%) were ART defaulters (i.e. participants had started treatment but stopped due to severe side effects). Commencement of ART within the post-conception group generally coincided with HIV diagnosis, but other pregnant women spent up to 2,925 days without treatment after HIV diagnosis (**Table 2**). A total of 53 out of 63 (84.1%) of the self-reported ART-naïve pregnant women only knew of their HIV status at enrolment into our study, but overall, 555/608 (91.3%) of the women were aware of their HIV status, exceeding the expectations of the first joint UNAIDS's 90–90–90 goal post. Out of 555 women who knew their HIV status, 543 (97.8%) were on ART, also well above the second joint UNAIDS 90–90–90 goal post by year 2020.

Median maternal age at enrolment was at least 5 years older in women in the pre-conception ART initiation group compared to the other 2 groups. Furthermore, this group of relatively older pregnant women could afford ~$10 more on food every month and also had significantly higher frequencies of unplanned pregnancies (61% compared to the frequencies around 50% observed in the two other groups; **Table 1**).

Gestational age at first antenatal care booking was much later (at 7 months) for the self-reported ART-naïve women compared to 6 months for the other 2 groups. There were no statistically significant differences in the marital status, level of education, religion, ethnicity, current employment status, reported household food security, mid upper arm circumference

TABLE 1 | Characteristics of the study population.

Maternal factors Median; (IQR), min-max (%)	Sample size/ subgroups	Overall N = (606)	Self–reported ART naïve (n = 63)	Post–conception ART initiation (n = 219)	Pre–conception ART initiation (n = 324)	p–value
Socio–demographics						
Age (years)		30; (25–34), 17–46	25; (22–30), 18–46	28; (24–33), 17–42	33; (28–35), 18–45	**1.05e⁻¹⁵**
Categorised age (years)						**2.65e⁻⁰⁵**
<20		21 (3.5%)	5 (7.9%)	11 (5%)	5 (1.5%)	
20–35		474 (78.2%)	56 (88.9%)	174 (79.5%)	244 (75.4%)	
>35		111 (18.3%)	2 (3.2%)	34 (15.5%)	75 (23.1%)	
Gravida		3; (2–4), 1.–10	2, (1–3), 1–4	3.0, (2–3), 1–6	3, (2–4), 1–10	**1.15e⁻¹²**
Gestational age at first		6; (5–7), 1–9	7; (6–7.5), 3–9	6; (5–7), 1–9	6; (5–7), 2–9	**6.26e⁻⁰⁵**
ANC booking (months)		(missing = 2)			(missing = 2)	
Religion						
Apostolic		152 (25.2%)	20 (32.3%)	60 (27.5%)	72 (22.2%)	0.148
Non–apostolic		452 (74.8%)	42 (67.7%)	158 (72.5%)	252 (77.8%)	
		(missing = 2)	(missing = 1)	(missing = 1)		
Ethnicity						
Shona		500 (83.0%)	53 (84.1%)	190 (86.8%)	257 (79.3%)	0.078
Non–Shona		106 (17.0%)	10 (15.9 %)	29 (13.2%)	67 (20.7%)	
Marital status						
Married		564 (93.1%)	59 (93.7%)	199 (91.0%)	306 (94.4%)	0.257
Not married		42 (6.9%)	4 (6.3%)	20 (9.0%)	18 (5.6%)	
Level of education						
Primary		179 (29.5%)	20 (31.7%)	59 (26.9%)	100 (30.9%)	0.558
At least secondary		427 (70.5%)	43 (68.3%)	160 (73.1%)	224 (69.1%)	
Employment status						
Employed		175 (28.9%)	14 (22.2%)	58 (26.5%)	103 (31.8%)	0.203
Unemployed		431 (71.1%)	49 (77.8%)	161 (73.5%)	221 (68.2%)	
Money spent on food per month (US $)		56; (40–100), 0–450 (missing = 6)	50; (40–80), 0–200 (missing = 2)	50; (40–100), 0–450 (missing = 3)	60; (50.–100), 0–350 (missing = 1)	**0.009**
Food secure						
Yes		447 (73.8%)	48 (76.2%)	168 (76.7%)	231 (71.3%)	0.344
No		159 (26.2%)	15 (23.8%)	51 (23.3%)	93 (28.7%)	
Planned pregnancy						
Planned		273 (45.1%)	30 (47.6%)	117 (53.4%)	126 (39%)	**0.004**
Unplanned		332 (54.9%)	33 (52.4%)	102 (46.6%)	197 (61%)	
		(missing = 1)			(missing = 1)	
Concurrent medications and alcohol use						
Zinc supplementation						
Yes		46 (7.5%)	1 (1.6%)	13 (6%)	32 (10%)	**0.037**
No		560 (92.5%)	62 (98.4%)	206 (94%)	292 (90%)	
Iron supplementation						
Yes		306 (50.5%)	29 (46%)	124 (56.6%)	153 (47%)	0.075
No		300 (49.5%)	34 (54%)	95 (43.4%)	171 (53%)	
Antibiotics use						
Yes		110 (18.2%)	5 (8%)	21 (10%)	84 (26%)	**4.19e⁻⁰⁷**
No		496 (81.8%)	58 (92%)	198 (90%)	240 (74%)	
Alcohol use in pregnancy						
Yes		59 (10%)	4 (6.3%)	21 (10%)	34 (10.5%)	0.673
No		547 (90%)	59 (93.7%)	198 (90%)	290 (89.5%)	

Demographic, life style and medication use characteristics of all HIV infected pregnant women at least 20 weeks gestational age (N = 606) at enrolment are indicated, stratified by timing of ART initiation: self–reported ART naïve, post–conception and pre–conception ART initiation (2 ART defaulters during the post–conception period were excluded).

ANC, antenatal care; ART, antiretroviral therapy; IQR, interquartile range; min, minimum; max, maximum; US $, United States dollars.

Statistical methods used: Shapiro Wilk test for normalcy, continuous variables – Kruskal–Wallis test, categorical variables – Fisher's exact test. Overall column was not included in p–value determination. Bold font(s) indicate(s) a p-value of <0.05.

TABLE 2 | HIV and ART related parameters of the study population.

Maternal factors Median; (IQR), min-max (%)	Sample size/ subgroups	Overall N = (606)	Self–reported ART naïve (n = 63)	Post–conception ART initiation (n = 219)	Pre–conception ART initiation (n = 324)	p–value
HIV and ART related factors						
Days since HIV diagnosis		561; (34–1502), 0–7985	0; (0–0), 0–7259	49; (16–110), 1–2983	1421; (797–2139) 219–7985	**<2.2e^{-16}**
Days without ART after HIV diagnosis		0; (0–29), 0–7259	0; (0–0) 0–7259	0; (0– 10.0), 0–2925	8; (0–67.75), 0–3658.0	**9.19e^{-13}**
Disclosed HIV status						
No		64 (10.6%)	40 (63.5%)	18 (8.2%)	6 (1.9%)	**<2.2e^{-16}**
Yes		542 (89.4%)	23 (36.5%)	201 (91.8%)	318 (98.1%)	
Ever missed ART dose (n = 543)						
Yes		80 (14.7%)	N/A	21 (1.6%)	59 (18.2%)	**0.006**
No		462 (85.3%) (missing = 1)		198 (98.4%)	264 (81.8%) (missing = 1)	
Spouse tested for HIV						
Yes		414 (68.5%)	22 (35.5%)	118 (53.9%)	274 (84.8%)	**<2.2e^{-16}**
No		128 (21.2%)	31 (50.0%)	65 (29.7%)	32 (9.9%)	
Don't know		62 (10.3%) (missing = 2)	9 (14.5%) (missing = 1)	36 (16.4%)	17 (5.3%) (missing = 1)	
ART side effects (n = 543)						
Present		114 (21.6%)	N/A	65 (30.5%)	49 (15.6%)	**5.96e^{-05}**
Absent		414 (78.4%) (missing = 15)		148 (69.5%) (missing =6)	266 (84.4%) (missing = 9)	
ART stock supply always available (n = 543)						
No		12 (2.2%)	N/A	1 (0.5%)	11 (3.4%)	**0.033**
Yes		531 (97.8%)		218 (99.5%)	313 (96.6%)	
Ever switched ART regimen (n = 543)						
No		445 (82%)	N/A	215 (98.2%)	230 (71.0%)	**< 2.2e^{-16}**
Yes		98 (18%)		4 (1.8%)	94 (29.0%)	
Comorbidities						
Hypertension						
Present		73 (12%)	6 (9.5%)	37 (16.9%)	30 (9.3%)	**0.026**
Absent		533 (88%)	57 (90.5)	182 (83.1%)	294 (90.7%)	
Self–reported depression						
Present		9 (1.5%)	3 (4.8%)	2 (1%)	4 (1.2%)	0.102
Absent		596 (98.5%) (missing = 1)	60 (95.2%)	216 (99%) (missing = 1)	320 (98.8%)	
Clinical data						
MUAC (cm)		27.5; (25–30), 20–41 (missing = 2)	27, (25–29), 21–39	28; (25–30), 21–38	27.7, (25–30), 20–41 (missing = 2)	0.348
WHO clinical staging						
Stage 1		496 (82.1%)	59 (93.7%)	190 (86.8%)	247 (76.7%)	**0.0003**
Stage 2		60 (9.9%)	3 (4.8%)	21 (9.6%)	36 (11.2%)	
≥ Stage 3		48 (8.0%) (missing = 2)	1 (1.5%)	8 (3.6%)	39 (12.1%) (missing = 2)	
CD4$^+$ T–lymphocyte count (cells/μL)						
<200		76 (13.2%)	12 (19.6%)	32 (15.5%)	32 (10.4%)	**0.004**
200–350		160 (27.8%)	17 (27.9%)	71 (34.3%)	72(23.5%)	
>350		339 (59%) (missing =31)	32 (52.5%) (missing = 2)	104 (50.2%) (missing = 12)	203 (66.1%) (missing = 17)	
CD4$^+$ T–lymphocyte count (cells/μL)		395; (257–531), 26–1153. (missing =31)	350;, (258.0–525.0), 39.0–828.0 (missing = 2)	353.0, (237.0–490.0), 26.0–1017.0 (missing = 12)	433.0, (287.5–556.0), 30.0–1153.0 (missing = 17)	**0.0009**

(Continued)

TABLE 2 | Continued

Maternal factors Median; (IQR), min-max (%)	Sample size/ subgroups	Overall *N* = (606)	Self–reported ART naïve (*n* = 63)	Post–conception ART initiation (*n* = 219)	Pre–conception ART initiation (*n* = 324)	*p*–value
VL (copies/mL)		0, (0–629.2), 0–614706	14000, (1800–58591), 0–614706	104, (0–1767), 0–436309	0, (0–19), 0–440619	**< 2.2e^{-16}**
VL (copies/mL)						
≤50 (UDV) [1]		371 (61.2%)	6 (9.5%)	88 (40.2%)	277 (85.5%)	**< 2.2e^{-16}**
≥1,0000 (HV)		92 (15.2%)	38(60.3%)	36 (16.4%)	18 (5.6%)	
VL (copies/mL)						
≤50 (UDV) (1)		371 (61.2%)	6 (9.5%)	88 (40.2%)	277 (85.5%)	
51–1,000 (1)		102 (16.8%)	9 (14.3%)	71 (32.4%)	22 (6.8%)	**< 2.2e^{-16}**
VL (copies/mL)						
<200 (5, 6)		426 (70.3%)	10 (15.9%)	127 (57.9%)	289 (89.2%)	**< 2.2e^{-16}**
>200		180 (29.7%)	53 (84.1%)	92 (42.1%)	35 (10.8%)	
VL (copies/mL)						
<400		444 (73.3%)	12 (19.1%)	138 (63%)	294 (90.7%)	**< 2.2e^{-16}**
>400		162 (26.7%)	51 (81.0%)	81 (37%)	30 (9.3%)	
VL (copies/mL)						
≤1,000 [1]		473 (78.1%)	15 (23.8%)	159 (72.6%)	299 (92.3%)	**< 2.2e^{-16}**
>1,000		133 (21.9%)	48 (76.2%)	60 (27.4%)	25 (7.7%)	

Clinical, immunological and virological characteristics of all HIV infected pregnant women at least 20 weeks gestational age (N = 606) at enrolment stratified by timing of ART initiation (2 ART defaulters during the post–conception period were excluded).

ART, antiretroviral therapy; CD4, cluster of differentiation−4; HIV, human immunodeficiency virus; HV, high viremia; MUAC, mid upper arm circumference; N/A, not applicable; UDV, undetectable viremia; VL, viral load; IQR, interquartile range; min, minimum; max, maximum; US $, United States dollars.

Statistical methods used: Shapiro Wilk test for normalcy, continuous variables – Kruskal–Wallis test, categorical variables – Fisher's exact test. Overall column was not included in p–value determination. Bold font(s) indicate(s) a p-value of <0.05.

and alcohol consumption between self-reported ART-naïve, post- and pre-conception ART initiation groups (**Tables 1**, **2**).

HIV- and ART-Related Factors

Self-reported adherence to ART differed between groups: only 1.6% in those who initiated ART in pregnancy compared to 18.2%, who were already on ART before conceiving, reported to have ever missed their ART dosages (**Table 2**). This could be at least partially explained by the longer period of ART use in the pre-conception group. In addition, there were significant differences in the frequencies of presence of ART side effects (15.6% in the pre-conception vs. 30.5% in the post-conception ART initiation group). Constant availability of ART was generally high, with only 0.5 and 3.4% of women in pre- and post-conception ART groups, respectively, reporting ART stock unavailability at the health centres.

Of the 543 women on ART, 536 (98.7%) were on Tenofovir, Lamivudine and Efavirenz (TENOLAM-E) with only 7/543 (1.3%) women, all in the pre-pregnancy ART initiation subgroup, on other different regimens: 2 women on TENOLAM plus Atazanavir, 2 on TENOLAM plus Nevirapine, 1 on Tenofovir, Efavirenz plus Atazanavir, 1 on Zidovudine, Lamivudine plus Nevirapine and 1 on Zidovudine, Lamivudine plus Atazanavir. Overall, 98 (18%) reported ever switching ART regimen, and of these, 83 (84.7%) were VS (VL ≤1,000 copies/ml). Since 98.7% of the women were on the same ART regimen and the remaining
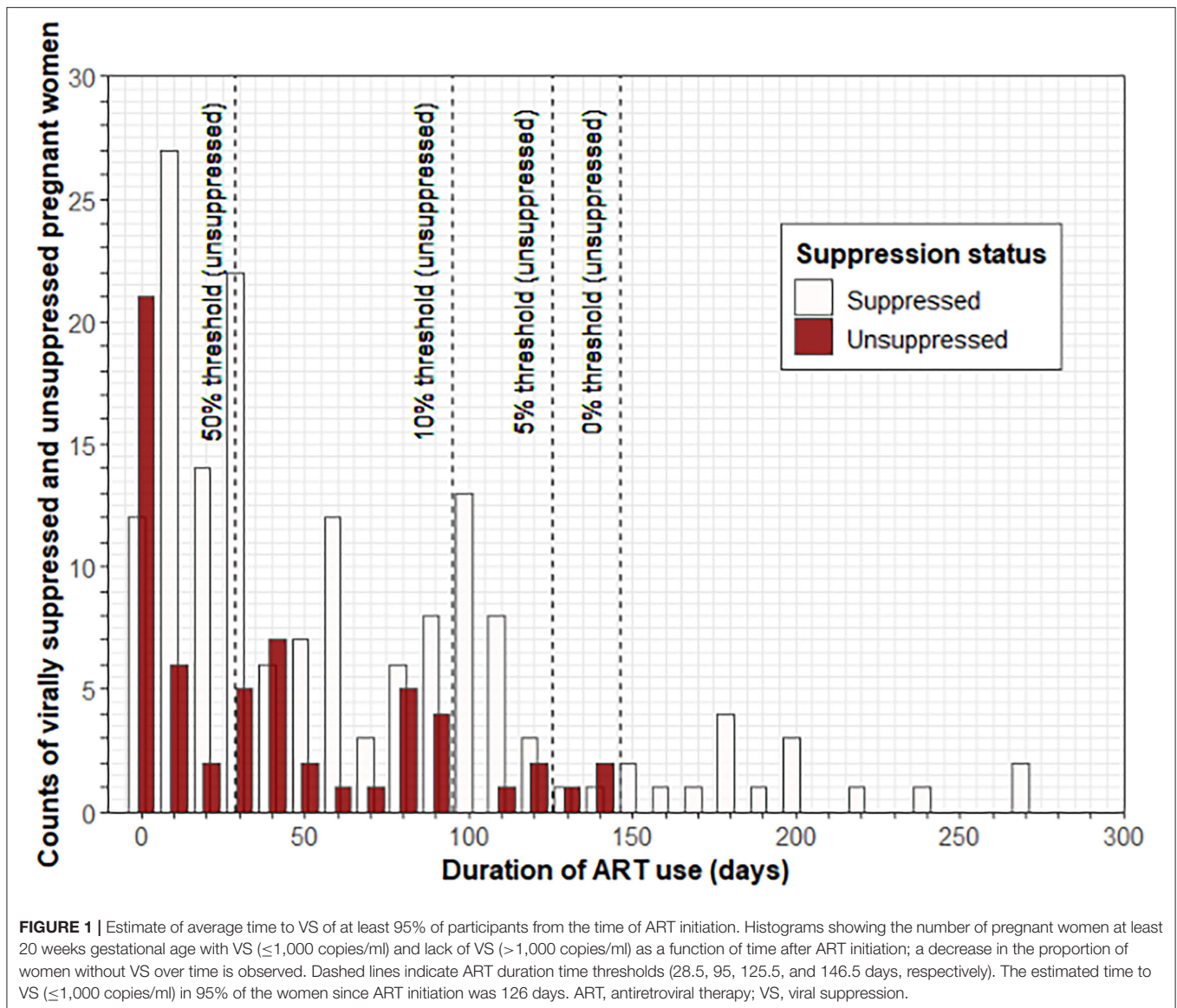
women were receiving heterogeneous regimens, no subgroup analysis according to the type of ART was done, and the ART regimen was not tested as a predictor for VS.

Overall, 68.5% of the women were aware of their spouses/intimate partners' HIV status including whether or not they were on ART, if infected. Frequency of awareness of spouses/intimate partners' HIV status was highest in women who initiated ART before pregnancy, intermediate in women who initiated during pregnancy and lowest in the self-reported ART-naive (84.8, 53.9 and 35.5%, respectively). Strikingly, 62 (10.3%) women did not know whether their spouses/intimate partners had undergone HIV testing or not, and up to 21.2% reported that their spouses/intimate partners were yet to be tested for HIV (**Table 2**).

HIV Staging and Presence of Comorbidities

WHO clinical staging assessment showed that an overall 82.1% of HIV-infected pregnant women were asymptomatic. As expected, we observed the highest (12.1%) frequency of advanced disease (WHO stage ≥3) in women in the pre-conception group who probably had been infected for longer periods compared to the self-reported ART-naïve women and the post-conception group (1.5 and 3.6%, respectively; **Table 2**).

Absolute CD4$^+$ T-lymphocyte assessments showed that most women were immunocompetent (339/575, 59%) with CD4$^+$ T-lymphocyte ≥350 cells/μl. This rate was highest in women who

FIGURE 1 | Estimate of average time to VS of at least 95% of participants from the time of ART initiation. Histograms showing the number of pregnant women at least 20 weeks gestational age with VS (≤1,000 copies/ml) and lack of VS (>1,000 copies/ml) as a function of time after ART initiation; a decrease in the proportion of women without VS over time is observed. Dashed lines indicate ART duration time thresholds (28.5, 95, 125.5, and 146.5 days, respectively). The estimated time to VS (≤1,000 copies/ml) in 95% of the women since ART initiation was 126 days. ART, antiretroviral therapy; VS, viral suppression.

were on ART before pregnancy (66.1%) compared to about 50% in the other two groups, demonstrating the benefit of ART.

Generally, the frequencies of self-reported depression were low at 1.5% but somewhat higher (4.8%) in self-reported ART-naïve individuals (not significant). Moreover, women who initiated ART in pregnancy were more likely to be hypertensive (16.9%) compared to 9.3% of women who were already on ART pre-conception and 9.5% among self-reported ART-naïve women (**Table 1**).

Estimate of Average Time to VS of at Least 95% of Participants From the Time of ART Initiation

When plotting the number of women with VS (≤1,000 copies/ml) and lack of VS (> 1,000 copies/ml) as a function of time after ART initiation, we noted an increase in the proportion

of women with VS over time (**Figure 1**). We estimated the time to VS (≤1,000 copies/ml) in 95% of women since ART initiation to be 126 days.

Undetectable VL (≤50 Copies/ml)

Overall, 371/606 (61.2%) pregnant women had undetectable VL with frequencies increasing with longer exposure to ART, being 6/63 (9.5%), 88/219 (40.2%) and 277/324 (85.5%) in the self-reported ART-naïve, post- and pre-conception groups, respectively (**Table 2**).

LLV (51–1,000 Copies/ml)

Overall 102/606 (16.8%) pregnant women had LLV, but the highest frequency was observed in women initiating ART in pregnancy (71/219, 32.4%), intermediate in self-reported ART-naïve women (9/63, 14.3%) and lowest in those who were on ART before conception (22/324, 6.8%; **Table 2**).

VS (≤1,000 Copies/ml) as Per 2021 WHO Guidelines

Overall, 473/606 (78.1%) pregnant women had VS. This rate was considerably lower than the 90% expected by the third joint UNAIDS goal post by year 2020. Women who were on ART before pregnancy surpassed this threshold (299/324) at 92.3%. Frequencies of VS increased with increasing duration of ART exposures, being 15/63 (23.8%) in self-reported ART-naïve individuals (possibly indicating natural immunity), 159/219 (72.6%) in the post-conception group and 299/324 (92.3%) in the pre-conception group, respectively (**Table 2**).

Among the unsuppressed women, 28/133 (21.1%) were on ART for more than 126 days, with a median duration of ART exposure of 1,619 days since HIV diagnosis, probably demonstrating complacency in self-reported ART adherence associated with long-term duration of ART use. In addition, 25% of these women reported to have missed their ART doses, whilst 53.6% had a history of changing their ART regimens.

Very High Viremia (>10,000 Copies/ml)

Very high viremia was observed in 92/606 (15.2%) of pregnant women. Such high levels of viremia are generally observed either in untreated individuals or in the ART experienced in the presence of HIV drug resistance. In our study, frequencies decreased with increasing duration of ART exposure, being 38/63 (60.3%) in individuals without treatment, 36/219 (16.4%) in the post-conception group and 18/324 (5.6%) in the pre-conception group. In the latter group, ART exposure was more likely >126 days, and persistent very high viremia may reflect drug resistance (**Table 2**).

Factors Associated With Undetectable VL (≤50 Copies/ml)

In a bivariate analysis comparing 371 women with undetectable VL (≤50 copies/ml) with 235 women with detectable VL, those with detectable VL were approximately 4 years younger, booked for antenatal care 1 month later and were less likely to have their spouses/intimate partners tested for HIV. Furthermore, these women set aside relatively less money aside every month to buy food and less likely to be on concurrent antibiotic treatment (**Supplementary Table 1**).

Women who had disclosed their HIV status were 2.3 times more likely to have undetectable VL compared to their counterparts with undisclosed HIV status. ART side effects were less frequently reported in women with undetectable VL (17.4% vs. 30.4%), and these women also had lower rates of self-reported depression (1.1% vs. 2.1%). As expected, women with undetectable VL were more immunocompetent with higher counts of $CD4^+$ T-lymphocytes. However, there were no differences between the two groups when immune status was assessed using the less-sensitive WHO clinical staging (**Supplementary Table 1**).

Factors Associated With LLV (51–1,000 Copies/ml)

In a bivariate analysis comparing 371 women with undetectable VL (≤50 copies/ml) with 102 women with LLV; VL 51–1,000 copies/ml, those with LLV were approximately 3 years younger, more likely to be of apostolic religion and unaware of their spouse/intimate partner's HIV status, but less likely to have disclosed their HIV status. In addition, they were more likely to be immunocompromised ($CD4^+$ T lymphocyte count of <350 cells/μl) and had experienced ART-related side effects, both factors with borderline significance (**Supplementary Table 2**).

Factors Associated With VS (≤1,000 Copies/ml)

Differences in clinical and epidemiological parameters were found when we compared 473 women with VS and 133 women without VS. These differences were highly reminiscent of the comparison of detectable (>50 copies/ml) to undetectable VL (≤50 copies/ml) as described above. Specifically, we noted a higher maternal age (4-year difference), a lower gestational age at first antenatal care booking (1 month earlier), higher rates of HIV status disclosure (94.5% vs. 71.4%), spouse testing for HIV (74.4% vs. 47.3%), lower rates of ART side effects (19.1% vs. 35.4%) and lower frequencies of self-reported depression (0.8% vs. 3.8%) in suppressed women (**Table 3**). As expected, unsuppressed women had lower median $CD4^+$ T-lymphocyte counts of 295 cells/μl vs. 428 cells/μl (not shown).

Predictor of Undetectable VL and VS for All Women in Multivariable Regression Analyses

To test for predictors of undetectable VL and VS, we computed multivariable logistic regression models. We first computed models including all 606 HIV-infected pregnant women, regardless of ART exposure (excluding the 2 defaulters). We computed both complete models including all risk factors without variable elimination (**Supplementary Table 3**) and optimised shorter models upon automated variable elimination (**Table 4**).

The most important predictor for both undetectable VL and VS was being on ART with an OR (CI): 8.1 (3.2–24.4) for undetectable VL and 8.9 (4.2–19.5) for VS (p<0.001). Other relevant predictors included older age, longer days after HIV diagnosis and disclosure of HIV status (**Table 4**; **Supplementary Table 3**). However, some of these parameters did not reach statistical significance in all models.

Predictors of Undetectable VL and VS for Women on ART in Multivariable Regression Analyses

We also computed models including all 543 HIV-infected pregnant women on ART. We computed both complete models including all risk factors without variable elimination (**Supplementary Table 4**) and optimised shorter models upon automated variable elimination (**Table 5**). In this analysis,

TABLE 3 | Parameters associated with VS (≤1,000 copies/mL).

Maternal factors Median; (IQR), min-max (%)	Sample size/ subgroups	Overall N = (606)	Suppressed VL (≤1,000 copies/mL) (n = 473)	Unsuppressed VL (>1,000 copies/mL) (n = 133)	p–value
Socio–demographics					
Age (years)		30; (25–34), 17–46	31; (27.–35), 17–45	27; (22.–32), 18–46	**1.50e^{-07}**
Categorised age (years)					
<20		21 (3.5%)	13 (2.8%)	8 (6.0%)	0.102
>20		585 (96.5%)	460 (97.2%)	125 (94.0%)	
Gestational age at first ANC booking (months)		6.0; (5.0–7.0), 1.0–9.0 (missing = 2)	6.0; (5.0–7.0), 1.0–9.0 (missing = 2)	7.0; (6.0–7.0), 3.0–9.0	**0.002**
Ethnicity					
Shona		500 (82.5%)	388 (82%)	112 (84.2%)	0.607
Non–Shona		106 (17.5%)	85 (18%)	21 (15.8%)	
Main religion					
Apostolic		152 (25.2%)	119 (25.2%)	33 (25%)	1
Non–apostolic		452 (74.8%) (missing = 2)	353 (74.8%) (missing = 1)	99 (75%) (missing = 1)	
Marital status					
Married		564 (93.1%)	442 (93.4%)	122 (91.7%)	0.562
Not married		42 (6.9%)	31 (6.6%)	11 (8.3%)	
Education level					
Primary		179 (29.5%)	137 (28.9%)	42 (31.6%)	0.591
At least secondary		427 (70.5%)	336 (71.1%)	91 (68.4%)	
Employment status					
Employed		175 (28.9%)	141 (29.8%)	34 (25.6%)	0.387
Unemployed		431 (71.1%)	332 (70.2%)	99 (74.4%)	
Food secure					
No		159 (26.2%)	127 (26.8%)	32 (24.1%)	0.578
Yes		447 (73.8%)	346 (73.2%)	101 (75.9%)	
Money spent on food per month (US $)		56; (40–100), 0–450 (missing = 6)	60; (50–100), 0–350 (missing = 3)	50; (40–80), 0–450 (missing = 3)	**0.021**
MUAC (cm)					
<25		100 (16.6%)	81 (17.2%)	19 (14.3%)	0.509
≥25		504 (83.4%) (missing = 2)	390 (82.8%) (missing = 2)	114 (85.7%)	
HIV and ART related factors					
Disclosed your HIV status?		64 (10.6%)	26 (5.5%)	38 (28.6%)	**4.63e^{-12}**
No					
Yes		542 (89.4%)	447 (94.5%)	95 (71.4%)	
Days since HIV diagnosis		561; (34–1502), 0–7985	779; (98–1040),0–7985	12; (0–285),0–7259.	**< 2.2e^{-16}**
Spouse tested HIV					
Yes		414 (68.5%)	352 (74.4%)	62 (47.3%)	
No		128 (21.2%)	79 (16.7%)	49 (37.4%)	**3.49e^{-08}**
Don't know		62 (10.3%) (missing = 2)	42 (8.9%)	20 (15.3%) (missing = 2)	
ART side effects (n = 543)					
Yes		114 (21.6%)	85 (19.1%)	29 (35.4%)	**0.002**
No		414 (79.4%) (missing = 15)	361 (80.9%) (missing = 12)	53 (64.6%) (missing = 3)	
ART stock supply always available (n = 543)					
No		12 (2.2%)	9 (2%)	3 (3.5%)	0.413
Yes		531 (97.8%)	449 (98%)	82 (96.5%)	

(Continued)

TABLE 3 | Continued

Maternal factors Median; (IQR), min-max (%)	Sample size/ subgroups	Overall N = (606)	Suppressed VL (≤1,000 copies/mL) (n = 473)	Unsuppressed VL (>1,000 copies/mL) (n = 133)	p–value
Ever switched ART regimen (n = 543)					
No		445 (82%)	375 (81.9%)	70 (82.4%)	1
Yes		98 (18%)	83 (18.1%)	15 (17.6%)	
CD4$^+$ T–lymphocyte count (cells/μL)					
<200		76 (13.2%)	42 (9.3%)	34 (27.2%)	**2.26e^{-08}**
200–350		160 (27.8%)	117 (26.0%)	43 (34.4%)	
>350		339 (59.0%) (missing =31)	291 (64.7%) (missing = 23)	48 (38.4%) (missing = 8)	
WHO clinical staging					
>stage 2		48 (8.0%)	38 (8.1%)	10 (7.5%)	0.783
Stage 2		60 (9.9%)	49 (10.4%)	11 (8.3%)	
Stage 1		496 (82.1%) (missing = 2)	384 (81.5%) (missing = 2)	112 (84.2%)	
Comorbidities					
Hypertension					
Yes		73 (12%)	56 (11.8%)	17 (12.8%)	0.764
No		533 (88%)	417 (88.2%)	116 (87.2%)	
Self–reported depression					
Yes		9 (1.5%)	4 (0.8%)	5 (3.8%)	**0.028**
No		596 (98.5%) (missing = 1)	468 (99.2%) (missing = 1)	128 (96.2%)	
Concurrent medications					
Iron supplementation					
Yes		306 (50.5%)	229 (48.4%)	77 (57.9%)	0.062
No		300 (49.5%)	244 (51.6%)	56 (42.1%)	
Antibiotics					
Yes		110 (18.2%)	96 (20.3%)	14 (10.5%)	**0.011**
No		496 (81.8%)	377 (79.7%)	119 (89.5%)	

Demographic, clinical, immunological and virological characteristics of HIV infected pregnant women of at least 20 weeks of gestational age stratified by VS (cut–off 1,000 copies/mL). 2 ART defaulters during the post–conception period were excluded.

ANC, antenatal care; ART, antiretroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; IQR, interquartile range; min, minimum value; max, maximum value; MUAC, mid upper arm circumference; VL, viral load; US $, United States dollars; VS, viral suppression; WHO, World Health Organisation.

Statistical methods used: Shapiro Wilk test for normalcy, continuous variables—Mann Whitney–U test, categorical variables—Fisher's exact test. Overall column was not included in p–value determination. Bold font(s) indicate(s) a p–value of <0.05.

longer duration of ART use (>126 days) was the most important predictor for virus control with an OR (CI) 8.5 (5.6–13.1) for undetectable VL and 6.7 (3.3–14.0) for VS. Other relevant predictors were maternal age at enrolment, days since HIV diagnosis and ART side effects, but not all of these predictors yielded statistical significance in the regression models. Furthermore, self-reported depression (though only significant in the short model) predicted approximately 10.8-fold lower rates of VS.

Spouse-Related Factors as Predictors for Undetectable VL and VS

In another analysis, we included 'spouse on ART' and 'spouse tested for HIV' as additional predictors into the models. Strikingly, after variable elimination, 'spouse on ART' was a

consistent and significant strong predictor for VS with OR values ranging from 1.8 to 4.0 in all models independent of the threshold of VL (≤50 or ≤1,000 copies/ml) in all women whether on ART or not and women on ART.

DISCUSSION

Pregnancy is a period of life with high vulnerability, and any hazards, including HIV infection, will affect both the mother and the unborn child. In that respect, PMTCT is of utmost importance since foetus/infant HIV infection results in poor infant outcomes and higher mortality rates. In Zimbabwe, one in 15 children dies before his or her fifth birthday (69 deaths per 1,000 live births), with 70% of these deaths occurring in infancy (26). Therefore, improving maternal health through effective

TABLE 4 | Predictors of virological outcomes for all women (naïve + on ART) with variable elimination.

	Predictors for ≤50 copies/mL			Predictors for ≤1,000 copies/mL		
	OR	CI	p–value	OR	CI	p–value
Intercept	0.023	0.003–0.152	**0.0001**	0.061	0.016–0.216	**1.81e^{-5}**
Age (per year)	1.042	1.006–1.079	**0.022**	1.054	1.012–1.097	**0.01**
Are you on ART? (Yes)	8.084	3.191–24.364	**4.30e^{-5}**	8.858	4.231–19.511	**1.78e^{-8}**
Self–reported depression (Yes)	0.696	0.139–3.836	0.66	0.255	0.053–1.284	0.086
Was this pregnancy planned? (Unplanned)	1.415	0.965–2.077	0.075	1.086	0.693–1.699	0.718
Disclosed HIV status to anyone? (Yes)	2.317	1.040–5.314	**0.041**	1.808	0.817–3.826	0.13
Days since HIV diagnosis (per day)	1.0006	1.0004–1.0008	**1.13e^{-6}**	1.0002	0.999–1.0004	0.106
Currently living with spouse under one roof (Yes)	1.699	0.840–3.412	0.136	–	–	–
MUAC (cm)	0.973	0.920–1.029	0.335	–	–	–

Predictors of undetectable VL at a cut–off of ≤50 and VS at a cut–off of ≤1,000 copies/mL for all HIV infected pregnant women (naïve + on ART) of at least 20 weeks gestational age (602 observations).

ART; antiretroviral therapy; CI–95% confidence interval HIV; human immunodeficiency virus; MUAC; mid upper arm circumference; OR; odds ratio.

Statistical tests used: Logistic regression with variable elimination. Bold font(s) indicate(s) a p-value of <0.05.

TABLE 5 | Predictors of virological outcomes for women on ART with variable elimination.

	Predictors for ≤50 copies/mL			Predictors for ≤1,000 copies/mL		
	OR	CI	p–value	OR	CI	p–value
Intercept	0.564	0.099–3.097	0.513	0.997	0.276–3.643	0.997
ART duration >126 days? (Yes)	8.487	5.565–13.131	**<2e^{-16}**	6.652	3.293– 14.031	**2.61e^{-07}**
ART side effects (Yes)	0.693	0.423–1.138	0.145	0.579	0.336–1.013	0.051
Was this pregnancy planned? (Unplanned)	1.18	0.767–1.810	0.448	0.94	0.559–1.572	0.813
Self–reported depression (Yes)	0.24	0.041–1.462	0.102	0.092	0.015–0.547	**0.006**
MUAC (per cm)	1.006	0.946–1.070	0.855	–	–	–
Age (per year)	–	–	–	1.043	0.998–1.091	0.063
Days since HIV diagnosis (per day)	–	–	–	0.9997	0.9994–0.99999	**0.039**

Predictors of undetectable VL at a cut–off of ≤50 and VS at a cut–off of ≤1,000 copies/mL for HIV infected pregnant women on ART and at least 20 weeks of gestational age (523 observations).

ART, antiretroviral therapy; CI – 95% confidence interval HIV, human immunodeficiency virus; MUAC, mid upper arm circumference; OR, odds ratio.

Statistical tests used: Logistic regression with variable elimination. Bold font(s) indicate(s) a p-value of <0.05.

HIV management is a critical public health task essential for the survival of children.

We report results regarding VS from 608 HIV-infected pregnant women in the UZBCS. The key findings are as follows: (i) In the overall study population, 78.1% of the women had VL ≤1,000 copies/ml, but only 61.2% showed optimal controlled HIV RNA levels ≤50 copies/ml. (ii) The most important predictors for poor viral control were not being on ART and duration of ART use of <126 days. (iii) Self-reported depression, non-disclosure of HIV status and younger maternal age were additional risk factors, while having a spouse also on ART predicted a better virological outcome.

Virus Suppression

UNAIDS declared the 95–95–95 global HIV management targeted to end the pandemic by 2030, but an intermediate goal of 90–90–90 was set for 2020. In our cohort, (i) 91.3% of pregnant women were aware of their HIV status, (ii) 98.4% of the expecting women with known HIV status were on ART and 84.3 and 61.2%

of women on ART had VL below the 1,000 and 50 copies/ml thresholds, respectively. Therefore, at least for this cohort of pregnant women, two out of the three UNAIDS global 90–90–90 targets were met. Considering that only 78.1% and 61.2% of women had VL ≤1,000 and ≤50 copies/ml, respectively, our study points towards a significant proportion of pregnant women for whom management of HIV should be urgently improved.

Generally, in resource-limited settings, frequencies of undetectable VL (<50 copies/ml) in pregnancy range from 53 to 70% (27–30), well in line with our frequency of 61.2%. Women with detectable VL (>50 copies/ml) were ~4 years younger with lesser money set aside every month to buy food, booked for antenatal care 1 month later and were less likely to be on concurrent antibiotic treatment.

In previous Zimbabwean studies assessing VL in pregnant women, the average rate of undetectable VL (by then <400 copies/ml) was about 28% (31); however, these studies were done during the single-dose Nevirapine era, where single-dose Nevirapine therapy was only administered during labour. A

recent Tanzanian study in pregnant women in their third trimester reported a VS rate (<400 copies/ml) of 88% (7). Applying the same threshold to our study population would translate to an overall rate of VL<400 copies/ml of 73.3% and up to 90.7% in women who initiated ART before pregnancy but only 63% in women who initiated ART during pregnancy.

In a review summarising 31 studies examining LLV among adults on ART, the prevalence of LLV ranged from 2.7 to 26%, but the main challenges were differences in the definitions of LLV among studies [67]. Thus, the frequency of 16.8% of LLV observed in our study was within this range being highest among women initiating ART in pregnancy (32.4%) and lowest (6.8%) in those who were on ART before conception. This was expected as the latter group had been on ART for long enough time to facilitate optimal ART exposure to enable complete VS. In any case, LLV is clinically highly relevant since HIV MTCT may occur within this LLV range (31–33), possibly in the presence of co-infections like cytomegalovirus (34). It is therefore essential to evaluate LLV among pregnant women on ART for factors that contribute to failure of reaching undetectable VL.

Rates for lack of VS (VL>1,000 copies/ml) in pregnant women in Sub-Saharan Africa ranged from 8.1 to 15.2% (7, 27, 35–37). Similarly, a previous Zimbabwean study during the Option B+ era demonstrated an 86% VS rate (<1,000 copies/ml) with nearly all HIV-infected pregnant women reporting taking ART (20). Even better VS rates (<1,000 copies/ml) of 94% were observed in a 2017 rural study of 1,112 pregnant women from Mazowe district, 50 km northwest of Harare (10). However, in this study, only 32% of participants underwent VL testing.

In any case, in most studies in low-resource settings, the third goal of UNAIDS of ≥90% VS rate in PLWHA on ART has not been met, just as in the case of our study where the overall (regardless of ART exposure) rate of VS (VL ≤1,000 copies/ml) was 78%, improving to 84.3% in pregnant women who knew their HIV status and were already on ART at enrolment. Therefore, more concerted effort is required to improve on the third 90 of the UNAIDS 90–90–90 goal at least in our study population to ensure optimal health outcomes for mothers and babies including PMTCT.

Risk Factors for Lack of VS

When assessing potential risk factors for good HIV control in multivariable regression models, we identified two dominating protective factors: ART treatment ("are you on ART") in the whole population with an OR of 8.1. Furthermore, in women already on ART, sufficient length of ART treatment (>126 days) was of overriding importance as a predictor for HIV suppression with an OR of 8.5. Therefore, screening all young women for HIV even before pregnancy and starting ART as soon as possible in all infected individuals would help to improve health outcomes of pregnant women as a highly vulnerable population. In that respect, it should be noted that pregnant women registered rather late at antenatal care clinics at 6 months of pregnancy. Furthermore, mothers lacking VS (i.e. with VL >1,000 copies/ml) registered even later at 7 months after conception. Financial hardships with inability to afford US $25 required for antenatal care might have contributed to these late registrations. Therefore,

financial support of mothers with very limited resources or abolishing antenatal care user fees might lead to earlier antenatal registration to facilitate an earlier start of HIV management and thus allow more time to achieve optimum VS and might ultimately avert or reduce MTCT and save lives.

The period of 36 weeks of pregnancy to labour is critical since 50% of HIV MTCT occur within this time period (20% occurring before 36 weeks and 30% after delivery) in non-breastfeeding populations (38). However, in breastfeeding populations, intra-uterine transmission is the major route of MTCT (39). Recent observational studies concluded that ART should be initiated at least 16 weeks (112 days) prior to the date of birth to achieve the desirable undetectable HIV VL by the time of delivery (40–42). In light of our finding of VS in >95% of women only after 126 days, an even earlier start of ART might be advantageous. Considering the late antenatal care bookings, VS rates might also improve with the new TENOLAM-D regimen (Dolutegravir), being offered since 2018 which has been shown to suppress VL more rapidly with at least a 2 $\log_{10}$ decrease by week 2 of therapy (43).

ART Side Effects and Self-Reported Adherence to ART

Overall ART side effects were reported by 21.6% of the women, disproportionally occurring in those who initiated ART during pregnancy compared to those initiating before pregnancy. Reported adverse effects included dizziness (56.1%), vomiting and nausea (17.5%) and general body weakness (14%). Furthermore, 2/219 women who initiated ART during pregnancy stopped HIV treatment due to intolerable vomiting and nausea (ART defaulters). ART side effects contributed to lower VS with effects bordering statistical significance. Therefore, frequent consulting with HIV specialists would be desirable, especially for women initiating HIV therapy after conception since rates of adverse effects were higher in this population.

A recent systematic review and meta-analysis found that 46% of the PLWHA receiving NNRTI-based first-line ART regimen re-suppressed at the next VL assessment, indicating that in many cases, elevated baseline VL may have been due to poor adherence (44). Simple and affordable measures recommended by WHO to assess adherence include self-reporting, pill counts and assessment of pharmacy refill records (45). In addition, composite adherence measures such as combining self-report with tablet recount or pharmacy refill records would have been more accurate. In any case, since in our study, 14.7% of women reported ever missing ART dosage, more adherence counselling interventions might be necessary.

Teenage Mothers

In our cohort age <20 years was associated with reduced rates of both VS and undetectable VL. VS rates were relatively lower at 61.9% for the (21/608) teenage pregnant women in our cohort. In line with these observations, in a previous Zimbabwean study of non-pregnant adolescents (10–19 years old) following 12 months of being on ART, only 57% achieved VS at VL≤1,000 copies/ml (46). In the same study, risk factors for lack of VS in non-pregnant adolescents included poor ART adherence, alcohol consumption and non-disclosure of HIV status (46).

Poorer outcomes in younger mothers could be explained since they were less likely to be in an established position in the family structures or had less economic resources within their control, thus making them more vulnerable. Higher economic vulnerability might, in turn, lead to lower adherence to ART. A longitudinal qualitative study on HIV-infected Kenyan adults showed that livelihood interventions such as a microfinance loan or agricultural and financial training improved food security and poverty and consequently led to improved ART adherence, VS and CD4$^+$ T-lymphocyte counts (47, 48). This observation underscores the need for economic empowerment for women since economic insecurity is a major barrier to HIV treatment adherence.

Unplanned Pregnancies

Overall, the rate of unplanned pregnancies observed in our cohort was 54.9%. This seems quite high especially in this urban setting with good contraception coverage. The highest frequencies of unplanned pregnancies (61%) were reported in generally older women who were on ART before pregnancy, underscoring the need for integrating family-planning services into HIV care and treatment settings. These findings are comparable to a previous 1997 Harare study ($N = 923$) that observed a 41% rate of unplanned and a 9% rate of unwanted pregnancies (regardless of HIV status), with women >35 years being 3 times more likely to present with an unplanned pregnancy compared to the younger ones (49). Rates of contraception failure in women on ART have been shown to be high (29, 50), and unplanned pregnancy might also be an indicator of being on ART before conception.

Self-Reported Depression

Self-reported depression was rare in our cohort (1.5% of all HIV-infected mothers); however, depression was associated with the highest likelihood among all predictors for not achieving VS among women on ART (OR 0.092, corresponding to a 10.8-fold higher likelihood of not being virally suppressed). In line with these observations, mental disorders have previously been described as barriers to efficient HIV therapy in Zimbabwean adolescents (51).

Depression contributes to poor HIV outcomes and every 365 days of depression was shown to increase mortality by 71% (52, 53). Depression has been linked to low adherence to HIV medication (54), most likely explaining suboptimal VS. Nurse-delivered cognitive behavioural therapy has been shown to improve depression and adherence to HIV medication in South Africa (55). However, access to mental health care is limited in Zimbabwe, more so in high-density areas where most eligible women may not be able to afford medication or other psychiatric or psychotherapeutic interventions. Since rates of self-reported depression likely underestimated mental diseases/disorders, the true impact of depression might even be higher in our study population.

Non-disclosure of HIV Status and Stigma

Deliberate non-disclosure of HIV status may be a function of personal interests or priorities to avoid loss of trust and ensure self-preservation while simultaneously (re)constructing self-identity and reaffirm or redefine existing social interactions with the spouse/intimate partner (56). This probably may also have been the case in our study where 1.8% of women had an undisclosed HIV status, up to 7,259 days after being diagnosed of HIV. It is possible that women did not disclose due to fear of potential violence, blame or even divorce. Future studies focusing deeper into women's sexual practises including marriage issues such as extra-marital affairs may inform the dynamics of HIV status disclosure, ultimately improving HIV control in the populations at risk.

In our study, HIV status disclosure increased the likelihood of undetectable VL, confirming findings from previous studies. In a South African study of women with a new HIV diagnosis during pregnancy and immediate initiation of ART, disclosure of HIV status to their spouses/intimate partner was associated with a reduced risk of detectable VL >50 copies/ml at delivery (29). Conversely, non-disclosure of HIV status has also been associated with decreased odds for VS in Ugandan pregnant women initiating lifelong ART (57, 58) and Zimbabwean adolescents with mental disorders (51). This points to HIV-related stigma as possibly one reason for reduced rates of ART adherence.

Having a spouse on ART increased the likelihood of VS and undetectable VL. In our cohort, 21.2% of the women reported that their spouse/intimate partner had not yet undergone HIV testing, whilst 10.3% did not even know whether their spouses/intimate partners had undergone HIV testing or not. This suggests that stigmatisation and lack of efficient/open communication regarding HIV infection was prevalent within couples. The rate of 21.2% of spouses/intimate partners not tested for HIV in our cohort is corroborating the findings of the 2015 Zimbabwe Demographic and Health survey that performed interviews and HIV testing for 3,151 cohabitating couples and found that 15% of the men who tested positive had never been tested before this survey (26). Therefore, in a concerted effort to reduce new HIV infections, there is a great need to sensitise and motivate men to go for regular HIV screening. Male-friendly environments and policies may be key to increase male involvement. Previous studies have observed that when men are not involved, they may be less aware that their actions may put the lives of their spouse/intimate partner and the unborn baby at risk, for example, by stealing the spouse/intimate partner's medication or not allowing them to go for resupplies.

Strengths and Limitations of the Study

Our study has several strengths and some limitations. Strengths include the large size of our cohort with >600 HIV-infected pregnant women. Furthermore, we performed extensive clinical characterisation of participants and provided comprehensive clinical, anthropometric and socio-demographic information. The main limitation is the cross-sectional nature of this analysis with VL testing done only once. Therefore, for most women, HIV diagnosis was already known before inclusion in our cohort, and the time after initiation of ART until VS could not be directly estimated. The ART-naïve status was not verified.

In conclusion, in a cohort of pregnant women in a low-resource setting in Sub-Saharan Africa, 21.9% of the women had

HIV VL >1,000 copies/ml and 38.7% had VL >50 copies/ml in late pregnancy. Analysis of risk factors re-confirmed being on ART and a sufficient period of ART use (>126 days) as the most important factors for VS. Maternal depression, ART side effects and non-disclosure of HIV status were additional risk factors of lower importance. Conversely, having a spouse on ART improved VS rates. Thus, HIV screening in all young individuals and initiation of ART immediately after diagnosis are the most important measures to suppress VL in pregnancy and reduce HIV transmission. HIV MTCT rates may be further reduced by addressing challenges of adolescent mothers, late antenatal care presenters, couple HIV testing at antenatal care centres and also economic empowering interventions.

Couples of reproductive age should be encouraged to go for a pre-conceptual visit for HIV counselling and testing for timely diagnosis and early treatment of any new infections before pregnancy. Concerted efforts are needed to optimise pregnancy health outcomes in a positive move towards attaining the ambitious UNAIDS 95–95–95 strategy aiming to end the AIDS epidemic by 2030.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Joint Research Ethics Committee (JREC) for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals, reference number: JREC/18/15 and the Medical Research Council of Zimbabwe; reference number: MRCZ/A/1968. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The study was conceived by KD, EG, and LRM. The study was designed by KD, EG, LRM, and TM. PTM, TM, AJM, and SB were responsible for data collection, entry and validation overseen by KD and EG. PTM and AJM performed the statistical analysis supervised by BM and SBUJ. BM, SBUJ, KD, PTM, and AJM were involved in the interpretation of findings. The manuscript was written by KD and BM. All authors were involved in manuscript revisions and approved the final draft.

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SUPPLEMENTARY MATERIAL

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