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ORIGINAL ARTICLE | HIVViral Load

Detectable HIV-RNA Viral Load Among HIV-Infected Pregnant Women on Treatment in Northern Uganda

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ABSTRACT

Background / Objectives: Detectable HIV viral load among HIV-infected pregnant women remains a public health threat. We aimed to determine factors associated with detectable viral load among HIV-infected pregnant women in Lira, Northern Uganda.

Methods: We conducted a cross-sectional survey among 420 HIV-infected pregnant women attending Lira Regional Referral Hospital using a structured questionnaire and combined it with viral load tests from Uganda National Health Laboratories. We conducted multivariable logistic regression while adjusting for confounders to determine the factors associated with detectable viral load and we report adjusted odds ratios and proportion of women with viral load less than 50 copies/ml and above 1000 copies, respectively.

Results: The prevalence of detectable viral load (>50 copies/ml) was 30.7% (95%CI: 26.3% - 35.4%) and >1000 copies/ml was 8.1% (95% CI: 5.7% - 11.1%). Factors associated with detectable viral load were not belonging to the *Lango* ethnicity (adjusted odds ratio = 1.92, 95%CI: 1.05 - 3.90) and taking a second-line (protease inhibitor-based) regimen (adjusted odds ratio = 4.41, 95%CI: 1.13 - 17.22).

Conclusions and Global Health Implications: HIV-infected pregnant women likely to have detectable viral load included those taking a protease inhibitor-based regimen and those who were not natives of Lira. We recommend intensified clinical and psychosocial monitoring for medication compliance among HIV-infected pregnant women that are likely to have a detectable viral load to significantly lower the risk of vertical transmission of HIV in Lira specifically those taking a protease inhibitor-based regimen and those who are non-natives to the study setting. Much as the third 90% of the global UNAIDS 90-90-90 target has been achieved, the national implementation of PMTCT guidelines should be tailored to its contextual needs.

Key words: • HIV • Women • Pregnancy • Pregnant women • Viral load • Viral suppression • PMTCT • Antiretroviral therapy • Uganda

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I. Background and Introduction

Worldwide, there were 37.9 million people living with HIV (PLH) in 2018 and about 65% had access to antiretroviral therapy (ART) by June 2019. ¹ Eastern and Southern Africa bear the biggest burden of the epidemic¹ and Uganda is no exception.² Women are disproportionately affected by HIV compared to males² which translates into potential risk of HIV transmission from a mother to her offspring when getting pregnant. The World Health Organization as well as the Uganda national ART guidelines recommend combination ART for pregnant and breastfeeding HIV infected women regardless of their immune status,^{3,4} and the most common is a fixed drug combination taken once daily. In Uganda, more than 95% of HIV infected pregnant women received ART in 2017 to reduce the risk of HIV transmission to their offspring.²

One of the indicators used in the prevention of mother-to-child transmission of HIV-1 (PMTCT) programs is maternal plasma HIV-1 RNA viral load.⁵ Detectable or high maternal viral load increases risk of mother to child transmission of HIV.⁶ Detectable or high maternal viral load among HIV infected pregnant women has also been associated with various risk factors such as poor adherence to antiretroviral drugs^{7,8} and type of antiretroviral regimen being ingested.^{9–11} However, these risk factors vary across various study contexts therefore interventions targeted towards the virtual elimination of mother to child transmission of HIV in one context may not necessarily work for another – they may need to be context-specific.

Detectable viral load is a public health threat that can potentially translate into virologic failure and HIV drug resistance. We therefore set out to determine the factors associated with detectable viral load among HIV infected pregnant women in Lira, Northern Uganda. The objective of the study was to determine the factors associated with detectable viral load among HIV infected pregnant women in Lira, Northern Uganda.

2. Methods

2.1. Study Design

We conducted a cross-sectional study among 420 HIV positive pregnant women on ART between

August 2018 and July 2019. We have followed the STROBE guidelines in drafting of this paper.¹²

2.2. Setting

Lira Regional Referral Hospital (LRRH) serves all 8 districts of the Lango sub region in Northern Uganda. It has an annual outpatient attendance of almost 100,000 patients, an annual antenatal care attendance of about 5,000 patients and conducts approximately 6,000 to 7,000 deliveries annually. Lira is one of the sentinel sites in Uganda with the highest antenatal HIV prevalence at 13.5%¹³ making it a suitable site for our study due to the availability of an accessible population of interest. HIV care and treatment at LRRH is entirely supported and offered freely by the Government of Uganda through the Ministry of Health. At the time of conducting the study, the Uganda national HIV care and treatment policy guidelines recommended that once an HIV-infected pregnant woman has been initiated on ART, viral load testing should be done six months after initiation of treatment and thereafter once every year.

2.3. Sample Size Estimation

We calculated a sample size for detecting a difference between two independent proportions using STATA version 14.0 (StataCorp; College Station, TX, USA). We assumed that 23% of HIV infected pregnant women had detectable viral load ¹⁴ and that 12% of HIV infected women that had detectable viral load were taking a protease inhibitor-based regimen.¹⁵ Two sample size calculations were done for the prevalence and factors associated respectively. After accounting for 11% non-response the final sample size was 420 (Figure 1). The sample size obtained was sufficient to cover the sample sizes required for estimating the prevalence as well as investigating the factors associated with detectable viral load.

2.4. Participants

Study participants were identified, consented and recruited consecutively through the existing Ugandan program for HIV treatment, care and support for pregnant women at the PMTCT clinic. Participants were recruited onto the study as they



Figure 1: Study flow chart

came into the clinic until the estimated sample size was reached. Participants included in this study commenced their ART at different points in time and only those who had been on ART for at least six months or more, had viral load test done and results available were included in the analysis. The Ugandan ART treatment guidelines recommend viral load monitoring for HIV infected pregnant women who have taken ART for at least six months.⁴ Participants with a viral load count of 1,000 or more copies/ml were referred for intensive adherence counselling.

2.5. Study Variables

2.5.1. Dependent variable

Detectable viral load, the main outcome of the study, was defined as the presence of 50 or more copies of HIV-I RNA per millilitre (ml) of blood plasma.³ Viral load counts below 50 copies/ml were categorized as 'undetectable viral load'. This was done for comparability purposes. The presence of 1,000 or more copies/ml was called 'viral non-suppression'. Blood was drawn from HIVinfected pregnant women who were due for viral load monitoring and the blood samples shipped under cold chain to the Uganda National Health Laboratories where the viral load tests were done following the recommended scheduled routine as per the consolidated guidelines for the prevention and treatment of HIV in Uganda.⁴ The Roche cobas 8800 system technology (Hoffmann-la roche Ltd, Basel, Switzerland) with a level of detection of 40 copies/ml was used for viral load testing. The recommended schedule for virologic monitoring among HIV-infected pregnant women was having the viral load monitored six months after initiation of ART and thereafter once every 12 months.Viral load results were then available after two to three weeks.

2.5.2. Independent variables and covariates

The independent variables and covariates included in the analysis were socio-demographic-related like age, education, marital status, employment status, religious affiliation, ethnicity and socioeconomic index. Reproductive-related covariates included were: parity, gestational age, birth control use and intention to have baby. HIV-related covariates included were: HIV status disclosure, ART regimen and duration of ART.

Ethnicity was categorized as 'Lango ethnicity' or 'other'. Antiretroviral treatment was categorized as 'efavirenz-based', 'nevirapine-based' or 'protease inhibitor-based'. The latter is commonly a secondline regimen.

We created a composite index of wealth (socio-economic status) using principle component analysis (PCA) because it is the most-suitable choice to use when calculating wealth indices from categorical variables.¹⁶ We used PCA on house ownership, availability of electricity in the house, source of drinking water and fuel used for cooking. Scores were obtained and categorized into four groups (quartiles) ranging from the poorest to the least poor.

The interviews were conducted in *Lango* (the main language spoken in the study setting) or in English by trained study staff. The interviews followed a structured questionnaire with questions on socio-demographic, reproductive-related and HIV-related information. The questions were translated into *Lango* and back translated into English to ensure accuracy and minimize interpretation bias.

2.6. Statistical Analysis

Data were entered by two independent data entrants using EpiData software (www.epidata. dk, version 4.4.3.1) and exported for analysis into Stata version 14.0 (StataCorp, College Station, Texas, USA.). Continuous data, if normally distributed, were

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summarized into means and standard deviations and if not, were summarized into medians with their corresponding interquartile ranges. Categorical variables were summarized into frequencies and percentages. The proportion of HIV-infected pregnant women with detectable viral load was estimated and its confidence limits calculated using the exact method. We used multivariable binary logistic regression to estimate the adjusted odds ratios (OR) of the independent variables on detectable viral load while controlling for other variables like age, education status, person to whom HIV status was disclosed and duration of taking ART. Initially, all these variables were included in the crude analyses. Variables with a p-value of <0.25 and those with biological or epidemiological plausibility were included in the final model.

2.7. Ethical Approval

Approval to conduct the study was granted by the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council for Science and Technology and the Norwegian Regional Committee for Medical and Health Research Ethics in the West. Administrative clearance was granted by the Lira district health officer and LRRH. Service providers / counsellors at the PMTCT clinic were introduced to the study and its procedures and were requested to identify, mobilize and link willing participants with the research team. Participants received verbal and written information detailing the purpose and process of the study. All participants provided written informed consent confirming their voluntary participation in the study. Those that declined participation were not penalised or denied standard health care. Confidentiality and privacy of all data collected was observed during the course of the study through restricted access.

3. RESULTS

3.1. Sociodemographic Characterisitcs

A total of 518 HIV infected pregnant women were screened for eligibility from the antenatal care clinic at LRRH (Figure 1) and 420 women were included in the analysis. The participants had a mean age of 30.0 (SD 5.2). Socio-demographic characteristics

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are presented in table 1a. More than half (54.1%) of the women were 30 years or more. A total of 197 (46.8%) had attained formal education for a duration of at least six years or more. The majority (95%) of the women were married (or cohabiting) and not formally employed (60.5%). They were predominantly Christian (96.2%) and *Lango* speaking (90.5%) (Tables 1a and 1b). A considerable proportion of these women had disclosed their HIV status (98.3%).

3.2. Outcome Variable

The majority of the participants had undetectable viral load (Table 2). The prevalence of detectable viral load (>50 copies/ml) was 30.7% (95% CI: 26.3% - 35.4%). Of those with detectable viral load, the majority (n=82, 19.5% 95% CI: 15.8% - 23.6%) had viral load between 50 and 400 cps/ml.The proportion of women with a viral load \geq 1000 cps/ml was 8.1% (95% CI: 5.7% - 11.1%).

3.3. Covariates

Not belonging to the *Lango* ethnicity was associated with having detectable viral load among HIV infected pregnant women. Women belonging to other groups of ethnicity were almost twice as likely to have detectable viral load as their *Lango* counterparts (Table 3). Women who were on second-line treatment regimen were four times likely to have detectable viral load as those who had been taking a first-line efavirenz-based regimen.

4. Discussion

4.1. Discussion

One third of our study's participants had detectable viral load which is higher than that documented in other studies using the same cutoff of 50 copies/ml. Studies from South Africa^{11,14,17} and Malawi¹⁸ documented lower prevalence of detectable viral load among HIV infected pregnant women ranging from 10% to 23%. Much as various studies have demonstrated the association between detectable viral load and poor or non-adherence to ART,^{7,19-22} we cannot speculate non-adherence as a plausible explanation for the high prevalence of undetectable viral load since we did not measured non-adherence at this point in time.

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Characteristics	Total (N=420)	Undetectable viral load <50 copies/ml (N=291)	Detectable viral load ≥50 copies/ml (N=129)	
	n (%)	n (%)	n (%)	
Socio-demographic				
Age				
≤ 20 years	17 (4.0)	10 (3.4)	7 (5.4)	
21 – 29 years	176 (41.9)	128 (44.0)	48 (37.2)	
≥30 years	227 (54.1)	153 (52.6)	74 (57.4)	
Education				
0 – 6 years	223 (53.1)	155 (53.3)	68 (52.7)	
7 – 10 years	135 (32.1)	90 (30.9)	45 (34.9)	
11 – 13 years	43 (10.3)	31 (10.6)	12 (9.3)	
≥14 years	19 (4.5)	15 (5.2)	4 (3.1)	
Marital status				
Married	399 (95.0)	275 (94.5)	124 (96.1)	
Single	21 (5.0)	16 (5.5)	5 (3.9)	
Employment status				
Employed	166 (39.4)	114 (39.2)	52 (40.3)	
Not employed	254 (60.5)	177 (60.8)	77 (59.7)	
Religious affiliation				
Christian	404 (96.2)	280 (96.2)	124 (96.1)	
Moslem	16 (3.8)	(3.8)	5 (3.9)	
Ethnicity				
Langi	380 (90.5)	268 (92.1)	112 (86.8)	
Other	40 (9.5)	23 (7.9)	17 (13.2)	
Socioeconomic index				
Group I (poorest)	105 (25.0)	76 (26.1)	29 (22.5)	
Group 2	107 (25.5)	73 (25.1)	34 (26.4)	
Group 3	145 (34.5)	98 (33.7)	47 (36.4)	
Group 4 (least poor)	63 (15.0)	44 (15.1)	19 (14.7)	

Table	Ia: Socio-demographic	characteristics of	HIV infected	pregnant women	receiving a	antenatal	care
at Lira	a Regional Referral Hos	pital, Northern Ug	ganda				

The cut-off used for detectable viral load will also determine its prevalence. The lower the cut-off, the higher the prevalence is likely to be. A study in Malawi ²³ reported a similar prevalence of detectable viral load like our study, while researchers from Rwanda²⁴ reported a higher prevalence than ours. These studies, however, used a lower cut-off. In our study, the prevalence of virologic non-suppression (>1000 cps/ml) was 8%. Studies in Uganda²² and Malawi²⁵ reported a similar prevalence of virologic non-suppression among HIV infected pregnant women. The low prevalence of virological nonsuppression among women presenting for antenatal care in Lira can be used as an argument for the success of the universal treatment program in maintaining viral suppression and of the progress towards the last 90% of the UNAIDS 90-90-90 target.²⁶ Much as we have achieved the desired target for viral suppression today, the cut-off of 1,000 copies/mL used in Uganda is too high. This puts the focus on HIV-infected pregnant women with higher virologic profiles and less emphasis on those with

Table 1b: Other study	characteristics among stud	ly participants Lira	Regional Referral H	Hospital,
Northern Uganda				

Characteristics	Total (N=420)	Undetectable viral load <50 copies/ml (N=291)	Detectable Viral load ≥50 copies/ml (N=129)	
	n (%)	n (%)	n (%)	
Reproductive-related				
Parity				
I – 4	289 (68.8)	203 (69.8)	86 (66.7)	
5 – 9	3 (3 .)	88 (30.2)	43 (33.3)	
Gestational age (in weeks)				
20 – 27	225 (53.6)	158 (54.3)	67 (51.9)	
28 – 35	138 (32.9)	94 (32.3)	44 (34.1)	
≥ 36	57 (13.5)	39 (13.4)	18 (14.0)	
Accompanied to antenatal care by partner				
Accompanied	42 (10.2)	31 (10.6)	II (8.5)	
Not accompanied	378 (89.8)	260 (89.4)	118 (91.5)	
Use of birth control				
Did not use	198 (47.1)	136 (46.7)	62 (48.1)	
Used 6 months prior to pregnancy	222 (52.9)	155 (53.3)	67 (51.9)	
Type of contraceptive used				
None or "safe days"	196 (46.7)	133 (45.7)	63 (48.8)	
Effective contraception	224 (53.3)	158 (54.3)	66 (51.2)	
Intention to have baby				
No	182 (43.3)	127 (43.6)	55 (42.6)	
Yes	238 (56.7)	164 (56.4)	74 (57.4)	
HIV-related				
HIV status disclosure				
Disclosed	413 (98.3)	287 (98.6)	126 (97.7)	
Not disclosed	7 (1.7)	4 (1.4)	3 (2.3)	
Fear about others' opinion on HIV status				
Had no fear	199 (47.4)	137 (47.1)	63 (48.8)	
Had fear	221 (52.6)	154 (52.9)	66 (51.2)	
Antiretroviral treatment				
Efavirenz-based	370 (88.1)	263 (90.4)	107 (83.0)	
Nevirapine-based	39 (9.3)	24 (8.2)	15 (11.6)	
Protease inhibitor-based	11 (2.6)	4 (1.4)	7 (5.4)	
Duration of antiretroviral treatment				
6 – 36 months	216 (51.4)	160 (55.0)	56 (43.4)	
37 – 119 months	180 (42.9)	121 (41.6)	59 (45.7)	
≥ 120 months	24 (5.7)	10 (3.4)	14 (10.9)	

lower but detectable HIV-1 RNA, and yet it is those with detectable viral loads that are likely to translate into virologic non-suppression.

It is rather surprising that our study found that women who belong to other groups of ethnicity other than the *Lango* ethnicity (that is predominant in the study setting) had a higher likelihood of having a detectable viral load. A study in Benin²⁷ found the opposite, that the predominant ethnicity of the study setting was more likely to have a detectable viral load. More qualitative studies

Table 2:Viral loads of HIV infected pregnant women receiving antenatal care in Lira Regional Referral Hospital, Northern Uganda

Viral load count (copies/ml)	Frequency (n=420)	Percentage (%)
<50	291	69.3
50 to 400	82	19.5
401 to 999	13	3.1
≥ 1000	34	8.1

are needed in our study context to understand reasons for this finding.

We also found that taking a second-line protease inhibitor-based regimen increased the odds of having detectable viral load, which is quite a common finding. Studies in Uganda⁹ and the United States of America²⁸ found that protease inhibitor-based regimens were associated with lower probability of viral suppression than first-line efavirenz-based and nevirapine-based regimens among HIV infected pregnant women. However, there was no difference in the rate of viral suppression among women using protease inhibitor-based regimens and those using efavirenz-based or nevirapine-based regimens in the postpartum period.^{9,29,30}. This finding also be can be

Table 3: Multivariable analysis of factors associated with a detectable viral load (250 copies/ml of HIV
RNA in the blood)

Variables	Unadjusted OR	Adjusted OR (95% CI)	
	(95% CI)		
Age			
≤ 20 years	1.45 (0.53 – 3.95)	0.85 (0.29 – 2.53)	
21 – 29 years	0.78 (0.50 - 1.19)	0.73 (0.46 – 1.16)	
≥ 30 years	I	I	
Education status			
0 – 6 years	I	l	
7 – 10 years	1.14 (0.72 – 1.8)	1.21 (0.75 – 1.96)	
II – I3 years	0.88 (0.43 – 1.82)	0.85 (0.40 - 1.81)	
Tertiary	0.61 (0.19 - 1.90)	0.52 (0.16 – 1.76)	
Ethnicity			
Langi	I	l	
Other	1.77 (0.91 – 3.44)	1.92 (1.05 – 3.90)	
Person disclosed to			
Spouse	I	I	
Sibling	0.67 (0.36 - 1.22)	0.68 (0.36 – 1.26)	
Other	1.2 (0.54 – 2.70)	1.32 (0.57 – 3.05)	
Antiretroviral treatment			
Efavirenz-based	I	I	
Nevirapine-based	1.54 (0.77 – 3.04)	1.25 (0.58 – 2.71)	
Protease inhibitor-based	4.3 (1.23 – 14.99)	4.41 (1.13 – 17.22)	
Duration of antiretroviral treatment			
6 – 36 months	0.72 (0.46 – 1.11)	0.66 (0.41 – 1.06)	
37 – 119 months	I	I	
≥ 120 months	2.87 (1.20 – 6.85)	2.08 (0.77 - 5.53)	

explained further by the concept of reverse causality. HIV-infected women will be switched to a secondline ART regimen because of treatment failure of the first-line regimens which is mainly due to nonadherence.^{31,32} It is probable that the underlying challenges of adherence that forced these women onto second-line regimens may be aggravated during the use of second-line ART regimens. Non-adherence may be influenced by a number of factors and these may include side effects to antiretroviral drugs, pill burden in the context of pregnancy and increased psychosocial stressors related to pregnancy or care giving.³¹

4.2. Limitations

Our study had some limitations. This study was done in a hospital setting; therefore, the findings may only be generalizable to the study context or those similar to it. We did not report any adherence rates at this point in time because this is a baseline study of a cohort of HIV-infected pregnant women for whom adherence to ART will be measured as followup is being done. However, a strength of our study is that it is the first to describe virologic profiles among HIV-infected pregnant women in Northern Uganda and also demonstrates that in fact disparities in viral suppression do exist across various groups of ethnicity in this study setting.

5. Conclusion and Global Health Implications

HIV-infected pregnant women likely to have detectable viral load included those taking a protease inhibitor-based regimen and those who were not natives of Lira. Having a detectable viral load during pregnancy increases the risk of MTCT of HIV. We recommend intensified clinical and psychosocial monitoring of medication compliance among HIVinfected pregnant women that are likely to have detectable viral load to significantly lower the risk of vertical transmission of HIV in Lira specifically those taking a protease inhibitor-based regimens and those who are non-natives to the study setting. Much as the third 90% of the global UNAIDS 90-90-90 target³³ has been achieved in the study setting, the national implementation of PMTCT guidelines should be inclusive of HIV-infected pregnant women that are

most at-risk of having detectable viral load in this study context and those similar to it.

Compliance with Ethical Standards

Conflicts of Interest: The authors declare no conflict of interest. Funding Disclosure: The study was funded by the Norwegian Programme for Capacity Development in Higher Education and Research for Development (NORHED) by the Norwegian Agency for Development Cooperation (Norad), Norway through the Survival Pluss Project at Makerere University (no. UGA-13-0030). Ethics Approval: The study received ethical approval from the following issuing/ approving bodies: Uganda National Council for Science and Technology; Norwegian Regional Committee for Medical and Health Research Ethics in the West; and Makerere University College of Health Sciences School of Medicine Research and Ethics (SOMREC) committee. **Acknowledgements:** We are grateful to Lira regional referral hospital, the study participants and the research assistants for their contribution to this survey.

Key Messages

- Detectable HIV-RNA is high among HIV-infected pregnant women.
- HIV-infected pregnant women likely to have detectable viral load included those taking a protease inhibitor-based regimen and those who were not natives of Lira, Uganda.
- Clinical and psychosocial monitoring of medication compliance among HIV-infected pregnant women that are likely to have a detectable viral load to significantly lower the risk of vertical transmission of HIV in Lira specifically those taking a protease inhibitor-based regimens and those who are non-natives to the study setting should be intensified.

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