




# Virological Outcomes Among Pregnant Women Receiving Antiretroviral Treatment in the Amhara Region, North West Ethiopia

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**Background:** Globally, approximately 35 million people are infected with HIV infection. Sub-Saharan countries contributed 71% of global burden. Women are the most affected groups accounting for 51% of global infection and 90% of HIV infections in children (<15 years) are a result of mother to child transmission. In the absence of any intervention, mother-to-child transmission has been estimated to 30–40% that could occur at various periods like during pregnancy, delivery, and post-partum, via breastfeeding. For future generations to be born HIV-free, evidences on the level of viremia and contributing factors in pregnant mothers is important.

**Objective:** The objective of this study is to determine the magnitude of viral non-suppression rate among pregnant women and identify the risk factors associated with viral non-suppression.

**Methods:** A cross-sectional study was conducted from July 01, 2021 to June 30, 2022, in pregnant women who are on antiretroviral treatment and attending HIV viral load testing in Amhara region viral load testing sites, North West Ethiopia. Socio-demographic, clinical, and HIV-1 RNA viral load data were collected from the excel database. The data were analyzed in SPSS 23.0 statistical software.

**Results:** Overall viral non-suppression rate was 9.1%. In other words, the viral suppression rate was 90.9%. Pregnant women being at AIDS stages III and IV and with fair treatment adherence and suspected testers were statistically associated with increased viral non-suppression rate.

**Conclusion:** Relatively low viral non-suppression rate among pregnant mothers that had almost met the third 90 of UNAIDS target. But, still, some mothers received a non-suppressed viral replication specifically the odds of having a non-suppressed viral load was higher in pregnant women with poor treatment adherence and WHO Stage III and IV and suspected testers.

**Keywords:** virological outcomes, viral suppression in pregnancy, antiretroviral treatment adherence, viremia in pregnancy

## Background

Globally, around 35 million people in the world are infected with HIV. Sub-Saharan African countries contributed 71% of global burden.<sup>1</sup> Women are the most affected groups accounting for 51% of global infection and 90% of HIV infections in children (<15 years) are a result of mother to child transmission (MTCT). The largest group of individuals living with HIV in Africa are women of childbearing age contributing more than 60% of HIV-infected adults in sub-Saharan Africa.<sup>1,2</sup> In Ethiopia, one of the sub-Saharan African countries, there were more than 613,000 Ethiopians infected with HIV/AIDS in 2017. The majority of this figure is composed of child-bearing mothers<sup>3,4</sup> due to early sexual debut, intergenerational sex, violence and sexual abuse, and transactional sex including the exchange of sex for money or goods as a consequence of dangerous socioeconomic conditions and low AIDS awareness.<sup>5</sup>

It is agreed that women demand more healthcare and earlier initiation of ART than men; they may be more likely to show incomplete ART adherence.<sup>6</sup> Child-care responsibilities, economic pressures, and lack of partner support contribute compromised adherence to ART in women.<sup>6</sup> Besides this, during pregnancy, treatment outcomes may be compromised.<sup>2</sup> This might be related to

the evidence that pregnancy is associated with an increase in blood volume and body mass index, which may lead to underdosing of drugs.<sup>7,8</sup>

Additionally, levels of cytochrome p450, and in particular CYP3A isoenzymes, may rise during pregnancy,<sup>9</sup> increasing the metabolism of two antiretroviral drugs lopinavir, and nevirapine; thus pregnant women may experience reduced concentrations of both drugs.<sup>7,9-11</sup> Moreover, during pregnancy the level of beta-estradiol increase substantially; diminish the efficacy of stavudine,<sup>12</sup> first-line ARV drug.<sup>2</sup> The combined effect of these physiologic processes, lead to incomplete adherence to ART which in turn increases women's risk of virologic failure and subsequent clinical progression.<sup>6</sup>

Prevention of mother-to-child transmission (PMTCT) through the use of antiretrovirals (ARVs) has been approved as one of the most successful approaches to prevent new HIV infection.<sup>13</sup> In the trend of HIV infection, antiretroviral therapy (ART) has reduced the mortality of people living with HIV infection.<sup>14,15</sup> However, the provision of ART especially in low-income countries with sub-optimal medication and patient follow-up may lead to drug-resistance.<sup>16</sup>

Even though mother-to-child transmission (MTCT) of HIV has significantly reduced over the previous decade, it remains to subsidize to the disease's load in many nations in Africa especially in sub-Saharan Africa. It has been projected that approximately 300,000 infants have been diseased in Africa in 2011<sup>17</sup> and more than 50% of them were anticipated to die before the age of two years.<sup>18</sup> In the absence of any intervention, mother-to-child transmission has been estimated to 30–40%<sup>19</sup> that could occur at various periods like during pregnancy, delivery, and post-partum, via breastfeeding.<sup>20</sup>

According to previous research data, the transmissibility of virus from mother to their child during vaginal delivery, breastfeeding and utero infection contributes 60–70%, 20–30% and less than 10% respectively.<sup>21</sup> In the absence of PMTCT service, the HIV viral load that circulates in the blood is high; low chance to reduce viral transmission from mother to their child resulting in 25–40% of newborns from HIV-positive mothers will acquire the virus.<sup>21</sup> But, with the presence of antiretroviral treatment in PMTC program, the transmission rate from mother to child was less than 2%.<sup>22</sup> However, the success of treatment is dependent on both the inherent properties of the ARV drugs and the person's adherence to the treatment.<sup>21</sup> Studying the magnitude of viral non-suppression rate among pregnant mothers and identifying the risk factors associated with viral non-suppression with the presence of antiretroviral treatment is significant if upcoming generations are to be born as HIV-free.

## Methods

### Outcome Measures

Viral non-suppression after six months following initiation of ART was primary outcome variable for this study, defined as viral load of at least 1000 copies/mL of blood.<sup>3</sup>

### Study Design and Period

A cross-sectional study was conducted to determine the magnitude of viral non-suppression rate and associated risk factors among pregnant women who were on antiretroviral treatment and tested for HIV viral load in the Amhara region viral load testing sites, North West Ethiopia from July 01, 2021 to June 30, 2022.

### Study Area and Setting

According to the 2021 Amhara Regional State Health bureau report, the prevalence of HIV in the Amhara region was 1.6%, and there were more than 91,092 HIV-infected patients tested for HIV viral load among 145,206 ART patients in 373 ART sites in the region including pregnant women. The overall regional ART and ANC coverage was 69% and 91%, respectively, with 66% HIV viral suppression rate among treatment currents. In the Amhara region, where this study was conducted, there are seven viral load testing sites for viral load testing for monitoring HIV ART treatments after the 90-90-90-ambitious plan. These seven testing sites receive samples from different peripheral health facilities which are linked based on their geographical proximity through a sample referral system. These testing sites also receive samples from nearby neighboring health facilities of the Afar, Oromia, and Benishangul-Gumuz regions. These testing sites provide only viral load testing services based on their referral linkage. Plasma specimens collected at different health

facilities transported to these testing sites through postal system and submitted to the respective testing sites reception. Similarly, postal services deliver results back to referring facilities from testing sites after laboratory analysis.

## Definition

### Adherence

Adherence level was determined by pill-count/self-reports/pharmacy refill records and sub-categorized as “poor” (<85%), “fair” (85–94%) or “Good” adherence (>95%), based on the 2018 National consolidated guidelines for comprehensive HIV prevention, care and treatment in Ethiopia.<sup>3</sup>

### Suspected Viral Load Testers

Suspected viral load testers are those pregnant women that have tested if they have signs of clinical/immunologic treatment failure as well as those tested virally unsuppressed viral load at some point part of routine testing.<sup>3</sup>

### Virological Failure

Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with enhanced adherence support following the first viral load test.<sup>3</sup>

### Viral Non-Suppression

Virological non-suppression is a viral load  $\geq 1000$  copies/mL of blood after six months of ART initiation.<sup>3</sup>

## Study Population

The study population were all pregnant mothers who received HIV viral load testing services in all viral load testing during the study period. Each specimen from pregnant women was a study unit. Pregnant women with complete request form and accepted specimen were included in the study. Poor specimen quality such as hemolysis and missed pregnancy status were exclusion criteria. Specimens that fit inclusion criteria were included in the study and selected successively.

## Data Collection Procedure

The data abstraction tool was organized by the investigators and used to gather data. Variables were collected from the requests and excel database. When postal runners deliver specimens at the reception of the respective testing sites, sample quality and requests completeness were evaluated. Socio-demographic and clinical information were extracted from the laboratory request. Each specimen was labelled with a specific identifier in all testing sites and given to the molecular laboratory testing. Qualified laboratory expert examined the viral load test following according to the standard operating procedure. In brief, nucleic acid extraction of plasma performed by an automated m2000sp machine (Abbott Molecular inc., Germany). Extraction reagents were: mlysis to lyse the membrane; magnetic particle to capture RNA after lysis; mWash1 and mWash2 to wash successively the target; Elution buffer to elute the viral RNA. The unrelated RNA sequence was also included in the sample at the beginning and extracted together with target sample as an internal control to monitor the extraction process for each specimen. Negative, low positive, and high positive controls per run were used to control the run. Then, the elute mixed with amplification reagents (thermostable polymerase enzyme in a buffered solution, oligonucleotides, quencher, reference dyes, and activation reagent) to amplify and detect HIV1 RNA with automated m2000rt machine (Abbott Molecular inc., USA). After amplification completed, results were read as not detected and detected (number of HIV RNA copies). The lower and upper detection limit of the platform is 150 and 10,000,000 RNA copies per mL, respectively. Viral copies >1000 HIV RNA copies/mL considered as unsuppressed viral load.

## Statistical Analysis

The excel data exported to the SPSS version 23 statistical packages for analysis. Frequencies were presented to describe study participants and chi square test was done to compare the difference in viral non-suppression rate among different categories of study participant. The association of viral non-suppression with independent variables (age, sex, test reason, WHO stage, and adherence) were measured using the backward likelihood ratio (LR) method in the multivariable logistic regressions. A significant association of dependent variable with independent variables was done using the adjusted odds ratio (AOR) and 95% confidence interval. P-value < 0.05 was considered as significant association.

## Results

### Socio-Demographic and Clinical Characteristics

A total of 992 pregnant women were tested for viral load during the study period. Most of them 694 (70%) were between the age of 23–33 years. Breastfeeding pregnant women accounted for 56 (6%) of the total participants. Viral load testing was requested to check anti-retroviral treatment failure among 36 (4%) suspects, and to monitor routine viral load among 956 (96%) pregnant mothers. About 902 (90.9%) of pregnant women had the WHO stage one category. There was good HIV treatment adherence in 974 (98%) pregnant women. Almost all (99.1%) participants were treated with adult first-line drugs. Pregnant women were treated with a combination of NRTI + NNRTI (73.9%), NRTI + PI (22.1%), NRTI + NNRTI + PI (2.1%), and NRTI + NRTI (1.9%) antiretroviral drugs. The most widely used drug combination was 3TC+ EFV+ TDF (46.9%) (Table 1).

### HIV Viral Load Non-Suppression Status

Of the total participated pregnant women, the viral non-suppression rate was 9.1% (95% CI: 7.1–10.9%). In other words, the viral suppression rate was 90.9% (95% CI: 89.1–92.7%). A significantly high suppression rate was observed among mothers who were on WHO stage I and WHO stage II compared to WHO stage III and WHO stage IV (91%, 92% vs 76 and 63%;  $p=0.006$ ). Similarly, a significant suppression rate difference was observed among pregnant women with good, fair, and poor adherence to ART (91% vs 69% vs 40% respectively;  $p<0.05$ ). Moreover, a significant difference in viral suppression rate was also observed among those tested routinely and suspected testers (92% vs 58% respectively;  $p<0.05$ ). But, no statistical difference in viral suppression was observed between pregnant women of different age groups; those who take first and second-line drugs; breastfeeding and non-feeding mothers, and those who take different treatment combinations (Table 2).

As shown in Table 3, on univariate analysis WHO Stage, Treatment Adherence, and Test reason were selected for multivariate analysis. On multivariate analysis, WHO Stage, Treatment Adherence, and Test reason were associated with the viral non-suppression rate. Pregnant women with WHO stage III and IV had a significantly higher prevalence of viral suppression failure compared to the prevalence of viral suppression failure in pregnant women with WHO stage I and II

**Table 1** Demographic and Clinical Characteristics of Pregnant Women Attending ART Clinics for ART Follow-Up in Amhara Region, 2021/2022

Variables		Number	%
Age	12–22	79	8.0%
	23–33	694	70.0%
	34–45	216	21.8%
	≥46	3	0.3%
Breastfeeding	No	936	94%
	Yes	56	6%
WHO Stage	I	902	90.9%
	II	65	6.6%
	III	17	1.7%
	IV	8	0.8%
Adherence	Good >95%	974	98%
	Fair (85–94%)	13	1%
	Poor <85%	5	1%
Test reason	Routine Viral load testers	956	96%
	Suspected Viral load testers	36	4%
Regimen Type	First Line	983	99.1%
	Second Line	9	0.9%
Combination Type	EFV Based	124	12.5%
	NVP Based	630	63.5%
	PI Based	217	21.9%
	NRTIs	21	2.1%

**Table 2** Non-Suppression Rate Difference Between Different Categories of Pregnant Women Attending ART Clinics for ART Follow-Up in Amhara Region, 2021/2022

Variables		Suppressed (n)	Non-Suppressed (n)	Suppression Rate (%)	P value
Regimen Type	First-line	895	88	91%	0.168
	Second-line	7	2	77.8%	
Age	12–22	73	6	92%	0.409
	23–33	628	66	90%	
	34–45	199	17	92%	
	≥46	2	1	67%	
Breastfeeding	No	852	84	91%	0.399
	Yes	50	6	89%	
Stage	I	824	78	91%	0.006
	II	60	5	92%	
	III	13	4	76%	
	IV	5	3	63%	
Adherence	Good >95%	891	83	91%	0.000
	Fair (85–94%)	11	7	61%	
Reason	Routine Viral load	881	75	92%	0.000
	Suspected Viral load	21	15	58%	
Treatment category	EFV Based	116	8	93.5%	0.649
	NVP Based	568	62	90.2%	
	PI Based	199	18	91.7%	
	NRTIs	19	2	90.5%	

**Table 3** Risk Factors Associated with Viral Non-Suppression Among Pregnant Women Attending ART Clinics for ART Follow-Up in Amhara Region, 2021/2022

Variables		Suppression Status		Crude OD Ratio (95% CI)	Adjusted OD Ratio (95% CI)	P value
		Suppressed (N)	Non-Suppressed (N)			
Age	12–22	73	6	1	-	0.580
	23–33	628	66	1.3 (0.536–3.053)	-	
	34–45	199	17	1.03 (0.395–2.738)	-	
	≥46	2	1	6.1 (0.479–77.187)	-	
Breastfeeding	No	852	84	1	-	0.660
	Yes	50	6	1.2 (0.507–2.923)	-	
WHO Stage	I	824	78	1	1	0.712
	II	60	5	0.9 (0.343–2.257)	0.8 (0.309–2.228)	
	III	13	4	3.3 (1.035–10.209)	3.4 (1.045–11.048)	
	IV	5	3	6.4 (1.487–27.023)	6.0 (1.317–27.512)	
Adherence	Good >95%	891	83	1	1	0.000
	Fair (85–94%)	9	4	6.8 (2.579–18.092)	5.1 (1.667–15.719)	
Test reason	Routine Viral load	881	75	1	1	0.000
	Suspected Viral load	21	15	8.4 (4.153–16.952)	6.7 (3.147–14.089)	
Treatment category	EFV Based	116	8	1	1	0.238
	NVP Based	568	62	1.58 (0.738–3.394)	-	
	PI Based	199	18	1.31 (0.553–3.111)	-	
	NRTIs	19	2	1.53 (0.301–7.741)	-	

(AOR: 3.397; 95% CI:1.045–11.048; P: 0.042 and AOR: 6.019; 95% CI:1.317–27.512; p:0.021). Similarly, those who were with a fair treatment adherence were 5 times more prevalent viral non-suppression rate compared to those who were with good adherence (AOR; 5.1; 95% CI:1.667–15.719; p<0.001). Those pregnant women who had tested as suspected failures were almost 7 times more at risk of viral suppression failure rate compared to those diagnosed as routine viral load (AOR: 6.659; 95% CI:3.147–14.089; P<0.001) whereas, Age (p=0.48), breastfeeding status (p= 0.66) and treatment category (p=0.468) were not associated with viral non-suppression rate.

## Discussion

Pregnant women are most likely to have an elevated viral load since their immunity is compromised during pregnancy. To create an AIDS-free generation, prevention of mother-to-child transmission is mandatory with enhanced adherence to ART drugs. In this study, we evaluated the rate of viral non-suppression rate and risk factors among pregnant women.

The overall rate of viral non-suppression rate was 9.1%. In line with this finding, 7.6% and 11% of HIV-positive pregnant women had viral non-suppression in Malawi and Uganda, respectively.<sup>23,24</sup> This highlights that the combination interventions for HIV preventions including behavioral risk reduction, test and treat, pre-exposure prophylaxis (PrEP), screening, and management of sexually transmitted infections, and use of antiretroviral medications<sup>3</sup> as well as the PMTCT program has contributed to a relatively low non-suppression rate among pregnant women that allows for enhanced follow-up of mothers during their pregnancy for targeted prevention of the virus to their fetuses.

Comparably an elevated viral non-suppression rate was observed in 15.2% of pregnant women in South Africa compared to our finding.<sup>25</sup> Similarly, a low non-suppression rate was observed among this study participants compared to the report conducted at Gondar among all group populations (14.7%)<sup>4</sup> and among children in the Amhara region (28.3%).<sup>26</sup> This indicates that many of HIV clients in the study have unsuppressed viral load that circulates in the blood causing to diminish their immunity which finally exposes them for other opportunistic infections. But our study subjects were pregnant women who were under PMTC service that permits mothers to be in close follow-up in addition to ART services. Even though a better non-suppression rate was observed in pregnant women in our study, still there were clients who received a non-suppressed viral load that carries to give a serious follow up since pregnant women with unsuppressed viral load is a high risk for transmission of HIV virus to their offspring.<sup>27</sup>

In this study, pregnant women with WHO stage III and IV had a significantly higher viral non-suppression rate compared to those pregnant women with WHO stage I as supported by different studies in different regions.<sup>28,29</sup> This evidence indicates that a high proportion of pregnant women with clinical stage III and IV have unsuppressed viral load compared to pregnant women with clinical stage I which is related with a more pronounced immunodepleted status to tackle viral replication in pregnant women with clinical stage III and IV than in those with clinical stage I.

The level of adherence to ART drugs is one of the most important factors for the success of ART services. Poor adherence to ART drugs may lead to increased viral non-suppression rates that expose HIV patients to opportunistic infections. A more worsening thing that finally proceed is the development of drug resistance. This drug resistance might produce a drug-resistant HIV virus that circulates in a community. Resistant viruses ultimately cause treatment non-respondent morbidity that finally causes increased mortality. In line with this fact, our study supports that there is an increased viral non-suppression rate among poorly adhered pregnant women compared with those who were on good ART drug adherence. This is strongly supported by different studies in different parts of the world. This finding is in congruent with studies conducted in Brazil, South Africa, Uganda, Tanzania and Ethiopia that reported virological failure among individuals living with HIV who were non-adherent on ART.<sup>6,24,30–34</sup>

Different studies had revealed that NVP-based ARTs were significantly associated with the increased viral non-suppression rate.<sup>26,35</sup> This finding indicates that the virus is still replicating even in the presence of treatments. This means the virus might have a mechanism to override this treatment. But, our study showed that there was no statistical association in viral non-suppression rate among EFV, NVP, and PI-based treatments as observed in some studies.<sup>36</sup>

## Conclusion and Recommendation

In summary, our findings showed that relatively low non-suppression rate among pregnant mothers that had almost met the third 90 of the UNAIDS target. This achievement might be related with provision of ART services as well as PMTCT services with a special emphasis for pregnant women to minimize the risk of HIV transmission to their fetus. Poor adherence and WHO Stage III and IV were significantly associated risk factors for increased viral non-suppression rate. Hence, enhanced adherence counseling and comprehensive follow-up of pregnant women should be promoted. Limitation of this study is that it does not perform drug resistance profile for clients who received high viral load result. Moreover, this study did not confirm virological failure since the study did not include two consecutive tests and drug resistance testing was not included.

## Abbreviations

3TC, Lamivudine; AOR, Adjusted Odds Ratio; APHI, Amhara Public Health Institute; ART, Anti-retroviral Therapy; AZT, Zidovudine; EFV, Efavirenz; HIV, Human Immunodeficiency Virus; LR, Likelihood Ratio; NVP, Nevirapine; PI, Protease Inhibitor; UNAIDS, United Nations Program on HIV/AIDS; WHO, World Health Organization report; NRTI, Nucleoside Reverse Transcriptase Inhibitors; NNRTI, Non-nucleoside Reverse Transcriptase Inhibitors; TDF, Tenofovir; LPV/r, Lopinavir/Ritonavir.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethical Approval and Consent to Participate

In this study, the data were not collected from the pregnant mothers directly since the specimens were collected from peripheral health facilities. The data were collected from the laboratory request, from the regional viral load excel database, and from the result of the specimens referred to the viral load testing laboratory. So, no need for consent from study participants. However, the permission to collect data from pregnant women were obtained during provision of health care services by trained service providers in each health facility complying the declaration of Helsinki. Ethics approval and official permission were obtained from the APHI research and technology transfer directorate to use the viral load data in the laboratory.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no competing interests.

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