# Universal antiretroviral therapy for the elimination of mother-to-child transmission of HIV in Northern Uganda

Studies on determinants, adherence, breastfeeding and viral load

Agnes Kasede Napyo

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
and Makerere University, Uganda
2021

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Date of defense: 24.06.2021

Year: 2021

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Print: Skipnes Kommunikasjon / University of Bergen

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Napyo, Agnes Kasede

Thesis for the Degree of Doctor of Philosophy (PhD)

Joint PhD; Makerere University, Uganda and University of Bergen, Norway, 2021

To my daughters, Shiisa, Aramba and Siima, and their father, Namonyo Thomas.

## Scientific environment

This thesis is the result of a close collaboration between the Centre for International Health, University of Bergen in Norway, Makerere University College of Health Sciences and Busitema University Faculty of Health Sciences, which is my regular working place.

The work 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). The aim of the Survival Pluss project was to increase the capacity for mama-baby survival in post-conflict Uganda and South Sudan. I have been the beneficiary of a PhD scholarship from the Survival Pluss project and the Norwegian Research School of Global Health that granted me numerous travel grants to attend courses and scientific conferences. The Survival Pluss project carried out formative research and interventions to improve capacity for survival of babies and their mothers. Among the topics addressed is HIV and mother-to-child transmission as a background for this thesis. The previous decrease in the transmission rate of HIV from mothers to their offspring has stagnated, especially in post-conflict Northern Uganda.

## Acknowledgements

It is with immense gratitude that I thank my supervisors: Prof Thorkild Tylleskär, Prof James K. Tumwine, Prof Grace Ndeezi, Prof Paul Waako and Dr Victoria Nankabirwa. This is because of their tremendous and unwavering effort in training and grooming me from commencement to completion of my PhD programme.

I am grateful to my fellow PhD candidates for their moral, physical and academic support: David Mukunya, Josephine Tumuhamye, Anna Agnes Ojok Arach, Beatrice Odongkara, Sr. Vincentina Achora, Justin Tongun Bruno, Alice Mugisha and Milton Musaba.

My mother – Mrs Beatrice Kasede, father – Mr Michael Kasede, and husband – Mr Thomas Namonyo, and my wider family have been quite instrumental in my PhD journey. Without their moral support, I would hardly have realised this PhD. I am grateful to my daughters, Nicole Shiisa, Aramba Natalie and Siima Blessed-Hope, for being patient, accommodative and adaptive, especially in moments when I had to be far away from them.

I mostly thank the Lord for gracing me with persistence and resilience, which is a good recipe for success.

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## Abstract

**Background**: Uganda's decrease in mother-to-child transmission of HIV (MTCT) has stagnated, making it almost impossible to achieve the target of zero new HIV infections.
**Objectives**: The aim of this study has been to determine, among a group of HIV infected women enrolled on universal antiretroviral treatment in Lira, Northern Uganda, the prevalence and factors associated with: a) unintended pregnancy, b) detectable viral load, c) infant nevirapine prophylaxis, and d) exclusive breastfeeding.
**Methods**: A survey of 518 HIV infected pregnant women in 2018 was to determine the prevalence and predictors for unintended pregnancy. Of the 518, 420 had their viral load monitored, from which we determined the risk factors for detectable viral load. These women were followed up on delivery and at 6 weeks, when 472 mothers and their babies were included in a prospective cohort analysis to measure barriers and enablers of adherence to infant nevirapine prophylaxis. The mother-infant pairs were followed up until 14 weeks, at which point the incidence and risk factors for non-exclusive breastfeeding was longitudinally measured. Data was analysed using logistic regression models and generalised estimation equations for the Poisson family.
**Results**: Of the 518 women enrolled in the study, 213 (41.1%) had unintended pregnancy (95% Confidence interval (CI): 36.8% - 45.5). Risk factors for unintended pregnancy were being single (adjusted odds ratio (AOR) = 3.74, 95% CI: 1.67 – 8.34), higher parity (parity of ≥5; AOR= 2.79, 95% CI: 1.85 – 4.22) and long-term ART (≥10 years; AOR=3.69, 95% CI: 1.57 – 8.67). Detectable viral load (>50 copies/ml) was prevalent among 120 women [120/420; 30.7%: 95% CI: 26.3 - 35.4%)] and viral non-suppression (>1000 copies/ml) was at 8.1% (34/420; 95% CI: 5.7 – 11.1%). Factors associated with detectable viral load that did not belong to the *Lango* ethnicity were: (other ethnicity: AOR = 1.92, 95% CI: 1.05 – 3.90), and taking a second-line regimen (protease inhibitor-based: AOR = 4.41, 95% CI: 1.13 – 17.22). A number of the infants did not keep to their nevirapine prophylaxis at 6 weeks of age (70/472; 14.8%, 95% CI: 11.7-18.4%). Barriers to infant adherence were younger maternal age (≤20 years; adjusted risk ratio (ARR) =1.55; 95% CI: 1.1 – 2.2), did not take a viral load test during pregnancy (ARR: 1.4; 95% CI: 1.1 – 1.7), and mothers not receiving nevirapine syrup for the baby after childbirth (ARR = 6.2; 95% CI: 5.1 – 7.6). Enablers were maternal characteristics including: having attained ≥14 years of schooling

(ARR = 0.7; 95% CI: 0.5 – 0.9), taking a nevirapine-based regimen (ARR = 0.6; 95% CI: 0.4 – 0.9), being on long-term ART (≥ 60 months ARR = 0.75; 95% CI: 0.6 – 0.9), being accompanied by a husband to hospital during labour and childbirth (ARR = 0.5; 95% CI: 0.4 – 0.7) and labour pains starting at night (ARR = 0.7; 95% CI: 0.6 – 0.8). The rate of exclusive breastfeeding decreased with increasing age of the infants, and by 14 weeks of age almost half were not exclusively breastfeeding (200/466; 42.9%, 95% CI: 38.3-47.5%). Risk factors for non-exclusive breastfeeding included the mother: belonging to the highest socioeconomic strata (ARR = 1.5, 95% CI: 1.01 – 2.1), delivering under the supervision of a non-health worker (ARR=1.6, 95% CI: 1.01 – 2.7), and the mother not adhering to her ART during pregnancy (ARR=1.3, 95% CI: 1.01 – 1.7).

**Conclusion**: HIV infected women at risk of infecting their infants include the younger age group, unmarried, non-native to Lira, non-adherent to ART, have recently just began taking ART, had deliveries unsupervised by a health worker, and those that did not receive nevirapine syrup for their infant after childbirth. We recommend that attention should be focused on these critical groups during the implementation of PMTCT programs in Lira, Northern Uganda and in contexts similar to it.

# Abbreviations and definitions

| | |
|---|---|
| ANC | Antenatal care |
| AOR | Adjusted odds ratio |
| ARR | Adjusted risk ratio |
| BF | Breastfeeding |
| CD4 | Cluster of differentiation 4 |
| CI | Confidence interval |
| EBF | Exclusive breastfeeding |
| HAART | Highly active antiretroviral therapy |
| HEI | HIV exposed infant |
| HEU | HIV exposed uninfected infant |
| HIV | Human Immunodeficiency virus |
| HUI | HIV unexposed infant |
| IAC | Intensive adherence counselling |
| LRRH | Lira Regional Referral Hospital |
| MTCT | Mother-to-Child Transmission of HIV-1 |
| NORHED | Norwegian Programme for Capacity Development in Higher Education and Research for Development |
| PCA | Principal component analysis |
| PLH | People living with HIV |
| PMTCT | Prevention of Mother-to-Child Transmission of HIV-1 |
| SES | Socio-economic status |
| TBA | Traditional birth attendant |
| UNICEF | United Nations Children's Fund |
| VL | Viral load |
| WHO | World Health Organization |
| WLH | Women living with HIV |

# Definitions

| | |
|---|---|
| **Complementary feeding** | The process by which infants start to ingest other foods when breast milk alone is insufficient to meet their nutritional requirements, and therefore other foods and liquids are needed alongside breast milk. This usually refers to the period after 6 months of age |
| **Contraception** | Any behavioural and technological methods used to avoid pregnancy that may be the result of vaginal intercourse |
| **Detectable viral load** | HIV infected pregnant woman on ART having a viral load count of 50 or more copies per ml blood |
| **Exclusive breastfeeding** | An infant only receiving breast milk without any additional food or drink, not even water with the exception of the nevirapine syrup for prophylaxis or other medication within 1 h of birth and thereafter for 6 months |

| | |
|---|---|
| **Facility-based delivery** | A birth or delivery taking place at a health facility under the supervision of a skilled birth attendant, who is mainly a health worker. |
| **Family planning** | A comprehensive medical education that enables individuals to determine freely the number and spacing of their children, and to select the means (contraceptive methods) by which this may be achieved. This education may also involve the choice of having no children and the age at which to have them. |
| **Highly effective contraception** | Maintaining a level, dose or concentration of a hormonal contraceptive in the blood that is optimal for the prevention of conception. |
| **HIV viral load non-suppression** | When an HIV infected pregnant woman who is on ART and has a viral load count of 1000 or more copies of HIV-RNA per ml blood |
| **Home delivery** | A birth or delivery that has taken place in a non-hospital setting, e.g. at the traditional birth attendant (TBA) at home or on the roadside, under the supervision of an unskilled birth attendant or a non-health worker. |
| **Medication adherence** | The degree to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider. |
| **Mixed feeding** | An infant receiving both breast milk and any other liquid or solid food in the first 6 months of life |
| **Modern contraceptive methods** | Products or medical procedures that interfere with reproduction resulting from acts of sexual intercourse |
| **Option B+** | An approach to the prevention of mother-to-child transmission of HIV-1 for HIV infected pregnant women in which these women are immediately offered treatment for life, regardless of their CD4 count. |
| **Pre-lacteal feed** | Any food except the mother’s breast milk that is given or fed to a newborn in the first few days of life |
| **Replacement feeding** | The infant receives no breast milk and is being fed suitable breast milk substitutes in the form of an infant formula |
| **Undetectable viral load** | HIV infected pregnant woman on ART with a viral load count <50 copies per ml blood |
| **Unintended pregnancy** | A pregnancy that is mistimed, unplanned or unwanted at the time of conception |
| **Universal ART** | Initiation of HIV infected persons on lifelong highly active antiretroviral therapy (HAART), irrespective of the CD4 count or immune status |
| **Unmet need for contraception** | A situation in which those who want to stop or delay childbearing are not using or do not have access to any method of contraception |
| **Viral load** | the number of copies of HIV-RNA in 1 ml blood |

# List of papers

**Paper I**
Agnes Napyo, Victoria Nankabirwa, David Mukunya, Josephine Tumuhamye, Grace Ndeezi, Anna Agnes Ojok Arach, Beatrice Odongkara, Paul Waako, Thorkild Tylleskär, James K. Tumwine: ***Prevalence and predictors for unintended pregnancy among HIV-positive pregnant women in Lira, Northern Uganda: a cross-sectional study.*** *Sci Rep. 2020;10:16319. doi:10.1038/s41598-020-73490-6*

**Paper II**
Agnes Napyo, James K Tumwine, David Mukunya, Josephine Tumuhamye, Anna Agnes Ojok Arach, Grace Ndeezi, Paul Waako, Thorkild Tylleskär:
***Detectable HIV-RNA viral load among HIV-infected pregnant women on treatment in Northern Uganda.*** *Int J MCH AIDS. 2020;9(2):232-241. doi:10.21106/ijma.374*

**Paper III**
Agnes Napyo, Thorkild Tylleskär, David Mukunya, Josephine Tumuhamye, Musaba Milton, Anna Agnes Ojok Arach, Paul Waako, James K Tumwine, Grace Ndeezi: ***Barriers and enablers of adherence to infant nevirapine prophylaxis against HIV 1 transmission among 6-week-old HIV exposed infants: a prospective cohort study in Northern Uganda.*** *PLoS ONE .2020; 15(10): e0240529. doi:10.1371/journal.pone.0240529*

**Paper IV**
Agnes Napyo, James K Tumwine, David Mukunya, Paul Waako, Thorkild Tylleskär, Grace Ndeezi: ***Exclusive breastfeeding among HIV exposed infants 1 from birth to 14 weeks of life in Lira, Northern Uganda: A prospective cohort study.*** *Global Health Action. 2020; 13(1): 1833510. doi:10.1080/16549716.2020.1833510*

All these articles were published in open access, peer reviewed journals.

# Introduction

Globally, the number of people living with the human immunodeficiency virus (HIV) increased from 36.7 million in 2016 to 38 million in 2019 (1). The prevalence of HIV in Uganda has been stable around 6.2% over the last half decade (2). Women are disproportionately affected by HIV in Uganda with 59.2% of adults living with HIV being women. In 2018, the HIV prevalence among Ugandan women was 7.1% compared to 4.4% among men. About 14,000 young women aged 15 – 24 years got infected in 2018 alone compared to 5,000 new infections among young men (2). Scrutinizing the statistics further, the HIV prevalence in mid-northern Uganda (Lango sub-region) is at 7.2% and Lira district has an antenatal HIV prevalence of 13.5%, which is by far the highest prevalence among sentinel sites located in major urban areas in Uganda (3). HIV infected women of reproductive age are at risk of passing on the HIV infection to their offspring when pregnant, giving birth or breastfeeding. Mother-to-child transmission (MTCT) of HIV is the main mode of HIV transmission among children under 15 years of age, the majority of these infections occurring in sub-Saharan Africa (4). In 2017 alone, 180,000 children became HIV infected in the 23 high priority countries, of which Uganda is one. Uganda contributed 3.3% to these new infections. The majority of these infections were by vertical transmission (5). With antiretroviral medications for prevention of mother-to-child transmission of HIV (PMTCT), the majority of mother-to-child transmitted HIV infections are preventable. Uganda has made significant progress towards PMTCT, which is evident by the 86% reduction in new infections among children between 2010 and 2016 (6). However, the proportion of HIV exposed infants who get tested for HIV remains at 45% due to low retention of mother-infant pairs in the PMTCT programs in Uganda (7). Keeping women and their infants in PMTCT programs after delivery has been a challenge and more infant infections have occurred during breastfeeding than during pregnancy because women do not remain in care (8).

### HIV treatment and monitoring

HIV is treated with antiretroviral drugs that stop the virus from replicating in the body thus preventing further damage. Antiretroviral therapy is prescribed in triplicate combination including different classes of drugs to prevent the virus from becoming resistant to any one

of the medications (9). The Ugandan HIV treatment and care program has implemented the 'test and treat' policy which calls for initiation of antiretroviral therapy (ART) immediately after an HIV diagnosis is made in an effort to eliminate HIV transmission and improve quality of life for people living with HIV (PLH) (10). HIV infected individuals taking ART benefit from HIV monitoring from which response to ART can be checked and HIV drug resistance detected early enough to impede ART failure. HIV monitoring is both clinical and laboratory-based. Clinical monitoring involves staging of HIV using either the presence or absence of HIV-related signs using the WHO staging system (9). Laboratory monitoring of HIV involves conducting a number of tests. A CD4 count test helps to find out the status of the immune system to gauge the risk for complications and opportunistic infections. Viral load tests primarily aid in monitoring the patient's response to ART and act as a proxy for disease progression. Organ function tests, like liver and renal function tests, are also conducted to monitor for drug toxicity, ART-related metabolic changes and HIV comorbidities like hepatitis B or C (11). Drug resistance testing checks whether the virus is resistant to the ART drugs due to mutations and consequently ART failure.

**Evolution of PMTCT**

The World Health Organization's (WHO) four-pronged approach to PMTCT (12) is based on:

1) prevention of new HIV infections among women of childbearing age (15-49 years)
2) prevention of unintended pregnancies among women living with HIV (WLH)
3) prevention of HIV transmission from women living with HIV (WLH) to their offspring
4) providing appropriate treatment, care and support to WLH, their children and families.

The third prong has been the primary focus for PMTCT programs for several years, giving less emphasis to prongs 1, 2 and 4. PMTCT treatment guidelines have dramatically changed several times in the past decades. WHO guidelines for prophylactic ARV regimens have progressed from single-dose nevirapine (NVP) to short course zidovudine (AZT); AZT-based "Option A"; to "Option B," which means initiation of triple-drug antiretroviral therapy (ART) to the mother during pregnancy through breastfeeding; and the subsequent "Option B+," pioneered in Malawi - nowadays often called "universal ART for all"- where

all HIV-infected pregnant and breastfeeding women are initiated on lifelong ART irrespective of the number of CD4+ T-lymphocytes in the blood (CD4 count) or clinical stage (9,13) Table 1. With each change, Uganda has attempted to harmonize its guidelines with the global recommendations. Over time, this has resulted in confusion, with success hampered by implementation challenges.

*Table 1: The 3 strategies or options for PMTCT in the recent WHO guidelines*

| | **Option A** | **Option B** | **Option B Plus (+) or universal ART for all** |
|---|---|---|---|
| WHO guidelines proposed in | 2010 | 2010 | 2013 and 2016 |
| **Mother (CD4 ≤ 350 cells/mm3) or WHO clinical stage III or IV** | Triple ARVs, starting from diagnosis and continued for life | Triple ARVs, starting from diagnosis and continued for life | Triple ARVs regardless of CD4 count, starting from diagnosis and continued for life |
| **Mother (CD4 > 350 cells/mm3) or WHO clinical stage I or II** | Prophylaxis: Antepartum: AZT from 14 weeks of gestation Intrapartum: single dose NVP at onset of labour and AZT/3TC Postpartum: AZT/3TC for seven days | Prophylaxis: Triple ARVs from 14 weeks of gestation until one week after exposure to breast milk has ended | |
| **Infant** | NVP (daily) from birth until one week after cessation of breastfeeding, or until age 4-6 weeks if replacement feeding | NVP or AZT (daily) from birth until age 4-6 weeks (regardless of infant feeding method) | NVP or AZT (daily) from birth until age 4-6 weeks (regardless of infant feeding method) |

The current PMTCT (option B+) program takes the form of a cascade or steps of interventions (14) designed to collectively reduce or virtually eliminate the risk of MTCT of HIV among mother-infant pairs (Figure 1).

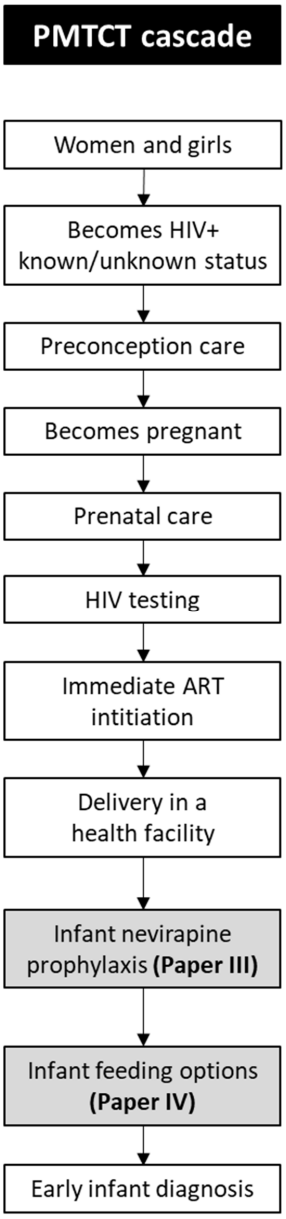


*Figure 1. The PMTCT cascade*

As women of known and unknown HIV status move along the cascade while receiving care through health service, each stage or intervention of the cascade is an opportunity for HIV prevention. However, if a woman misses out on any opportunity for HIV prevention as

illustrated in Figure 2, this could distort the cascade of interventions and increase the risk of MTCT.

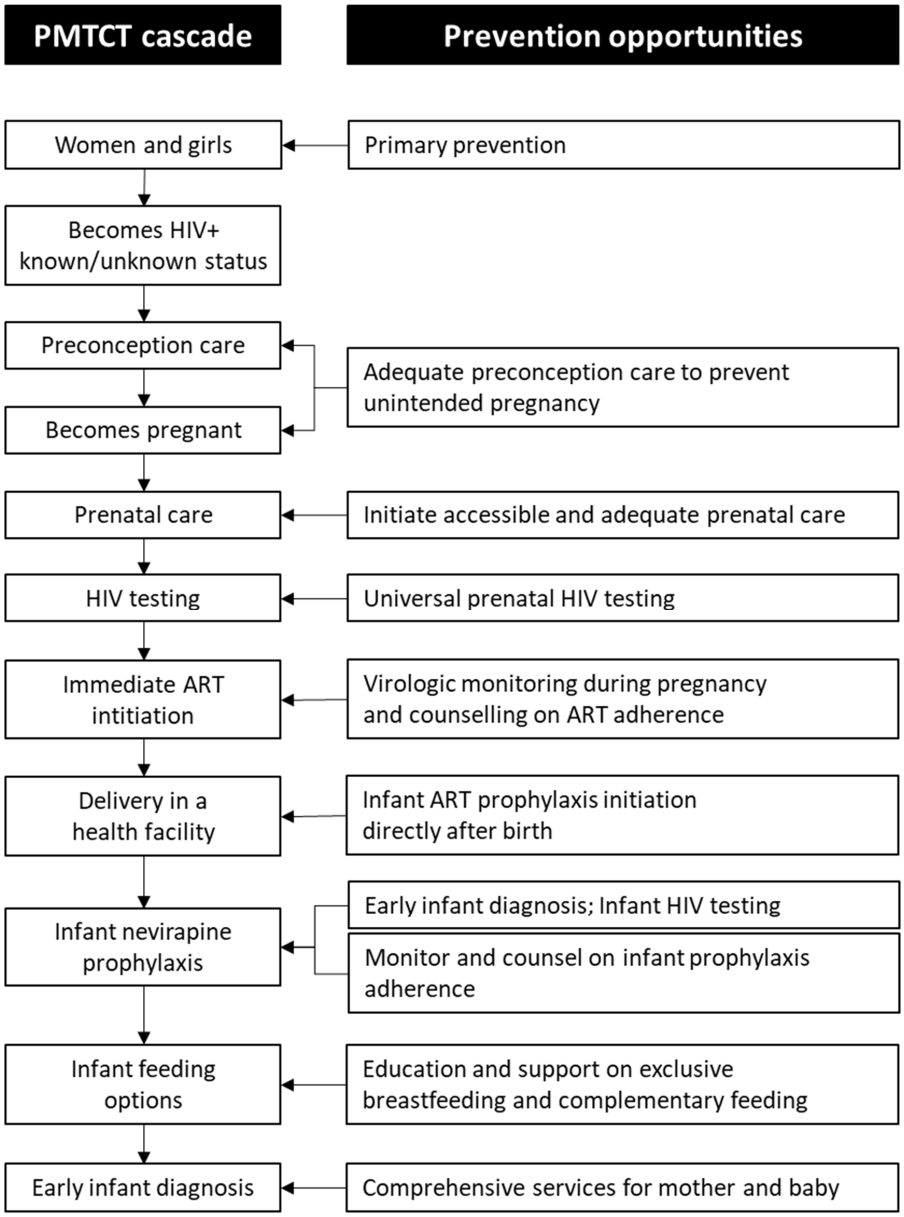


*Figure 2. The PMTCT cascade and opportunities for HIV prevention*

The preconception period avails an opportunity for HIV testing for the woman to know her HIV status. In this period, the woman also has a choice to plan for the timing and spacing of her births by using contraception, which is fully available through the integration of family planning services into HIV care (13). Preventing unintended pregnancies will reduce the number of infants that could potentially acquire HIV from their mothers and subsequently reduce the number of children that may require HIV services (15,16). Once a WLH becomes pregnant, she should initiate adequate prenatal care through receipt of ANC at PMTCT clinics that are usually located within public health facilities in Uganda. Antenatal care also avails an opportunity for HIV testing for all pregnant women, timely initiation of ART for life for all newly diagnosed women, and subsequently routine virologic monitoring to assess ART adherence and potential HIV drug resistance arising from ART failure. High maternal viremia is an important risk factor for MTCT and must be promptly addressed in WLH that intend to or those already pregnant (17–19). For pregnant WLH, facility delivery is emphasized to reduce on the risk of MTCT by availing the opportunity for skilled birth attendance during delivery (4). Skilled birth attendance avails the opportunity to prevent complications that arise during pregnancy and childbirth, to prevent maternal and neonatal mortality or morbidity. Most importantly, facility delivery has a number of benefits for the WLH: 1) it promotes the timely initiation of nevirapine prophylaxis for the baby; 2) it creates an atmosphere for continuous reinforcement of counselling messages on infant feeding, adherence to maternal ART and infant prophylaxis.(20). It is from these benefits that the reduction in risk of MTCT is achieved.

Nevirapine prophylaxis is given to the infant shortly after delivery to prevent residual HIV transmission from a mother to the infant during delivery and breastfeeding. This form of pre- and post-exposure prophylaxis involves timely initiation of ART (within 72 h) to the infant and should achieve therapeutic levels for optimal PMTCT (21). During the postpartum period, other interventions - early infant diagnosis and infant HIV testing -are essential for the early detection of infection. This promotes prompt ART initiation in case the infant is infected.

Infant feeding is crucial for all infants, whether exposed to HIV or not. Optimal infant feeding comprises exclusive breastfeeding (EBF) where the infant is given only breast milk

within one hour after birth, followed by maintenance of sole breastfeeding till the HEI is 6 months old and complementary feeding for 18 – 24 months with age appropriate foods (22).

**Pre-conception care among HIV infected women**

Fertility desires for WLH have increased over time because the PMTCT interventions available have enabled these women to have HIV-free babies (16,23–26). It is therefore important to support WLH in their fertility choices through family planning. Much as integration of family planning into HIV services exists, the unmet need for contraception persists, resulting in continuing high rates of unintended pregnancy (26–30). Surprisingly, the rates of unintended pregnancy among WLH in sub-Saharan Africa are higher (35 – 71%) (16,23,38,39,29,31–37) compared to rates in the general population (26 – 34%) (40,41). This is probably because WLH face high rates of unmet need for contraception ranging from 36 to 75% (29,37,39,42–45). Unintended pregnancy can also result from incorrect or inconsistent use of contraception, interaction of hormonal methods with ART making them less effective (46,47), relying on non-modern contraception and contraceptive failure (16,25,29,31,39,46–48).

Various factors have been associated with unintended pregnancy among WLH, including younger age, being single, ethnicity, education status, higher parity, having had a previous abortion, late or no ANC attendance, incorrect or inconsistent use of barrier methods, elevated VL and long term ART use (25,31,36,38,48–51).

**HIV virologic monitoring during pregnancy**

Viral load monitoring during pregnancy is important both in assessing whether the drugs are taken according to prescription (ART adherence) or resistance to the drugs has developed, and also in the evaluation of the risk of MTCT (17,51–53). The risk of HIV transmission from mother-to-baby reduces with lowering maternal viremia; transmission may occur even with maternal HIV-1 RNA as low as 50 - 400 copies/ml blood (54). It is therefore crucial to maintain maternal viral load at undetectable levels (<50 copies/ml blood). Challenges during pregnancy, such as cultural, social and hindrances to adherence, may make it difficult to maintain and achieve viral suppression (51). The Ugandan guidelines recommend that if a pregnant woman is newly diagnosed with HIV, she must be initiated immediately on ART and the first viral load monitoring will be done 6 months after

initiation, when the viral load should have decreased to an undetectable level. If instead her VL remains elevated (detectable but <1000 copies/ml), she will receive adherence support while continuing with her ART, thereafter VL monitoring is done once every year. If her VL is high (>1000 copies/ml), she will be offered intensive adherence counselling (IAC) with at least 3 sessions a month apart. A VL test is then done at the last session. If this VL is >1000 and found adherent, it is concluded her HIV has developed resistance and the woman is switched to a different ART regimen. For a pregnant woman who is already established on ART prior to conception, viral load testing is done at the first ANC visit and guidelines above apply (9,10). Unfortunately, the policy does not always translate into practice for viral load monitoring for HIV positive pregnant women. A considerable proportion of HIV infected pregnant women fail to have a viral load test done during pregnancy (55). Women who are newly diagnosed while pregnant are unlikely to have a viral load test done compared to those already established in ART prior to pregnancy (56). This is because women that are newly diagnosed could have been diagnosed in the later gestation during pregnancy, whereas those that are already established in ART care are mandated to have their viral load checked at the first antenatal visit.

Various predictors for persistently high levels of maternal viremia (detectable viral load and viral non-suppression) among pregnant women have been highlighted in a number of studies. These include late engagement into ANC, poor ART adherence, receipt of NNRTIs-based regimens, high baseline VLs, low baseline CD4 counts, ethnicity, drug abuse, Hepatitis C infection, unintended pregnancy, previous discontinuation of ART, medication concerns (side effects), MTCT of HIV, being employed, low education level, parity or gravidity, shorter ART duration and non-disclosure of HIV status to partner (51,57–65).

It is challenging to compare studies that report on detectable viral load and viral suppression in pregnancy, since they use varying cut-off limits for HIV-RNA levels. This is because different virologic tests use different HIV RNA assays that have varying lower limits of detection. These studies have also been done in varying contexts. Furthermore, women who have previously achieved viral suppression can experience viral load rebound near delivery, which is risky for MTCT of HIV (59). It is therefore important to focus the timing for virologic monitoring during pregnancy nearer to delivery. Most studies looking at predictors for persistent maternal viremia do so for mainly higher virologic profiles (>1000) and do not

consider detectable virologic profiles as alarming. It is these detectable viral loads that may eventually become unsuppressed. The threshold for detectable viral load varies, being determined by the lower limit of detection of the assays used for viral load testing. The threshold for viral non-suppression, particularly for Uganda, was adapted from the international guidelines for ART care and treatment (9).

**Infant ART prophylaxis for eMTCT**

It is vital for infants born to WLH to be immediately started on and remain adherent to prophylaxis after childbirth and through breastfeeding due to exposure to maternal HIV (9,10). The HEI should take prophylaxis for 6 to 12 weeks. A longer duration of prophylaxis is recommended for high-risk infants born to an HIV infected mother that has a viral load (VL) > 1000 copies/ml blood (9,10). For a high-risk infant, the mother's VL test should be done at 12 weeks postpartum and only if <1000 copies/ml should the infant stop taking nevirapine (NVP). If the maternal VL is not suppressed by 12 weeks, the infant should continue taking NVP until the mother's VL is <1000 copies/ml or otherwise continue with NVP until 4 weeks after cessation of all breastfeeding (10). These guidelines have been implemented in Uganda since 2012 (66). Challenges in achieving adequate infant adherence do exist and can be programmatic, maternal- or infant-related (21,67–69). Risk factors for non-adherence to infant nevirapine prophylaxis are: home deliveries, inadequate antenatal care, mother not receiving the nevirapine for her baby while at hospital, misplacing of the baby's drug, lack of transport and the mother staying with in-laws (70,71).

**Infant feeding in the context of HIV**

Exclusive breastfeeding (EBF) involves giving the infant only breastmilk within the first hour of birth and thereafter for 6 months (72). Breast milk (including colostrum) is a complete food for the newborn especially for the first 6 months of life. Colostrum, which is the first milk immediately after childbirth, is very rich in immune substances, like the secretory immunoglobulin A (sIgA) and other bioactive substances that act as a first line defence for the infant's immature innate immunity (72). HIV exposed uninfected and infected infants are 2 critical groups that can greatly benefit from exclusive breastfeeding as they are at greater risk of malnutrition, opportunistic infections like diarrheal and respiratory diseases, as well as death when compared to their HIV unexposed counterparts (73).

Breastfeeding is a major transmission route for HIV from a mother to her infant and therefore it should be practiced with caution. This has led to the development of various guidelines to create a balance between the infant benefiting from the breastfeeding and preventing the acquisition of HIV (22). As in the general population, WLH should initiate exclusive breastfeeding for the infant within the first hour after birth and continue with it for 6 months, and thereafter give age-appropriate complementary foods alongside the breastfeeding for 12 – 24 months or longer (22).

To lower the risk of MTCT of HIV, WLH and their infants have to be supported in adherence to both maternal ART and infant prophylaxis while breastfeeding (9). Studies have demonstrated the association between various factors and infant feeding practices. WLH who receive counselling on infant feeding and those that disclose their HIV status are more likely to breastfeed exclusively their HEIs (74). Barriers to breastfeeding include maternal factors, like breast problems, home delivery, cultural beliefs, lack of safe water, lack of counselling or support during continuation of infant feeding and infant factors, e.g. mouth ulcers (75–78).

The PMTCT cascade guided the development of this framework. The interplay between several factors increases the risk for mother-to-child transmission of HIV and subsequently contributes to an increase in the number of paediatric HIV infections. Individual or maternal factors influence outcomes, such as pregnancy intent, viral load suppression, adherence to infant ART prophylaxis and exclusive breastfeeding, which inadvertently heightens transmission risk. In addition, some of these outcomes can act as exposures. Virologic non-suppression has been associated with unintended pregnancy (51). Home delivery is associated with both non-adherence to infant nevirapine prophylaxis (69) and non-exclusive breastfeeding (75).

## Justification for the study

Each aspect of the PMTCT cascade is important and a deficiency in any of the interventions compromises the overall effectiveness, resulting in increased risk for MTCT of HIV. In this thesis work, we assessed particular points of the PMTCT cascade where adequate data in the study setting was lacking. These include unintended pregnancy, detectable viral load, adherence to infant nevirapine prophylaxis and infant feeding.

**Conceptual framework**

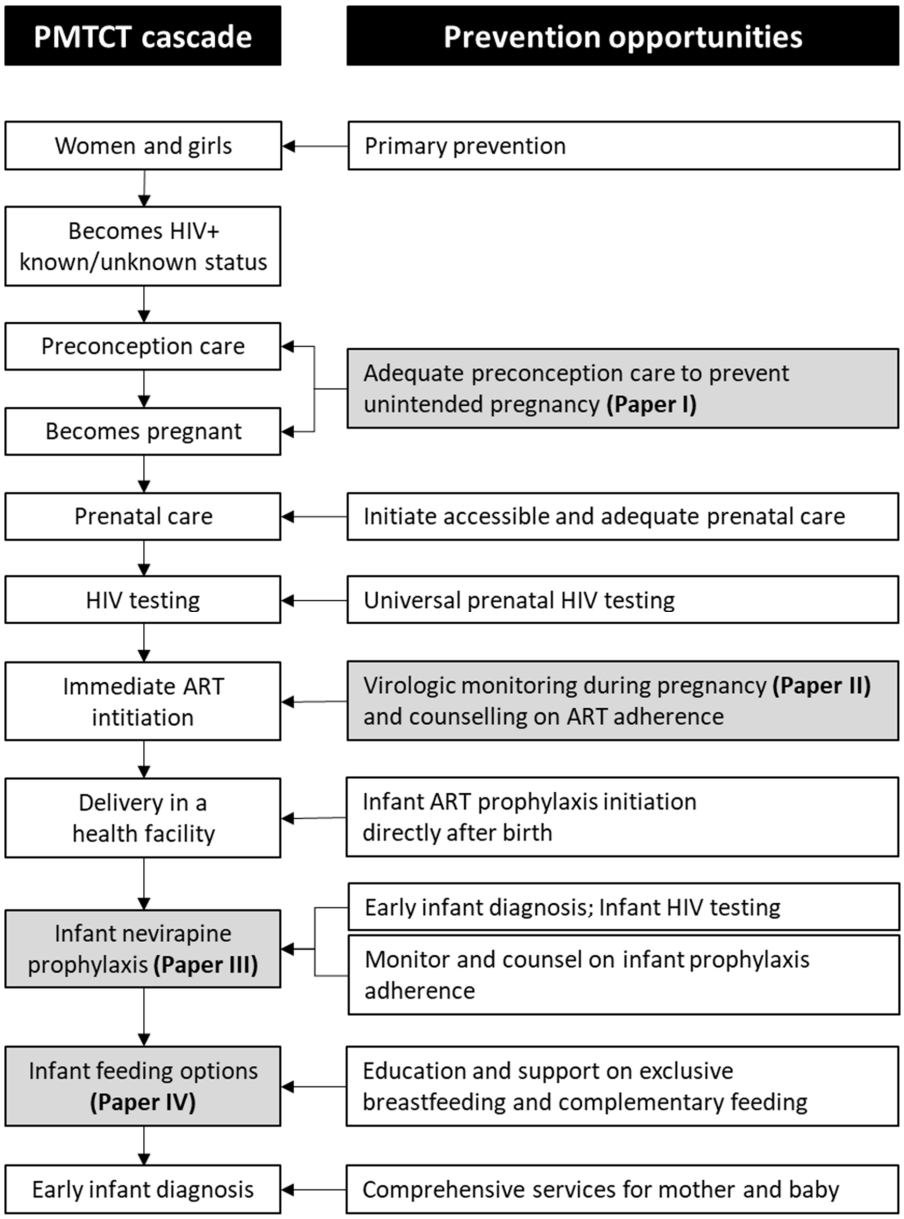


*Figure 3. Conceptual framework illustrating key priority areas for this thesis work.*

Several studies on unintended pregnancy among WLH this topic have mainly looked into predictors for contraceptive use in the context of HIV, and merely mention the rates of unintended pregnancy, but very few dig deep into predictors for unintended pregnancy in the context of HIV. This is why investigating the rates and associated factors of unintended pregnancy in this context is important. Maternal viremia is an important predictor for MTCT of HIV. Most studies looking at predictors for persistently raised maternal viremia do so mainly for higher virologic profiles (>1000) and do not consider detectable viral load counts as alarming. It is these detectable viral loads that may eventually become unsuppressed and increase the risk of MTCT of HIV. It is for this reason that studying detectable viral load among WLH in Lira is vital.

Poor adherence to infant nevirapine prophylaxis may contribute to MTCT of HIV. Evidence on adherence to infant nevirapine prophylaxis has mostly been qualitative and dates far back under previous treatment paradigms; it cannot be compared to today's situation. It is therefore important for newer evidence on this subject to be generated, especially in Lira. Even with guidelines available, mixed feeding in the first 6 months of life remains a common practice and EBF rates among HEI remain critically low (74,75,77–80). Risk factors for these low rates are not well understood and vary within different contexts. The settings for studies that have looked at EBF in the context of HIV have been heterogeneous and tend to vary from country to country. It is therefore important to find out what the status quo on EBF among WLH is in Lira.

It is against this background that we sought to determine the prevalence and factors associated with unintended pregnancy, detectable viral load, exclusive breastfeeding among HIV infected women enrolled on universal ART, as well as the proportion of babies born to HIV infected mothers that adhered to infant nevirapine prophylaxis and factors contributing to their non-adherence.

## Aim and objectives

The aim of this thesis work was to determine among a group of HIV infected women enrolled on universal antiretroviral treatment in Lira, Northern Uganda, the prevalence and factors associated with: a) unintended pregnancy, b) detectable viral load, c) infant nevirapine prophylaxis, and d) exclusive breastfeeding.

The specific objectives were:

1. To determine the prevalence and predictors for unintended pregnancy among HIV infected pregnant women in Lira, Northern Uganda (Paper I)
2. To assess the factors associated with detectable viral load among HIV infected pregnant women in Lira, Northern Uganda (Paper II)
3. To identify barriers and enablers of adherence to infant nevirapine prophylaxis among 6-week-old HIV exposed infants in Lira district, Northern Uganda (Paper III)
4. To determine the risk factors for non-exclusivity of breastfeeding in the first 14 weeks of life of HIV exposed infants (Paper IV)

## Subjects and methods

The papers relating to this thesis work originate from studies of a single prospective cohort of HIV infected pregnant women receiving antenatal care at Lira Regional Referral Hospital in Northern Uganda. Participants were recruited into the cohort during the antenatal period (papers I and II) and followed at birth, 6 weeks postpartum (paper III) and 14 weeks postpartum (paper IV), Figure 7. The methods employed are described in detail in each paper, and in this section, we give a summary of them.

### Study area and setting


*Figure 6: Lira District in Northern Uganda.*

Lira district is one of the 8 districts within the Lango sub-region of Uganda. The majority of the population belongs to the ethnic group, Langi, the predominant language being *Lango*. The main municipal, administrative and commercial centre in the district, Lira, is located 350 kilometres by road north of Kampala. Lira district has 4 counties: Erute North county, Erute South county, Moroto county and Lira town council, as well as 28 sub-counties. There are 192 parishes with 2,247 villages. In 2014, Lira district was the home of 410,516 people (196,891 males and 213,625 females), with the municipality (the urban centre) having 99,059 people (81).

Lango sub-region is neighboured in the north by the great Acholi sub-region. The mentioned 2 sub-regions are in the great Northern region of Uganda that was severely hit by the great LRA insurgency (war) for over 20 years. To date, the conflict has seen more than 10,000 people massacred or mutilated, and twice the number of women and children abducted and forced to work as soldiers, porters and sex slaves. About 1.8 million people were displaced, many of whom lived in government run camps. The war came to an end about 10 years ago. The war had a grave effect on various health indicators, including HIV as evidenced by the high HIV prevalence of 7% in the general population and high antenatal HIV prevalence of 13.5% (3). The effect of the insurgency on most social services, including health, make Lira a unique setting for research as findings in this region may be different from those in a more "ideal" setting.

The district has 27 health facilities: 11 health centre IIs at parish level, 11 health centre IIIs at county level, 3 health centre IVs at the sub-district level and 2 hospitals (one of which is a regional referral hospital) (82). This study was conducted at Lira regional referral hospital (LRRH), which serves all 8 districts of the subregion, including Amolatar, Apac, Dokolo, Lira, Otuke, Alebtong, Kole and Oyam. Lira hospital serves a population of 408,043 in Lira district (81). It is a government-owned health facility at tertiary level, with 254 beds. LRRH offers health services, including promotive, preventive, curative, maternity, surgery, emergency, inpatient, outpatient blood transfusion and laboratory services. Maternal and child health services include antenatal care, delivery, postnatal care, immunisation and HIV care services. These services are available free for the patients (82). The services are categorized and offered in respective clinics/departments/wards, as outpatient and inpatient clinics. The HIV care services are categorized into general HIV care and PMTCT services.

PMTCT services are offered in an independent clinic within the hospital; this is where HIV infected women receive antenatal and HIV care when pregnant. At the time of delivery, HIV infected women in Lira are free to deliver at a health facility of their choice. In LRRH, they deliver in the labour suite at the maternity ward, at which point the mother is supposed to receive nevirapine syrup for her newborn infant. However, in LRRH, HIV infected women that have just delivered their baby return to the PMTCT clinic with their infant for weighing and classifying of their newborn to determine the dosage and receive the nevirapine syrup for their infant. The mother-infant pairs continue to receive HIV care at the PMTCT clinic until the infant is 6 weeks old. However, the immunization services for the infant are not offered at the PMTCT clinic. The mother has to take her infant to the young child clinic within LRRH or another health facility of her own choice for immunization. The mother-infant pair is discharged from the PMTCT clinic at 6 weeks postpartum and transferred to the early infant diagnosis (EID) clinic, which is an independent stand-alone department from the PMTCT clinic. The first DNA-PCR test for infant HIV diagnosis is done at the EID clinic for 6-week old infants. The mother-infant pairs continue to receive their HIV care at the EID clinic until the infant is 18 months old, at which point the first HIV antibody test is done. The mother and her infant will then be discharged from the EID clinic when the infant is 24 months old and transferred to the general HIV care clinic.

The LRRH also has annually an outpatient attendance of almost 100,000 patients, antenatal care attendance of about 5,000 women, and conducts 6,000 – 7,000 deliveries (82).

**Study design and procedures**

We screened for eligibility, consented and recruited consecutively onto the study and followed up HIV infected pregnant women at different time-points at the PMTCT clinic in LRRH. Women were eligible for participation when 20 or more weeks pregnant, newly tested or already established into HIV care. Women did not participate in the study if their partner declined their participation or they had received their ART care from another facility (Figure 7). To minimize loss to follow-up, information on telephone contacts and physical addresses were collected. All study visits except the one around the time of delivery were done at the PMTCT clinic and were timed to coincide with the mother's routine visits for ART care. It is these time-points of follow-up that constitute the different papers described in the following paragraphs (Figure 7). This prospective cohort study applied quantitative

methods to observe outcomes (unintended pregnancy, detectable viral load, adherence to infant nevirapine prophylaxis at 6 weeks, exclusive breast feeding at 14 weeks), and related them to other associated or risk factors.

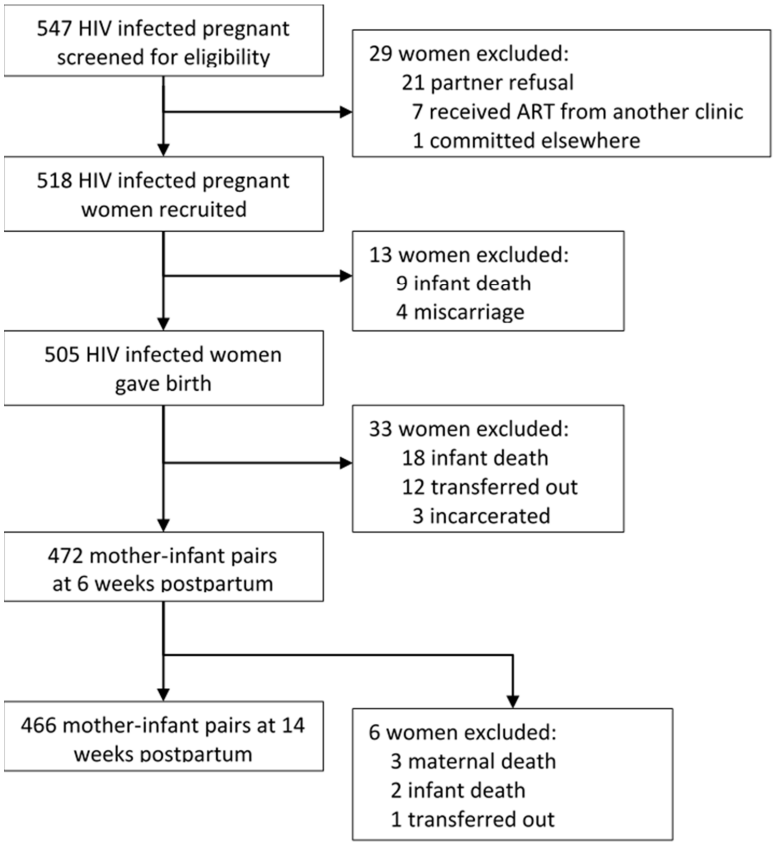


*Figure 7: Flow chart of the thesis work*

**Paper I and II**

These 2 studies employed a cross-sectional design and were conducted among HIV infected pregnant women recruited at baseline. They were interviewed on socio-demographic related, reproductive-related and HIV-related information, using a structured questionnaire and combined it with viral load tests from Uganda National Health Laboratories for those who had been on ART for at least 6 months. All women recruited were included in the analysis for paper I. Only those that had a viral load test done and results available were included in the analysis for paper II. These two studies were designed to investigate the

association between a number of covariates on pregnancy intent (paper I) and detectable viral load (paper II), respectively (Table 2).

*Table 2. Overview of the 4 papers in the thesis*

| Paper | Study design and analysis | Sample size | Exposure(s) | Outcome(s) |
|---|---|---|---|---|
| | | | Exposures common for all papers: maternal age, education, marital status, employment status, religious affiliation, ethnic belonging, socio-economic status, parity, gestational age, HIV status disclosure, ART regimen, ART duration | |
| I | -Cross-sectional study<br>-Multivariable analysis | 518 HIV infected pregnant women | Exposures common for all papers + accompanied to ANC by partner; use of birth control, type of contraceptive used, person disclosed to her HIV status, fear about others' opinion on HIV status. | Unintended pregnancy |
| II | -Cross-sectional study<br>-Multivariable analysis | 420 HIV infected pregnant women from the above group | All exposures in paper I + intention to have baby | Detectable viral load |
| III | -Prospective cohort<br>-Multivariable analysis | 472 HIV infected lactating women from the above group and their exposed infants | Exposures common for all papers + viral load count during pregnancy, type of delivery, time of onset of labour, place of delivery, person who supervised the delivery, person escorting mother during labour and delivery, mother given nevirapine syrup for baby at delivery, maternal ART adherence. | Adherence to infant nevirapine prophylaxis at 6 weeks |
| IV | -Prospective cohort<br>- Multivariable analysis | 466 HIV infected lactating women from the above group and their exposed infants | Exposures common for all papers + viral load count during pregnancy, type of delivery, time of onset of labour, place of delivery, person who supervised the delivery, infant given pre-lacteal feeds, maternal ART adherence, infant's adherence to nevirapine prophylaxis, EBF at 6 weeks. | EBF at 14 weeks postpartum |

**Paper III**

This was a prospective cohort study to determine the barriers and enablers of adherence to nevirapine prophylaxis among 6-week-old HEI. WLH that had given birth to a live baby in the cohort from paper III were followed up at 6 weeks postpartum and asked about the infant's adherence to nevirapine prophylaxis. A total of 472 mother-infant pairs were included in the final analysis for paper III.

**Paper IV**

This study employed a prospective cohort study design to determine the incidence of exclusive breastfeeding among HIV exposed infants from birth to 14 weeks of life, as well as risk factors for non-exclusive breastfeeding. The mother-baby pairs from study IV were followed up; when the infants were 14 weeks of age, women were asked about exclusivity of breastfeeding through a face-to-face interview. Complete information was obtained for 466 mother-infant pairs and analysed for paper IV.

**Variables**

Some exposure variables were common across all the papers, one being age which was collected as continuous, but later categorised for each paper. Education was categorised as 0 – 6, 7 – 10, 11 – 13 and ≥14 years of schooling; marital status was categorised into single (if the woman was separated, divorced, widowed or not married) and married (if the woman was married or cohabiting). Employment status was categorised into employed (if the woman was formally or self-employed) and unemployed. Religious affiliation was either Christian or Muslim. Ethnic belonging was either Langi (if native to the study setting) or else as other. Wealth quartiles were calculated using principal component analysis (PCA). The PCA technique is one that reduces the dimensionality of large data sets. This involves the transformation of a large set of variables into smaller ones by combining and ranking of a number of variables into smaller and fewer variables without prejudgment, while maintaining the original information. PCA is considered a more accurate indicator of socio-economic status than single items, such as occupation or possession of particular items (83). Characteristics considered for PCA were: house ownership, availability of electricity in the house, source of drinking water, and fuel used for cooking. Categorization of other exposures was as follows: parity: ≤4 and ≥5 pregnancies ever carried, including the one at

the time of the study; gestational age: 20 – 27, 28 – 35 and ≥36 weeks of gestation; accompanied by partner to ANC: accompanied or not; use of birth control: used or didn't use any form of contraception 6 months prior to pregnancy; type of contraceptive used: none (if no contraceptive was used or relying on safe days) and effective contraception (if oral contraceptive, injectable contraceptive, implants, intrauterine device, condoms or emergency contraception was used 6 months prior to pregnancy); HIV status disclosure: (disclosed/undisclosed); person disclosed to: (husband/ ther); fear about others' opinion on HIV status: (had fear/no fear); ART regimen (efavirenz-based, nevirapine-based or protease inhibitor-based) ART duration: (<6 , 7 – 30, 31 – 119 and ≥120 months)

**Paper I:** The dependent variable for this study was unintended pregnancy. It was defined in any of the following ways; a pregnancy that occurred: when no more children were desired, earlier than it was desired or when the woman did not desire to become pregnant. Women were asked if the pregnancy came 'earlier than expected', 'later than expected', 'when expected' or 'not desired at all' (84). Women who had their pregnancy at the 'time desired' or 'later than expected' were combined, labelled as the 'intended' category. Women with an 'earlier than desired' or 'unwanted pregnancy' were combined into a single group, labelled "unintended pregnancy".

**Paper II**: Detectable viral load, the main outcome of this study, was defined as the presence of copies of HIV-1 RNA per ml blood plasma of ≥50 up to 999. Viral load counts <50 copies/ml were categorized as 'undetectable viral load'. The presence of ≥1,000 copies/ml was called 'viral non-suppression'. The independent variables maternal age, education, marital status, employment status, religion, ethnicity and socio-economic status, gestational age, accompanied to ANC by partner, use of birth control, type of contraceptive used, HIV status disclosure, fear about others' opinion on HIV status, ART regimen were all categorised as in study I. Other exposure variables were categorised and labelled as: parity (1 – 4 and 5 – 9), intention to have baby: (yes/no), ART duration: (6 – 36, 37 – 119, ≥120 months).

**Paper III:** The outcome variable of interest for this paper was "non-adherence to infant nevirapine prophylaxis". In the 7 days prior to the interview, infants reported by the mother or care giver to have missed 0 – 2 doses of their nevirapine syrup were collectively categorized and labelled as "adherent," and for those reported to have missed ≥3 doses were

collectively categorized and labelled as "non-adherent". Exposure variables of marital status, employment status, religion, ethnicity, parity, gestational age, HIV status disclosure and ART regimen were categorised as in paper I. Other exposures were categorised as follows: maternal age as: ≤ 20, 21 – 29, 30 – 39 and ≥40 years; education as: ≤6, 7 – 13 and ≥14 years of schooling; ART duration as: short-term (<60 months) or long-term (≥ 60 months); VL count during pregnancy (<50 copies/ml, ≥50 copies/ml or missing VL test result); mother given nevirapine syrup for baby at delivery as: either 'given' or 'not given'. Exposure variables categorised as in paper III are: type of delivery, time of onset of labour, place of delivery, person who supervised the delivery, person escorting during delivery and maternal ART adherence.

**Paper IV:** The outcome for this paper was "non-exclusivity" of breastfeeding, which was measured at birth, 6 weeks and 14 weeks postpartum. Prelacteal feeding was defined as the baby taking any liquid other than breast milk immediately after birth, with the exception of medicines (e.g. nevirapine). Infants reported by their mother to have taken any liquid other than breast milk were considered not to be exclusively breastfeeding. At the 6- and 14-week visits, infants reported by their mother to have taken any liquid or solid food other than breast milk in the 7 days prior to the respective visits were considered not be exclusively breastfeeding. All the infants who were not exclusively breastfed at the various visits were collectively categorised as "non-exclusively breastfed" and the rest as "exclusively breastfed". The exposures included in this study were: age (≤20, 20 – 21, ≥30 years); education level: (≤6, 7 – 13, ≥14 years); ART duration (≤6, 7 – 30, 31 – 119, ≥120 months); Viral load count (<50, 50 – 400, 401 – 499, >1000 copies/ml and missing viral load)

These exposures were categorized and coded as in the previous papers: marital status, employment status, religion, ethnic belonging, parity, gestational age, HIV disclosure, socio-economic strata, antiretroviral regimen, time of onset of labour, type of delivery, place of delivery, person who supervised delivery, maternal adherence to ART and adherence to infant nevirapine prophylaxis.

**Sample size estimation**

We planned to answer several questions with the same cohort of HIV infected pregnant women. For each question, the expected sample size needed was calculated, and basing on

the largest sample size with a 10% non-response rate, we recruited 518 HIV positive pregnant women who were receiving antenatal care at Lira Regional Referral Hospital (LRRH). For papers I, II, and IV, sample sizes for detecting a difference between two independent proportions were calculated using Stata version 14.0 (StataCorp; College Station, TX, USA), in particular the statistics, power and sample-size functions. We then used the population parameter method with the test of comparing two independent means. We assumed 80% power, 95% confidence interval (CI) and a 5% precision. For each of the respective papers, we assumed 2independent proportions specific to each outcome.

**Paper I**

For this study, it was assumed that 57.6% of WLH were not in a marital union (85) and that 31.5% of HIV infected women were married (31). On running this calculation through the statistical software, a sample size of 464 women was arrived at. We adjusted the sample size to 516 after accounting for a 10% non-response. We however, recruited 518 participants.

**Paper II**

In this paper, it was assumed that 23% of HIV infected pregnant women had detectable viral load (86), and that 12% of HIV infected women with a detectable viral load were taking a protease inhibitor-based regimen (87). After accounting for 11% non-response, the final sample size was 420 HIV infected women.

**Paper III**

For this study, we estimated a sample size for detecting an unknown proportion of infants adhering to infant prophylaxis using OpenEpi (openepi.com). We assumed a 50% proportion, 80% power, 95% confidence interval (CI) and 5% precision. The total sample size for this study was 384 HEI. After adjusting for 10% non-response and another 10% to allow for enough degrees of freedom in the multivariable analysis, the final sample size was 464; however, 472 mother-infant pairs were included.

**Paper IV**

We assumed that 70% of women (88) (Mpody, 2019) received EBF support and counselling at delivery, and that 42.5% of women were not advised or counselled on exclusive breastfeeding during pregnancy (89). The total sample size for this study was 418 HEI.

After accounting for 10% non-response, the final sample size was 464; however, 466 HEI were included.

**Data collection procedure and tools used**

**Data analysis**

For all papers, data were entered into EpiData software (www.epidata.dk, version 4.4.3.1) by 2 independent data entrants and analyzed with Stata version 14.0 (StataCorp, College Station, Texas, U.S.A.). Continuous data, if normally distributed, was summarised into means and standard deviations; if skewed, it was summarized into medians with their corresponding interquartile ranges. Categorical variables were summarized into frequencies and percentages. The proportion (incidence or prevalence) of HIV infected women with the outcome of interest in each paper was estimated and its confidence limits calculated using the exact method.

**Papers I and II:**

We used multivariable generalized linear model regression analysis with a logit link to estimate adjusted odds ratios with corresponding confidence intervals of the exposures for unintended pregnancy (paper I) and detectable viral load (paper II), while controlling for confounders. Variables with a $p<0.25$ at the bivariate level were include in the initial model at the multivariable analysis. All variables with $p<0.1$ and those with biological or epidemiological plausibility were included in the second model. We checked if the second model was significantly different from the initial model using the likelihood ratio test. If there was no difference, then the second model was adapted as the final model (90). All exposures without the null value in their corresponding 95% confidence intervals were considered to be associated with the outcome. We checked for confounders by calculating the percentage change in each effect measure while removing and introducing one variable at a time from the model. If a variable caused >10% change in any effect measure, it was considered a confounder.

**Paper III and IV**

Poisson regression models/analysis were used for bivariate and multivariate analyses (91) to estimate unadjusted and adjusted odds ratios with corresponding confidence intervals of the exposures for the respective outcomes (adherence to infant nevirapine prophylaxis and non-exclusivity of breastfeeding). We used a similar process for model building, while controlling for confounders as for papers I and II (90)

**Ethics**

Approval to conduct all the studies was granted by the following approving authorities:

1) Makerere University College of Health Sciences School of Medicine Research and Ethics (SOMREC) committee; approval number: REC REF No. 2017-004; 10 January 2018

2) Uganda National Council for Science and Technology; approval number: HS222ES; 24th September 2018

3) Norwegian Regional Committee for Medical and Health Research Ethics in the West; approval number: 2017/2489/REK vest; 26th January 2018.

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 neither penalized nor denied standard healthcare. Confidentiality and privacy of all data collected was observed during the course of the study through restricted access.

# Summary of results

### Study flow chart

A total of 547 HIV infected women were screened for eligibility, of which 518 were included in the study as the baseline cohort. It is from this baseline cohort that 2 outcomes were measured: 1) unintended pregnancy (Paper I); 2) detectable viral load (Paper II). This cohort was followed up until delivery time (n=505) and at 6 weeks postpartum (n=472), at which point adherence to infant nevirapine prophylaxis was assessed. When the infants were 14 weeks old (n=466), the outcome of exclusive breastfeeding was measured. Reasons for exclusion of women at the different time-points are included in the flow chart (Figure 7)

### Socio-demographic characteristics of HIV infected women

The commonalities in the socio-demographic profiles of the women across all the studies were as follows. Most of the women had attained a formal education for at least 6 years. The majority were married, unemployed, predominantly Christian and *Lango* speaking. Most of the women had been pregnant for at least 4 times, including the pregnancy at the time of the study, with more than half having been pregnant for 20- 28 weeks at enrolment. Almost half of the participants reported having used an effective form of contraception (including oral contraceptives, intrauterine devices, injectable contraceptives or implants) 6 months prior to the pregnancy at baseline. A considerable proportion of these women had disclosed their HIV status and most had disclosed this to their spouse. The majority of these women were taking an efavirenz-based regimen, which is also a first-line regimen. The majority had a viral load <50 copies/ml of blood.

### Paper I

### Prevalence and predictors of unintended pregnancy

The participants had a mean age of 29.2 (SD 5.5). Of the 518 women enrolled on the study, 213 experienced (41.1%, 95%CI: 36.8% - 45.5%) unintended pregnancy.

HIV infected women who were single were almost 4 times as likely to experience unintended pregnancy as their married counterparts (adjusted odds ratio (AOR) = 3.74, 95% CI: 1.67 – 8.34). Women who had a higher parity were 3 times as likely to experience unintended pregnancy as those with lower number or order of pregnancies (parity of ≥5;

AOR= 2.79, 95% CI: 1.85 – 4.22). Those who had taken ART for 10 years (120 months) or more were almost 4 times as likely to report that their pregnancy at the time was unintended than those that had taken ART for >6 months (≥120 months; AOR=3.69 (1.57 – 8.67)

**Paper II**

We included 420 women in the analysis for paper II, with a mean age of 30.0 (SD 5.2).

**Virologic profiles of HIV infected pregnant women in Lira**

The majority of the participants had an undetectable viral load. The prevalence of a detectable viral load (>50 copies/ml) was 30.7% (95%CI: 26.3 - 35.4%). Of those with a detectable viral load, the majority (82/420, 19.5% 95%CI: 15.8 – 23.6%) had a viral load between 50 and 400 cps/ml. The proportion of women with a viral load ≥1000 cps/ml was 8.1% (34/420, 95%CI: 5.7 – 11.1%) (Table 3).

*Table 3: Virologic profiles of HIV infected pregnant women*

| Viral load count (copies/ml) | Frequency n=420 | Percentage (%) | Percentage (%) 95% CI |
|---|---|---|---|
| **<50** | 291 | 69.3 | **Undetectable VL** 69.3% (95% CI: 64.6 - 74.7%) |
| **50 to 400** | 82 | 19.5 | **Detectable VL** 30.7% (95% CI: 26.3 - 35.4%) |
| **401 to 999** | 13 | 3.1 | |
| **≥ 1000** | 34 | **Viral non-suppression** 8.1 (95% CI: 5.7 – 11.1%) | |

**Factors associated with detectable viral load**

Belonging to ethnic groups other than Lango was associated with having detectable viral load among HIV infected pregnant women (AOR = 1.92, 95% CI: 1.05 – 3.90). Women who were taking a protease inhibitor-based regimen which is also a second-line treatment were 4 times more likely to have detectable viral load as those who had been taking a first-line efavirenz-based regimen (AOR=4.41 95% CI: 1.13 – 17.22).

**Paper III**

There were 472 women in this analysis. The mean age for the HIV-positive pregnant women at baseline was 29.4 years (SD 5.4). The majority had a spontaneous vaginal delivery in a hospital setting, were given nevirapine syrup by the health worker, and were adherent to their ART.

**Non-adherence to infant nevirapine prophylaxis among infants at 6 weeks**

A total of 70 infants (14.8%, 95%CI: 11.7 - 18.4%) missed between 3 and 7 doses in the week preceding the interview and were considered non-adherent.

**Barriers and enablers of adherence to infant nevirapine prophylaxis**

Barriers to adherence to infant nevirapine prophylaxis were the following maternal characteristics: younger age (≤20 years ARR=1.55; 95% CI: 1.1 – 2.2), having missed a viral load test during pregnancy (missing viral load ARR: 1.4; 95% CI: 1.1 – 1.7), and not receiving nevirapine syrup for the baby after childbirth (ARR = 6.2; 95% CI: 5.1 – 7.6). Maternal characteristics that enabled infant nevirapine adherence include: having attained ≥14 or more years of schooling (ARR = 0.7; 95% CI: 0.5 – 0.9), taking a nevirapine-based regimen (ARR = 0.6; 95% CI: 0.4 – 0.9), having taken ART for a longer period of time (long-term (≥ 60 months) ARR = 0.75; 95% CI: 0.6 – 0.9), accompanied by her husband to hospital during labour and childbirth (husband ARR = 0.5; 95% CI: 0.4 – 0.7), and having labour start during the night (ARR = 0.7; 95% CI: 0.6 – 0.8) (Table 3).

**Paper IV**

We included 466 HIV infected women with a mean age of 29.5 years (SD 5.4) in this analysis. Most of the mothers went into labour during the daytime and had spontaneous vaginal delivery. Three quarters delivered in a hospital setting, with most being supervised by a health worker. Almost a third did not adhere to their antiretroviral treatment in the week preceding delivery. Thirty percent of infants did not adhere to their nevirapine prophylaxis at 6 weeks of age.

**Infant feeding practices at delivery, 6 and 14 weeks postpartum**

The proportion of infants that were exclusively breastfed reduced with increasing age of the infant. Incidence of pre-lacteal feeding at birth was 12.7% (95%; CI: 9.8 - 16%). The

incidence of non-exclusivity of breastfeeding at 6 weeks and 14 weeks postpartum were 22.5% (95%; CI: 18.8 - 26.6%) and 42.9% (95%; CI: 38.3 - 47.5%), respectively. By the time the infants were 14 weeks of age, almost half were not exclusively breastfeeding. The infants were fed a number of different feeds (Table 4).

*Table 4: Feeds given to HIV exposed infants at 6 weeks and 14 weeks postpartum.*

| Type of infant's feed | Feeds given to infants at 6 weeks postpartum N=466 | | Feeds given to infants at 14 weeks postpartum N=466 | |
|---|---|---|---|---|
| | n | % | n | % |
| Only breast milk | 361 | 77.5 | 266 | 57.1 |
| Honey | 55 | 11.8 | 44 | 9.4 |
| Water | 23 | 4.9 | 36 | 7.7 |
| Cow's milk | 13 | 2.8 | 70 | 15 |
| Soup | 6 | 1.3 | 17 | 3.7 |
| Porridge | 5 | 1.1 | 21 | 4.5 |
| Infant formula | 3 | 0.6 | | |
| Juice | | | 11 | 2.4 |
| Solid food | | | 1 | 0.2 |

**Risk factors for non-exclusivity of breast feeding at 14 weeks of age**

Women who were in the topmost socio-economic strata were almost 45% more likely to give their infants liquids other than breast milk compared to those in the lowest socio-economic strata (ARR = 1.45, 95%; CI: 1.01 – 2.09). Women whose delivery was supervised by a non-health worker were 64% more likely to practice mixed feeding compared to those whose delivery had been supervised by a health worker (ARR=1.64, 95%; CI: 1.01 – 2.72). Women who had not adhered to their ART during pregnancy were also likely to practice mixed feeding for their infants compared to their adherent counterparts (ARR=1.29, 95%; CI: 1.01 – 1.74).

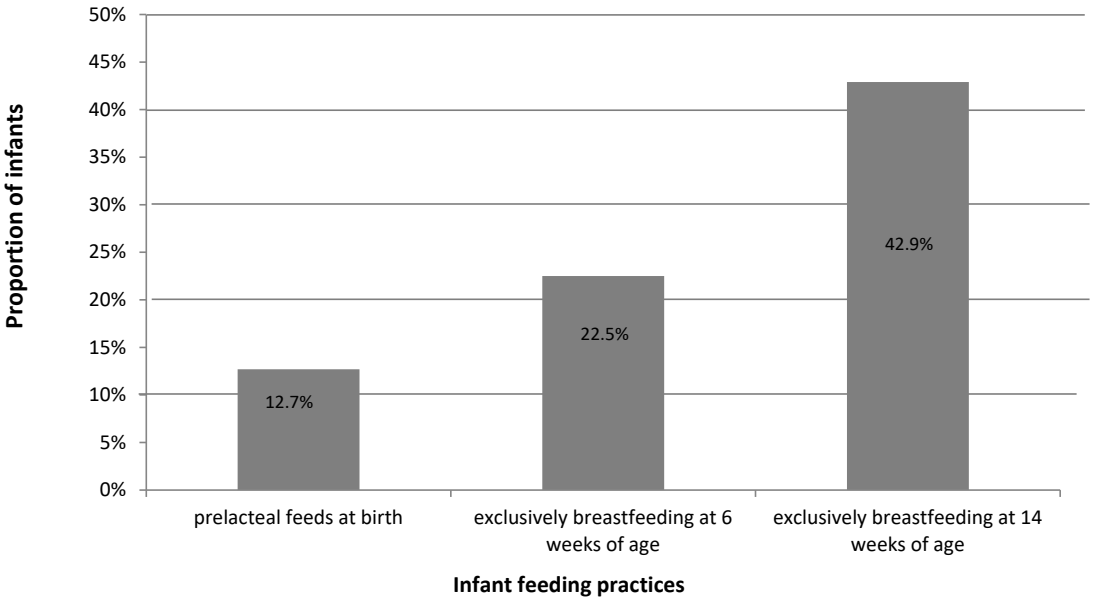


*Figure 8: Infant feeding practices among HIV exposed infants by HIV infected lactating women*

## Discussion of the findings

In this thesis, a group of HIV-infected pregnant women in Northern Uganda were studied; in brief we found that this group had high prevalence or incidence of unintended pregnancies, detectable viral load, non-adherence to infant nevirapine prophylaxis and non-exclusive breastfeeding.

### Proportion of and predictors for unintended pregnancy among HIV infected women

#### Prevalence of unintended pregnancy

Among HIV-infected pregnant women who were receiving antenatal care at Lira Regional Referral Hospital (LRRH), the prevalence of unintended pregnancy was >40%. This high level could be attributed to an unmet need for family planning. Generally, studies that report high rates of unintended pregnancy also report high rates of an unmet need of family planning (26,31,33,38,92–94), as in our study. Several studies have reported a high rate of unintended pregnancy ranging from 35 to 78% (16,24,31,33,38,39,49,93,95). Studies in Nigeria and Zimbabwe indicate lower rates of unintended pregnancy than our study (24,39). Other studies have reported higher rates of unintended pregnancy than our study (31,33,36,38,48,49,51,93,95), but they are not directly comparable. This might be due to several differences in methodology: first, the way unintended pregnancy was measured; several studies did not rely on the definitions of unintended pregnancy stipulated in the London Measure of Unintended Pregnancy (LMUP), as in our study. Second, the timing of asking about unintended pregnancy differs between studies. Most of the studies asked about the intention of the pregnancy long after the women had given birth, not while they were pregnant as in our study.

#### Predictors for unintended pregnancy among HIV infected pregnant women

HIV infected women who were single were more likely to experience unintended pregnancy. A plausible explanation for this is that, in a marital union, there are open communication channels between the 2 individuals who can discuss reproductive-related issues like child-bearing and the use of contraceptive. Other studies (43,44,49) have also documented that WLH in a relationship were more likely to use contraception if there was an open partner discussion in the relationship, this type of communication being absent

when a woman has no partner. Studies in Kenya, Swaziland, Botswana and South Africa have reported similar results (31,36,38,49,51,95).

Our study also showed that experiencing a higher number of pregnancies also increased the likelihood of experiencing unintended pregnancy among WLH. A probable explanation for this finding could be inconsistency in the use of contraception, lack of emergency contraceptives, side effects of the contraception (heavy bleeding), partner refusal, or no contraceptives being available at health facilities. Our findings were consistent with results from other studies in South Africa and Botswana (31,38,49), but different results were found in Cameroon and Uganda (32,85). One study in Kenya (95) showed that the odds of lower order pregnancies to be unintended were the same as those of higher order pregnancies, although the cohort in this study was adolescents, which could explain the difference.

It was unexpected to note in our study that HIV infected women who had taken ART for a long time were more prone to an unintended pregnancy. It might be that women on long-term ART become complacent and in so doing lack adherence to both ART and contraceptive use. In a study in Uganda (96), individuals who had taken ART for a long time hardly received any continuous ART adherence education, experienced treatment fatigue and were less likely to adhere to their treatment. Studies in South Africa, however, found that women who had been newly diagnosed with HIV were more likely to experience unintended pregnancy (31,49). More qualitative studies are needed in our study context to understand reasons for this finding.

**Detectable viral load among HIV infected pregnant women**

One third of our participants had detectable viral load while pregnant, a higher proportion compared to some other studies using the same cut-off of 50 copies/ml. Studies from South Africa and Malawi reported lower prevalences of detectable viral load among HIV infected pregnant women ranging from 10 to 23% (18,86,97,98). Other studies have demonstrated the association between detectable viral load and poor or non-adherence to ART (99–103). We did not measure non-adherence; despite this, non-adherence remains the most plausible explanation for the high prevalence of undetectable viral load.

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 reported a similar prevalence of detectable viral load like our study, whereas researchers from Rwanda reported a higher prevalence. These studies, however, used a lower cut-off (63,104). In our study the prevalence of virologic non-suppression (>1000 cps/ml) was 8%. Studies in Uganda and Malawi reported a similar prevalence of virologic non-suppression among HIV infected pregnant women (103,105). The low prevalence of virological non-suppression 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. Much as we have achieved the desired target for viral suppression today, the cut-off of 1000 copies/ml used in Uganda is too high. This puts a focus on HIV infected pregnant women with higher virologic profiles and less emphasis on those with lower, but detectable, HIV-1 RNA; and yet it is those with detectable viral load that are likely to translate into virologic non-suppression.

**Factors associated with detectable viral load among HIV infected pregnant women**

In our study, women belonging to other ethnic groups than the predominant *Lango* group had a higher probability of having a detectable viral load, which was unexpected. A study in Benin found the opposite, that the predominant ethnicity of the study setting was more likely to have a detectable viral load (61). More qualitative work is 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 a detectable viral load, which is a quite common finding. Studies in Uganda and the USA 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 (58,106). 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 (106–108). This finding can also be explained by the concept of reverse causality. HIV infected women will be switched to a second-line ART regimen because of treatment failure of the first-line regimens, which is mainly due to non-adherence (69,109). It is probable that the underlying challenges of adherence forcing 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, which may include side effects to antiretroviral drugs, pill burden in the context of pregnancy, and increased psychosocial stressors related to pregnancy or care giving (109).

**Non-adherence to nevirapine prophylaxis among 6-week-old HIV exposed infants**

We found that non-adherence to infant nevirapine prophylaxis was high at 14.8%. We relied on the mother or caregiver's report in measuring adherence of the infant to nevirapine prophylaxis. Studies in South Africa have reported levels of non-adherence to infant nevirapine prophylaxis ranging from 12 to 30%, a range within which our data on the incidence of non-adherence falls (21,110,111). Studies that rely on self-reported or caregiver's report indicate higher levels of non-adherence compared to those that have relied on electronic dose monitoring and plasma concentration of therapeutic levels of nevirapine in the infant's blood (21,70,110) All these studies measure adherence to infant nevirapine prophylaxis at different time-points, some at birth and the majority at 6 weeks, while factoring in variable recall periods. Even is this scenario could explain the disparities in rates of non-adherence across the different studies and ours, it is likely that actual differences in adherence rates do exist in the different study contexts. The most important and actionable reason for the high non-adherence to infant prophylaxis is that many women did not receive nevirapine for the baby after delivery.

**Barriers and enablers of adherence to infant nevirapine prophylaxis**

In the following section, we shall focus on barriers and enablers to infant nevirapine adherence that are important for policy. The barriers to infant adherence include younger maternal age, missed viral load test during pregnancy, and mothers not receiving nevirapine syrup for their infants after childbirth. Enablers to adherence included an HEI being born to a woman who: was well-educated (≥14 years of schooling), was taking a nevirapine-based regimen, has been on long-term ART, had a night-time onset of labour and was attended to by the husband during childbirth.

Our study showed that infants born to younger women were less likely to be adherent to their prophylactic treatment, a number of studies reaching a similar conclusion (21,109,112). Most young mothers in our cohort had taken ART for a shorter duration (<6

months). This means that their interface with the healthcare system was limited and that they had not had time to receive adequate ART adherence counselling, and subsequently were less well informed about the necessity to adhere to treatment and prophylaxis. This is supported by the fact that babies born to women on long term ART in our cohort were likely to be more adherent to prophylaxis than those born to women on shorter duration of ART. This finding further demonstrates that women who have been on ART for longer periods are aware of the benefits of adherence to ART compared to their counterparts that have been on ART for a shorter period. One study also demonstrated that women who have taken ART for shorter periods were more likely to report side effects of ART, which affected their adherence to ART (113). While conducting ART adherence counselling, health workers need to pay special attention to these younger mothers.

In our study, infants born to women who did not receive nevirapine syrup from the health worker for the baby were unlikely to adhere to infant ART prophylaxis. Many women in our cohort who never received nevirapine for the baby did not have a clinic delivery, mostly being home deliveries. Studies done in Zambia and South Africa, and a systematic review for sub-Saharan Africa, showed an association between home delivery and non-adherence to infant prophylaxis (110–112). Home deliveries have also been associated with the mother not receiving nevirapine syrup for the baby from the health worker at the time of delivery (70,112). Women delivering at home may not have been able to return to the hospital to get the infant's syrup for different reasons. Women delivering outside the hospital are less likely to receive counselling on the importance of their baby adhering to prophylaxis, due to the absence of a skilled birth attendant or health worker. Furthermore, HEIs born to women whose labour started in the night were more likely to adhere to nevirapine prophylaxis. Most women in our cohort are multiparous or of higher gravidity. Progress in labour for multiparous women is faster (114). Women whose labour begins in the night are most likely to deliver during daytime, which means they will be able to receive NVP syrup for the baby from the health worker at the PMTCT clinic. The PMTCT clinic is usually closed in the evening and night in our study setting. Women without NVP cannot administer it to the baby, and this contributes to non-adherence of the HEI to prophylaxis (112). An alternative strategy would be to provide all HIV infected pregnant women with NVP syrup for the baby from the ANC *prior* to delivery.

Infants born to women who did not have a viral load test done during pregnancy were less likely to adhere to the infant prophylaxis. The main reason for this was because they had been on ART for >6 months (10). Having had less time in healthcare, these women have not yet benefitted from on-going and continuous ART counselling. Women who have taken ART for shorter periods of time remain a critical target for adherence counselling.

We have shown that infants born to educated mothers were more likely to adhere to their prophylaxis. Educated mothers more likely read and comprehend concepts of adherence taught during ART adherence counselling sessions, and therefore are more likely to support their infants with adherence to prophylaxis. Some studies have shown no association between maternal education and infant adherence to nevirapine prophylaxis, whereas others have shown an association between lack of maternal education and low infant nevirapine adherence, as in our study (69,70,112).

Women who were taking an NVP-based regimen were more likely to have infants that adhere to infant prophylaxis. In our cohort, women taking NVP-based regimens have taken ART for longer periods of time, benefits that have been discussed above.

Women accompanied to the hospital by their husbands for labour and delivery were more likely to have infants that were adherent to their prophylaxis. The husband plays a key role in decision making when it comes to newborn care (115). Male involvement in PMTCT generally improves adherence to the whole PMTCT programme. Other studies have actually demonstrated that male involvement in maternal and child health services promotes adherence to infant nevirapine prophylaxis (112,116). This finding evidently shows that if PMTCT programs in our study context and those similar to it promoted male involvement, this would not only enhance adherence to infant prophylaxis, but to the entire PMTCT cascade of interventions.

**Exclusive breastfeeding among 14-week-old HIV exposed infants**

The proportion of infants that were exclusively breastfed reduced with increasing age of the infant; by 14 weeks of age, almost half were not exclusively breastfed. We found a low proportion of EBF of 57% among 14-week-old HEIs, probably because their mothers perceived that their breast milk was insufficient and that it would not satisfy the baby; therefore they resort to other feeding options for the infant, such as cow's milk, water and

porridge (89). Cultural beliefs surrounding breastfeeding also influence infant feeding practices, for example, believing that giving honey to the baby will protect them against false teeth and colic pain (115). Giving the baby prelacteal feeds also contributed to non-EBF. Studies from South Africa and Nigeria report a similar trend in exclusive breastfeeding among HIV exposed infants as they grew older (77,79). Some systematic reviews and observational studies have reported rates similar to those in our study (74,75,78,80). However, one study from Tanzania reported a higher prevalence of exclusive breastfeeding than our study (117). These disparities could be explained by the fact that they included infants of varying ages and were done in different socio-cultural contexts. However, we cannot dispute the fact that actual differences are most likely to exist.

It was common for mothers to give their infants prelacteal feeds after delivery. Women are most likely to give their babies prelacteal feeds because of sore breasts, perceived insufficient milk flow immediately after delivery, social and cultural issues, such discarding colostrum (89). Several studies of HEI infants demonstrate that mothers give infants these feeds due to insufficient breast milk shortly after delivery, because of breast problems or maternal death (78). One study from Northern Uganda, a context similar to our own, showed that lactating women discard colostrum shortly after delivery because they culturally perceive it to be dirty and harmful to the baby (89). This could possibly explain why infants in our cohort were given prelacteal feeds. An infant not receiving colostrum misses out on the essential benefits, i.e. building up the immune system and lining of the infant's gut to keep pathogens at bay. This is a potential risk for mother-to-child transmission of HIV and development of opportunistic infections.

**Risk factors for non-exclusivity of breastfeeding**

In our cohort, women of the highest socio-economic status were more likely not to exclusively breastfeed their infants compared to those in the lowest socio-economic strata. One study demonstrated an association between socio-economic status and exclusive breastfeeding (118). Most women in the topmost socio-economic strata in our cohort were actually employed and probably had to return to work shortly after delivery because of work-related demands and pressures.

Women whose delivery was supervised by a non-health worker were less likely to exclusively breastfeed and were likely to have had a home delivery. Having a home delivery deprives the mother of interacting with a health worker and a healthcare setting, thereby losing out on the benefits of counselling and support for exclusive breastfeeding. Some systematic reviews and observational studies showed that women who attended antenatal care clinics, those that delivered in a hospital and had infant adherence counselling, were more likely to practice exclusive breastfeeding (74,75,78,80,89,119). In a hospital setting, there is on-going infant feeding training for the healthcare worker and infant feeding counselling for the mother. Another study from Northern Uganda found that health workers were key decision-makers when it came to breastfeeding (115). These findings from various studies clearly explain why a mother whose delivery is not supervised by a health worker is most unlikely to exclusively breastfeed her infant. In light of this, it is important that infant feeding counselling is introduced in a combination of settings, and not just at health facilities, e.g. at the facility, workplace, community and home settings.

Our study demonstrated that women not adhering to ART during pregnancy were also unlikely to exclusively breastfeed their infants. Being non-adherent to ART can be a consequence of a low degree of interaction with the healthcare system (120). Therefore, these women will not achieve the benefits of this routine interaction with the healthcare system, e.g. continued counselling on infant feeding. Hence women who are non-adherent to ART will most unlikely be adherent to infant feeding guidelines, and will not exclusively breastfeed their infants. Non-adherence to ART will lead to higher viral loads and advanced HIV disease, which poses a high risk for transmission of HIV from a mother to her baby during breastfeeding. Few studies have examined antiretroviral adherence during pregnancy and its association with infant feeding practices. However, pregnancy in itself has been associated with low ART adherence (121). Drug-related factors, such as side effects and pill burden, as well as physiological changes during pregnancy, are barriers to ART adherence (122). Further qualitative studies should be done to shed more light on the association between ART adherence and breastfeeding.

This study generated key context-specific factors contributing to the increased risk of mother-to-child transmission of HIV in this resource-limited setting with its high burden of

antenatal HIV infection of 13.5%. These findings may form the basis for targeted interventions.

## Discussion of the methods

### Strengths and limitations of the methods and design

We have summarised the methodological strengths and weaknesses of the different sub-studies in Table 5.

In papers I and II, we employed a cross-sectional design. This design gave us the opportunity to collect information on various exposure and outcome variables in a reasonable period of time in order to measure prevalence and predictors of unintended pregnancy and detectable viral load in our study context.

We collected data for paper I and II at one time-point and were able to assess 2 outcomes. This was an inexpensive way of achieving our objective. The risk of loss to follow-up was minimized, since participants were not followed up after the initial encounter. However, some potential participants declined to participate in the survey at the beginning of the observation, mainly due to their spouses declining (Figure 7). Our survey included pregnant women most of whom were in a marital union or cohabiting. After given consent prior to participation in the study, most women reported that they had to first consult with their spouses for approval before participating in the study. However, some of the pregnant women's spouses had them decline participating, referring to it as a waste of time. This introduced some form of non-response bias. However, the study team took an extra step of sending an information sheet to the spouse through the participant, as well as making telephone calls to explain any questions that might have been unclear or caused anxiety.

We could not fully decide whether the established exposures in papers I and II preceded the outcomes of unintended pregnancy and detectable viral load, respectively. For this reason we could only establish associations, but not the causal relationship, between the exposures and these outcomes.

In paper I, we asked the women about pregnancy intent at 20 weeks of gestation or more. By this time, a woman might have already come to terms with an originally undesired pregnancy. Our results may therefore be some kind of 'under-estimation' of unintended pregnancies in this group. Furthermore, women with unintended pregnancy are more likely to seek abortion prior to 20 weeks of gestation. Since these women were not eligible to participate, it is possible that our estimation for the prevalence for unintended pregnancy

was lower than it would have been if we had asked them at an earlier time-point. On the other hand, we used a validated instrument in measuring pregnancy intent, which is a strength. We also measured pregnancy intention with regard to the index pregnancy while the women were pregnant. However, we did not classify unintended pregnancy into its subsets – untimed, unwanted or unplanned. It was difficult to make comparisons between our study and other evidence that had these classifications. However, these studies were very few.

Most studies on unintended pregnancy have investigated the general population and very few WLH. Some predictors for unintended pregnancy are unique to WLH, e.g. issues surrounding ART and viral loads. Therefore, it was a challenge to compare the findings from paper I with data on the general population.

In paper II, we did not report any adherence rates at the point of measuring detectable viral load. We could not rely on the adherence rates that were recorded on the participant's hospital record at enrolment/baseline. This information was inaccurately documented. More than half of the participants' hospital records lacked information on adherence assessment and scoring. We therefore dropped this variable during the analyses in paper II. However, we measured maternal ART adherence at the time of delivery, factoring in a 7-day recall.

We used a prospective cohort design in papers III and IV, and were able to follow one cohort of HIV infected women and study both the outcomes of adherence to infant prophylaxis and exclusive breastfeeding, for which we directly calculated incidence and relative risks. We followed up these participants at specified time intervals, at which points we measured the outcomes, employing a 7-day recall. This might have limited the possibility of recall bias.

It was clear for papers III and IV that the established exposures at the beginning of the observation preceded the outcomes of adherence to infant prophylaxis and exclusive breastfeeding; therefore there was clarity in the temporal sequence between the independent and dependent variables. Since the outcomes in papers III and IV were unknown when the exposure status was being established at the beginning of the observation, selection bias was unlikely.

The prospective cohort design enabled us to monitor the trends in exclusive breastfeeding in paper IV, as well as various infant feeding practices at birth, 6 weeks and 14 weeks. We found that the rate of exclusive breastfeeding among HIV exposed infants decreased with increase in the infants' age.

The prospective cohort study design was quite expensive and required a lot of time because we had to follow up this cohort at various time-points in order to reach the different outcomes of interest. Several participants that had been enrolled onto the study dropped off for various reasons (Figure 7), which caused loss to follow-up along the cascade. However, for purposes of follow-up we relied a lot on a functional telephone contact that the participant availed to the study team at baseline recruitment.

In paper III, we relied on the mother's or caregiver's report for measuring infants' adherence to nevirapine prophylaxis. Measuring medication adherence, while relying on self-reporting, is influenced by the period of recall. Our adherence estimates were likely to be overestimated due to the recall bias and social desirability inherent in self-reporting (110,114). However, other studies have demonstrated correspondence between relying on self-reports and other measures of adherence (21,123). The definitions of adherence adopted, the methods used to measure it, and the recall periods varied across different studies, making comparisons difficult.

In Paper IV, we measured exclusive breastfeeding at 6 and 14 weeks using a 7-day recall of the mother or care giver. It is well-known that infant feeding recalls are prone to bias. A 7-day recall is a "middle way" between 24-h recall which may be more accurate, but may not take into account all the feeds offered to the infant and "ever-recall," which may have even more recall bias.

All sub-studies were conducted in a hospital setting that is public in nature, a rural context, and among women attending and receiving antenatal care at LRRH. Therefore, findings for all outcomes in the studies in this thesis may only be generalizable to WLH from within this study context and those similar to it.

Our study on detectable viral load is the first to describe virologic profiles among HIV infected pregnant women in Northern Uganda, and demonstrates that actually disparities in viral suppression exist in this study setting. Most studies that have been conducted on

adherence to infant nevirapine prophylaxis are qualitative in nature. We measured exclusive breastfeeding continuously from birth till 14 weeks postpartum and relied on a 7-day recall, which helped to avoid exaggerating the incidence of exclusive breastfeeding in our cohort. We managed to create a cohort cascade that mimicked an actual PMTCT programmatic cascade and to retain 90% of the participants until the end.

The principal investigator was not an employee of the hospital in which these studies were conducted. Much as this could have been advantageous, but it could have had its disadvantages. Being an employee of LRRH would have compromised the candidate's position as a researcher in that she might not judge properly some study limitations; for example, it would be rather difficult to disclose that LRRH hospital records were problematic and incomplete. Even when the principal investigator could not speak *Lango,* the team that was recruited to enrol and follow up participants had to be fluent in the language predominant in the study context.

Another strength of our studies is the high completion rate of 90% along our cohort cascade (Figure 7). To minimize loss to follow-up, we documented the telephone contacts and residential mapping of each participant. A home visit was made when we could not reach the participant by phone.

A number of factors can affect the validity of a study, in particular in similar studies where the main data collection is through interviews. The 2 most commonly discussed are recall bias, where the person interviewed does not recollect (or correctly recall) events in the past, and social desirability bias, where the person consciously or unconsciously modifies his/her answers to be more socially acceptable (124).

Table 5: Strengths and weaknesses of the different sub-studies

| Sub-study | Strengths | Weaknesses |
|---|---|---|
| **All** | Across the sub-studies<br>- High completion rate of 90%<br>Papers I and II<br>- Less expensive<br>- No loss to follow-up<br>- Measure of prevalence for outcome was possible<br><br>Papers III and IV<br>- Studied multiple outcomes<br>- Minimised recall and selection bias<br>- Calculated directly the incidence of outcomes and relative risks<br>- Causal associations were established due to clarity in temporal relationships between exposures and outcomes | <br><br>Papers I and II<br>- Relying on self-reporting in the interviews could have introduced recall bias, social desirability<br>- Non-response bias<br>- Could not establish the causal relationships between exposures and outcome<br>Papers III and IV<br>- Expensive<br>- Time-consuming<br>- Loss to follow-up |
| **I** | - Universal definition of unintended pregnancy / validated instrument in measuring pregnancy intent<br>- Pregnancy intention measured with regard to the index pregnancy => limited recall bias | - Unintended pregnancy not sub-classified (untimed, unwanted or unplanned) hence difficult to make comparisons<br>- Women interviewed after 20 weeks of gestation which may mean that some women with unintended pregnancy may have had an abortion. Our prevalence estimation may be lower than the actual figure |
| **II** | - The first study to demonstrate that disparities in viral suppression exist in this study setting | - Incomplete data, many women did not have their viral load tested<br>- Maternal adherence not measured |
| **III** | - Most studies done on this subject matter are qualitative in nature and our prospective cohort study helped in describing the associations found in qualitative studies | - Self-reporting of the care giver => our adherence estimates may be over-estimated (recall bias and social desirability) |
| **IV** | - 7-day recall (instead of 24 h recall) likely to avoid exaggeration of the incidence | - 7-day recall (instead of 'ever'-recall) could introduce bias |

# Conclusion

HIV infected women in Northern Uganda were at higher risk of infecting their infants with HIV if they are: younger, not in a marital union, non-native to Lira, non-adherent to ART or had recently started on ART (those who miss having viral load tested during pregnancy), or had delivered outside the hospital (those whose births were unsupervised by a health worker and did not receive nevirapine syrup for their infant after childbirth). Special attention is needed regarding these critical groups during the implementation of PMTCT programs in Lira, Northern Uganda and similar contexts.

**Recommendations for policy**

We recommend that WLH with detectable viral loads be included in the category that is eligible for intensive adherence counselling, like those that are unable to achieve viral suppression. This is because WLH with detectable viral loads are more likely to develop resistance to and failure of the first-line regimen. Counselling also needs to be focused on groups of WLH found to be at risk of infecting their babies with HIV. This includes women who: are younger, not in a marital union, non-native to Lira, non-adherent to ART, had recently started on ART (those who miss having viral load done during pregnancy), or had delivered outside the hospital (those whose births are unsupervised by a health worker and do not receive nevirapine syrup for their infant after childbirth).

We recommend intensified clinical and psychosocial monitoring of medication compliance among HIV infected pregnant women who may have a detectable viral load to significantly lower the risk of vertical transmission of HIV. This is specifically valid for those taking a protease inhibitor-based regimen and who are non-natives to the study setting.

The health system needs to consider giving the infant nevirapine syrup to HIV infected pregnant women *before* birth to avoid delays and non-adherence. There is also a need to pay particular attention to younger women and those who recently started ART. We recommend ART adherence and infant feeding counselling to be emphasized and integrated in diverse settings, such as homes, workplaces, communities and health facilities.

**Recommendations for future research**

We recommend further qualitative investigation into the fact that disparities in viral suppression occur in this study context. We also recommend that the protective effect of night-time onset of labour against home delivery and non-adherence to infant nevirapine prophylaxis could be investigated in this setting.

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# Erratum

Page 10 under Definitions, second last row:

| | | |
|---|---|---|
| Was: | **Detectable viral load** | HIV infected pregnant woman on ART having a viral load count between 50 and 999 copies per ml blood |
| Is now: | **Detectable viral load** | HIV infected pregnant woman on ART having a viral load count of 50 or more copies per ml blood |

# I

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# Prevalence and predictors for unintended pregnancy among HIV-infected pregnant women in Lira, Northern Uganda: a cross-sectional study

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**Prevention of unintended pregnancies is a global strategy to eliminate mother-to-child transmission of HIV. Factors surrounding unintended pregnancy among women living with HIV are not well understood. We aimed to determine the prevalence and predictors for unintended pregnancy among these women in Northern Uganda. We conducted a cross-sectional survey among 518 women using a structured questionnaire. We asked questions on socio-demographic, reproductive-related and HIV-related characteristics. We conducted multivariable logistic regression and reported adjusted odds ratios. The prevalence of unintended pregnancy was 41.1%. The predictors for unintended pregnancy were: being single (not living with a partner or being in a marital union), having five or more children and taking antiretroviral drugs for long periods of time. HIV counselling services should target women living with HIV who are not in a marital union, those having a higher parity and those who have taken ART for longer periods.**

The Human Immunodeficiency Virus (HIV) prevalence in Uganda was 6.0% in 2017[1]. There has been a scale up of prevention of mother-to-child transmission of HIV-1 (PMTCT) services covering over 95% of pregnant women and as a result there has been a significant reduction in the mother-to-child transmission of HIV-1 (MTCT) rate to less than 5%[1]. The global strategy by the World Health Organisation (WHO) for PMTCT is multi-pronged and includes: (a) primary prevention of HIV infection among women of child-bearing age, (b) prevention of unwanted pregnancies among women living with HIV (WLH), (c) prevention of HIV transmission from WLH to their infants and (d) provision of appropriate treatment to WLH and their children[2]. Uganda has taken strides in PMTCT largely because of infections prevented due to the provision of antiretroviral therapy (ART) to pregnant WLH; these strides do not reflect infections averted due to preventing unintended pregnancies[1]. Fertility desires for WLH have increased overtime[3–7] and so it is eminent to support them in their fertility choices through family planning and contraception. To ensure provision of contraception, the consolidated guidelines for prevention and treatment of HIV in Uganda promote the availability of accessible and comprehensive contraceptive services for WLH to not only meet their birth control needs but to also reduce rates of unintended pregnancy[2]. Prevention of unintended pregnancy through reliable contraceptive methods reduces MTCTof HIV, improves women's health as well as reduce both maternal and infant mortality among WLH and their offspring[6]. Preventing unintended pregnancy also offers several additional benefits for WLH and their babies by reducing

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the number of infants who acquire HIV and consequently those who need HIV services as well as increased survival for HIV exposed infants[2].

Conversely, unintended pregnancy poses health consequences for mothers, their babies and families[8,9]. A woman who conceives and gets pregnant when she does not desire to will not to seek prenatal care early enough[8,10]. A baby born to a mother who did not desire her pregnancy is likely to have low birth weight and other life threatening issues[11]. Both parents to the baby may suffer economic hardship[11]. Most importantly, WLH that experience unintended pregnancy are more likely not to adhere to the ART and hence frequently have elevated viral load counts[12,13]. Such grave consequences undoubtedly increase the risk of MTCT of HIV.

Much as integration of family planning into HIV services exists, the rates of unmet need for contraception remain elevated[6] ranging from 36 to 75%[14–20] which results into high rates of unintended pregnancy[19,21] in sub-Saharan Africa that range from 35 to 71%[3,7,13,17,19,20,22–27]. Unintended pregnancy can also result from incorrect or inconsistent use of contraception[5,24], interaction of hormonal methods with ART making them less effective[28,29], miscalculation of safe days while relying on non-modern contraception[19,30] and contraceptive failure[7,20].

Existing evidence demonstrates that various factors have been associated with unintended pregnancy among WLH and these are younger age, being single, ethnicity, education status, higher parity, having had a previous abortion, late or no antenatal care attendance, incorrect or inconsistent use of barrier methods, elevated viral load, peri-partum CD4+ immune suppression and long term ART use[5,12,13,22–24,30–32].

Studies that have been done on this subject matter have mainly looked into predictors for contraceptive use in the context of HIV and only, in a few cases, mentioned the rates of unintended pregnancy but rarely, its predictors. Furthermore, the unmet need for contraception is higher among WLH than their HIV negative counterparts[21] translating into WLH facing higher rates of unintended pregnancy than their HIV negative counterparts[31]. Factors surrounding unintended pregnancy among WLH in Uganda are still not well understood yet they remain a public health challenge. We therefore aimed to determine the prevalence and predictors for unintended pregnancy among HIV infected pregnant women in Lira, Northern Uganda.

## Methods

**Study design.** We conducted a cross-sectional study among HIV infected pregnant women between August 2018 and July, 2019. The exposures of interest were potential predictors which included socio-demographic, reproductive-related and HIV-related factors. The outcome of interest was unintended pregnancy.

**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 utilized the statistics, power and sample-size functions. Using the population parameter method with the test of comparing two independent means (0.576 vs. 0.315), we assumed 80% power, 95% confidence interval (CI) and 5% precision. We also assumed that 57.6% of WLH were not in a marital union[33] and that 31.5% of HIV infected women were married[24]. On running this calculation in the statistical software, we arrived at a sample size of 464. We adjusted the sample size to 516 after accounting for a 10% non-response. We however, included 518 HIV positive pregnant women who were receiving antenatal care at Lira Regional Referral Hospital (LRRH).

**Setting.** LRRH serves all the 8 districts of the Lango subregion in Northern Uganda. It is a government-owned health facility at tertiary level that offers health services including maternal and child health services like HIV care, antenatal care and delivery. These services are at no cost to the patients.

LRRH also has an annual outpatient attendance of almost 100,000 patients, annual antenatal care attendance of about 5,000 women and conducts approximately 6–7,000 deliveries annually.

**Participants.** HIV infected women were identified, consented and recruited consecutively through the existing Ugandan HIV treatment, care and support program for pregnant women at the PMTCT clinic located within LRRH. Women were eligible for participation if they were: 20 weeks pregnant or more, newly tested for HIV or already established in ART care. Those who were severely ill at the time of recruitment were excluded from the study and referred to appropriate care services.

**Surveys and measures.** The interviews were conducted in *Lango* (the main language spoken in the study setting) or English by trained study staff. Interviews consisted of socio-demographic related, reproductive-related and HIV-related information. All measures were translated into *Lango* and back-translated into English to ensure accuracy and minimise interpretation bias. All procedures of the study were performed in accordance with the guidelines and regulations pertaining to all relevant approving bodies.

Unintended pregnancy, the main outcome of the study, was defined in any of the following ways: a pregnancy that occurred when no more children were desired or one that occurred earlier than it was desired or one that occurred when the woman did not desire to become pregnant. We adapted questions from the London Measure of Unplanned Pregnancy, a psychometrically validated measure of the degree of intention of a current or recent pregnancy. Women were asked if the pregnancy came 'earlier than expected', 'later than expected', 'when expected' or 'not desired at all'. Women who had their pregnancy at the 'time desired' or 'later than expected' were combined, labelled as the 'intended' category and coded 0. Women with an 'earlier than desired' or 'unwanted pregnancy' were combined into a single group, labelled "unintended pregnancy" and coded 1. Contraceptive use, was defined as any contraceptive method used in the 6 months preceding the pregnancy at the time. Unmet need for contraception was defined as those women who experienced unintended pregnancy and did not use any form of contraception 6 months prior to the pregnancy. Marital status was categorised into married and single. Those who were married or cohabiting were combined into one group, labelled "married" and coded 1.

Those who were separated, divorced, widowed or not married were combined into one group, labelled "single" and coded 2. Women who had been pregnant for four or less times including miscarriages, abortions and the pregnancy at the time of the interview were collectively categorised and coded 1 for the variable "parity", else were coded 2. Duration on treatment was categorised as "< 6 months", "7–30 months", "31–119 months" and "≥ 120 months". Duration on ART of ≥ 120 months (10 years) was referred to as long-term ART use[34,35] for comparability purposes.

We created a composite index of wealth (socio-economic status) using principle component analysis (PCA). Because the PCA technique allows combination and ranking of a number of variables into smaller and fewer variables without prejudgment, it is considered a more accurate indicator of socioeconomic status than single items such as occupation or possession of particular items[36]. 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.

**Data management and statistical analyses.** Data were entered into EpiData software (www.epidata.dk, version 4.4.3.1) by two independent data entrants and exported for analysis into Stata version 14.0 (StataCorp, College Station, Texas, U.S.A.). Continuous data, if normally distributed, was summarised into means and standard deviations and if skewed, was summarised into medians with their corresponding interquartile ranges. Categorical variables were summarised into frequencies and percentages. The proportion of HIV infected women with unintended pregnancies was estimated and its confidence limits calculated using the exact method. We used multivariable generalized linear model regression analysis with a logit link to estimate the adjusted odds ratios of the independent variables on unintended pregnancy while controlling for confounding. All variables with $p < 0.25$ at the bivariate level were included in the initial model at the multivariate analysis. All variables with $p < 0.1$ and those of biological or epidemiologic plausibility (from previous studies) were included in the second model. We checked for confounding by calculating the percentage change in each effect measure by removing or introducing one variable at a time into the second model. If a variable caused more than 10% change in any effect measure, then it was considered a confounder. Using the Likelihood-ratio test, we found that the first and second models were not significantly different. Therefore we adopted the second model as our final model. We used the visual inspection factor to check for collinearity among all the variables that were included in the initial model.

**Ethical considerations.** Approval to conduct the study was granted by the Makerere University School of Medicine Research and Ethics Committee, the Norwegian Regional Committee for Medical and Health Research Ethics in the West, and the Uganda National Council for Science and Technology. Meetings were held with the Lira district health officer and LRRH director to grant administrative clearance to conduct the study. Additional meetings were held with the counsellors who work within the PMTCT clinic to introduce to them the study and its procedures and to request them to identify, mobilise and link willing participants with the research team. 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.

## Results

A total of 547 HIV infected pregnant women were screened for eligibility from the antenatal care clinic at Lira Regional Referral Hospital (LRRH) (Fig. 1). A total of 518 women participated in the study. Women did not participate in the study if their partner declined their participation, if they received ART care from another facility other than LRRH or if they were committed elsewhere. The participants had a mean age of 29.2 (SD 5.5). Two hundred and fifty (48.3%) had attained a formal education for a duration of at least seven years or more. The majority of the women were married (or cohabiting) and not formally employed. They were predominantly Christian and *Lango* speaking (Table 1). Most of the women had been pregnant for at least four times including the pregnancy at the time of the study with more than half having a pregnancy ranging from 20 to 28 weeks of gestation. A considerable proportion of these women had disclosed their HIV status and most had disclosed to their spouse. Almost half of the participants reported having used an effective form of contraception (oral contraceptives, intrauterine devices, injectable contraceptives or implants) six months prior to the pregnancy at the time of the study (Table 2).

**Predictors for unintended pregnancy.** Being single was a significant predictor for unintended pregnancy among HIV infected pregnant women. HIV infected women who were single were almost four times as likely to experience unintended pregnancy as their married counterparts (adjusted odds ratio (AOR) = 3.74, 95% CI: 1.67–8.34). Women who had a higher parity were three times as likely to experience unintended pregnancy as those with lower number or order of pregnancies (parity of ≥ 5; AOR = 2.79, 95% CI: 1.85–4.22). Those who had taken ART for 10 years (120 months) or more were almost four times as likely to report that the pregnancy at the time was unintended as those that had taken ART for less than 6 months (≥ 120 months; AOR = 3.69 (1.57–8.67) (Table 3).

## Discussion

In this study we sought to determine the prevalence of unintended pregnancy and its predictors among WLH. The predictors for unintended pregnancy in our study were being single, having five or more pregnancies and taking ART for longer durations of time. In this setting we have documented a prevalence of unintended pregnancy of more than 40%. This high rate found in our study is probably due to the unmet need of family planning.

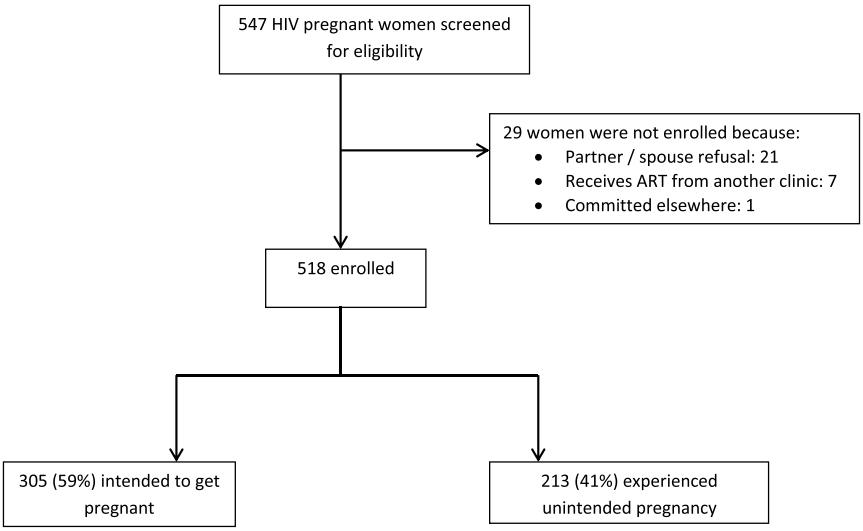


**Figure 1.** Flow diagram illustrating rationale for screening, enrolment and non-enrolment.

| Characteristics | Total (N = 518) n (%) | Pregnancy intended (N = 305) n (%) | Pregnancy not intended (N = 213) n (%) |
|---|---|---|---|
| *Socio-demographic* | | | |
| **Age** | | | |
| ≤ 20 years | 35 (6.8) | 23 (7.5) | 12 (5.6) |
| 21–29 years | 229(44.2) | 150 (49.2) | 79 (37.1) |
| ≥ 30 years | 254 (49.0) | 132 (43.3) | 122 (57.3) |
| **Education** | | | |
| 0–6 years | 268 (51.7) | 143 (46.9) | 125 (58.7) |
| 7–10 years | 171 (33) | 105 (34.4) | 66 (31) |
| 11–13 years | 51 (9.9) | 35 (11.5) | 16 (7.5) |
| ≥ 14 years | 28 (5.4) | 22 (7.2) | 6 (2.8) |
| **Marital status** | | | |
| Married | 484 (93.4) | 295 (96.7) | 189 (88.7) |
| Single | 34 (6.6) | 10 (3.3) | 24 (11.3) |
| **Employment status** | | | |
| Employed | 207 (40) | 129 (42.3) | 78 (36.6) |
| Not employed | 311 (60) | 176 (57.7) | 135 (63.4) |
| **Religious affiliation** | | | |
| Christian | 500 (96.5) | 292 (95.7) | 208 (97.7) |
| Moslem | 18 (3.5) | 13 (4.3) | 5 (2.3) |
| **Ethnic belonging** | | | |
| Langi | 472 (91.1) | 275 (90.2) | 197 (92.5) |
| Other | 46 (8.9) | 30 (9.8) | 16 (7.5) |
| **Socioeconomic index** | | | |
| Group 1 (poorest) | 139 (26.8) | 80 (26.2) | 59 (27.7) |
| Group 2 | 122 (23.6) | 69 (22.6) | 53 (24.9) |
| Group 3 | 170 (32.8) | 96 (31.5) | 74 (34.7) |
| Group 4 (least poor) | 87 (16.8) | 60 (19.7) | 27 (12.7) |

**Table 1.** Baseline demographic characteristics of HIV infected pregnant women receiving antenatal care at Lira Regional Referral Hospital.

| Characteristics | Total (N = 518) n (%) | Pregnancy intended (N = 305) n (%) | Pregnancy not intended (N = 213) n (%) |
|---|---|---|---|
| *Reproductive-related* | | | |
| **Parity** | | | |
| ≤ 4 | 375 (72.4) | 247 (81.0) | 128 (60) |
| ≥ 5 | 143 (27.6) | 58 (19.0) | 85 (40) |
| **Gestational age (in weeks)** | | | |
| 20–27 | 279 (53.9) | 165 (54.1) | 114 (53.5) |
| 28–35 | 171 (33) | 102 (33.4) | 69 (32.4) |
| ≥ 36 | 68 (13.1) | 30 (12.5) | 30 (14.1) |
| **Accompanied to antenatal care** | | | |
| Not accompanied | 465 (89.8) | 272 (89.2) | 193 (90.6) |
| Accompanied on day of interview | 53 (10.2) | 33 (10.8) | 20 (9.4) |
| **Use of birth control** | | | |
| Did not use | 258 (49.8) | 163 (53.4) | 95 (44.6) |
| Used 6 months prior to pregnancy | 260 (50.2) | 142 (46.6) | 118 (55.4) |
| **Type of contraceptive used** | | | |
| None or safe days | 267 (51.5) | 167 (54.8) | 100 (47) |
| Effective contraception | 251 (48.5) | 138 (45.2) | 113 (53) |
| *HIV-related* | | | |
| **HIV status disclosure** | | | |
| Disclosed | 501 (96.7) | 299 (98.0) | 202 (94.8) |
| Not disclosed | 17 (3.3) | 6 (2.0) | 11 (5.2) |
| **Person disclosed to** | | | |
| Husband | 398 (76.8) | 244 (80.0) | 154 (72.3) |
| Other | 120 (23.2) | 61 (20.0) | 59 (27.7) |
| **Fear about others' opinion on HIV status** | | | |
| Had no fear | 253 (48.8) | 139 (45.6) | 114 (53.5) |
| Had fear | 265 (51.2) | 166 (54.4) | 99 (46.5) |
| **Antiretroviral treatment** | | | |
| Efavirenz-based | 466 (90) | 279 (91.5) | 187 (87.8) |
| Nevirapine-based | 44 (8.5) | 23 (7.5) | 21 (9.9) |
| Protease inhibitor–based | 8 (1.5) | 3 (0.1) | 5 (2.4) |
| **Duration of antiretroviral treatment** | | | |
| Less than 6 months | 98 (18.9) | 64 (21) | 34 (16) |
| 7 to 30 months | 117 (22.6) | 70 (23) | 47 (22) |
| 31 to 119 months | 267 (51.5) | 159 (52.1) | 108 (50.7) |
| ≥ 120 months | 36 (7) | 12 (3.9) | 24 (11.3) |

**Table 2.** Other characteristics.

Generally studies that report high prevalence of unintended pregnancy also report high rates of unmet need of family planning[6,13,23,24,37,38] just like in our study. Several studies have reported high prevalence of unintended pregnancy ranging from 35 to 78%[4,7,13,20,23,24,31,38,39]. Studies in Nigeria[4] and Zimbabwe[20] reported lower prevalence of unintended pregnancy than our study. This could be attributed to the fact that in both studies, the way the outcome of unintended pregnancy was measured and defined was different from ours. A number of studies did not rely on the definitions of unintended pregnancy stipulated in the LMUP. Studies elsewhere[12,13,22–24,30,31,38,39] reported higher prevalence of unintended pregnancy than ours. Studies report varying rates because of the difference in the types of population from which they measure unintended pregnancy. Some studies have measured unintended pregnancy among adolescents[39] which creates a difference in risk factors between these studies and ours. The timing of asking about unintended pregnancy was different between the various studies and our study. Most of the studies asked about intention of the pregnancy long after the women in the cohorts had given birth to their babies not while they were still pregnant like in our study.

In our study, HIV infected women who were single were more likely to experience unintended pregnancy. A plausible explanation for this is that in a marital union there are open communication channels between the two individuals and this facilitates open discussion on reproductive-related issues like child-bearing and contraceptive use. Studies done elsewhere[15,16,31] also documented that WLH in a relationship were most likely to use contraception if there was open partner discussion among married couples. These communication channels

| Variables | Crude OR (95% CI) | *p* value | Adjusted OR (95% CI)[a] | *p* value | Adjusted OR (95% CI)[b] | *p* value |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| ≤20 years | 0.56 (0.27–1.18) | 0.13 | 0.74 (0.3–1.81) | 0.505 | – | – |
| 21–29 years | 0.57 (0.39–0.82) | 0.003 | 0.86 (0.55–1.34) | 0.501 | – | – |
| ≥30 years | 1 | | 1 | | – | – |
| **Education status** | | | | | | |
| 0–6 years | 1 | | 1 | | – | – |
| 7–10 years | 0.72 (0.49–1.06) | 0.098 | 0.88 (0.57–1.36) | 0.563 | – | – |
| 11–13 years | 0.52 (0.28–0.99) | 0.047 | 0.71 (0.35–1.44) | 0.345 | – | – |
| ≥14 years | 0.31 (0.12–0.79) | 0.015 | 0.5 (0.18–1.37) | 0.176 | – | – |
| **Marital status** | | | | | | |
| Married | 1 | | 1 | | 1 | |
| Single | 3.75 (1.75–8) | 0.01 | 3.81 (1.68–8.66) | 0.001 | **3.74 (1.67–8.34)** | 0.001 |
| **Employment status** | | | | | | |
| Employed | 1 | | 1 | | – | – |
| Not employed | 1.27 (0.89–1.81) | 0.195 | 1.13 (0.74–1.73) | 0.581 | – | – |
| **Parity** | | | | | | |
| ≤4 | 1 | | 1 | | 1 | |
| ≥5 | 2.83 (1.9–4.2) | 0.000 | 2.4 (1.5–3.86) | 0.000 | **2.79 (1.85–4.22)** | 0.000 |
| **HIV status disclosure** | | | | | | |
| Disclosed | 1 | | 1 | | 1 | |
| Not disclosed | 2.71 (0.99–7.46) | 0.053 | 2.55 (0.84–7.76) | 0.1 | 2.59 (0.86–7.78) | 0.09 |
| **Socioeconomic status** | | | | | | |
| Group 1 (poorest) | 1 | | 1 | | – | – |
| Group 2 | 1.04 (0.64–1.70) | 0.871 | 1.25 (0.73–2.14) | 0.425 | – | – |
| Group 3 | 1.05 (0.66–1.64) | 0.848 | 1.44 (0.87–2.38) | 0.16 | – | – |
| Group 4 (least poor) | 0.61 (0.35–1.07) | 0.087 | 0.91 (0.48–1.73) | 0.781 | – | – |
| **Type of contraceptive used** | | | | | | |
| None or safe days | 1 | | 1 | | 1 | |
| Effective contraception | 1.37 (0.96–1.94) | 0.081 | 1.33 (0.9–1.96) | 0.148 | 1.34 (0.92–1.95) | 0.132 |
| **Antiretroviral treatment** | | | | | | |
| Efavirenz-based | 1 | | 1 | | – | – |
| Nevirapine-based | 1.36 (0.73–2.53) | 0.328 | 0.93 (0.43–1.99) | 0.85 | – | – |
| Protease inhibitor-based | 2.49 (0.59–10.53) | 0.216 | 2.24 (0.4–12.41) | 0.356 | – | – |
| **Duration of antiretroviral treatment** | | | | | | |
| 0 to 6 months | 1 | | 1 | | 1 | |
| 7 to 30 months | 1.26 (0.72–2.2) | 0.409 | 1.25 (0.68–2.3) | 0.482 | 1.29 (0.71–2.36) | 0.398 |
| 31 to 119 months | 1.28 (0.79–2.07) | 0.318 | 1.15 (0.66–2.01) | 0.628 | 1.19 (0.7–2.03) | 0.517 |
| ≥120 | 3.76 (1.68–8.45) | 0.001 | 3.32 (1.24–8.92) | 0.017 | **3.69 (1.57–8.67)** | 0.003 |

**Table 3.** Predictors for unintended pregnancy among HIV infected women in Northern Uganda. The bold figures in Table 3 represent the significant predictors for unintended pregnancy. [a]$R^2 = 0.0902$. [b]$R^2 = 0.0789$.

are absent when the woman does not have a partner. Studies in Kenya[39], Swaziland[22], Botswana[23] and South Africa[12,24,31], demonstrate similar results.

Our study also found that experiencing a higher number of pregnancies increased the likelihood of experiencing unintended pregnancy among WLH. A probable explanation for this finding in our study could be inconsistency in the use of contraception, under-utilisation of emergency contraceptives, side effects of the contraception like heavy bleeding, partner refusal or constant stock outs of contraceptives at health facilities. Our finding was consistent with results from other studies in South Africa[24,31] and Botswana[23]. However, different results were found in Cameroon[33] and Uganda[26]. One study in Kenya[39] showed that the odds of lower order pregnancies to be unintended were the same as those of higher order pregnancies, though the cohort in this study was adolescents which could explain the variation in findings between this study and ours.

It is surprising to note that in our study HIV infected women who had taken ART for long periods of time were more likely to experience unintended pregnancy. Probably, in our study context, women on long-term ART experience complacency and in so doing become non-adherent to both ART and contraceptive use. In a study done in Uganda[40], it was found that individuals who had taken ART for a long time hardly received continuous ART adherence education, experienced treatment fatigue and were less likely to adhere to their treatment. Studies in South Africa[24,31] however found that women who had been newly diagnosed with HIV were more likely to

experience unintended pregnancy. More qualitative studies need to be done in our study context to understand reasons for this finding.

**Strengths and limitations.** The study was conducted in a hospital setting hence our findings may only be generalizable to WLH from within this study context and those similar to it. We did not classify unintended pregnancy into its variations—untimed, unwanted or unplanned. It was difficult to make comparisons between our study and the studies that made these classifications. However, these studies were very few. Women with unintended pregnancy are more likely to seek abortion prior to 20 weeks of gestation. Since these women were not eligible to participate in our study, it is possible that our prevalence estimation was lower than the actual.

Our study had its strengths too. We adapted use of a validated instrument in measuring pregnancy intent. We also measured pregnancy intention with regard to the index pregnancy while the women were pregnant. This discounts the plausibility of recall limitation. However, this does not remove the notion that at the time of measuring pregnancy intent in this cohort, some women might have already come to terms with their pregnancy. We measured pregnancy intent at 20 weeks of pregnancy or more. By this time, a woman might have already accepted and desired an originally undesired pregnancy. We, therefore, could have under reported on the prevalence of unintended pregnancy.

## Conclusions

WLH likely to experience unintended pregnancy included: those who were not in a marital union, those having a higher number of children and those who had taken ART for longer periods. We recommend that alongside integration of family planning services with existing HIV care, counselling services need to target WLH who are not living with a partner, those with high number of children and those that have been in HIV care for long periods of time.

## Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Received: 15 January 2020; Accepted: 17 September 2020
Published online: 01 October 2020

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## Acknowledgements

We are grateful to LRRH, the study participants and the research assistants for their tremendous contribution to this survey.

## Author contributions

A.N., J.K.T., T.T., V.N., G.N. and P.W. conceived, designed, and supervised the study as well as analysing the data and writing the first draft of the manuscript. D.M. was instrumental in the analysis and drafting of the manuscript. J.T., B.O., and A.A.A. were instrumental in drafting and revising the manuscript. All authors read and approved the final version to be published. A.N. is the corresponding author.

## Funding

The Survival Pluss Project at Makerere University (No. UGA-13 -0030) funded the survey. The Survival Pluss project is financed by the Norwegian Programme for Capacity Development in Higher Education and Research for Development (NORHED) by the Norwegian Agency for Development Cooperation (Norad), Norway.

## Competing interests

The authors declare no competing interests.

## Additional information

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# II

International Journal of Maternal and Child Health and AIDS (2020), Volume 9, Issue 2, 232-241

IJMA

Available online at www.mchandaids.org

INTERNATIONAL JOURNAL of MATERNAL and CHILD HEALTH and AIDS
ISSN 2161-864X (Online)
ISSN 2161-8674 (Print)
DOI: 10.21106/ijma.374

**ORIGINAL ARTICLE | HIV Viral 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

## 1. 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 epidemic[1] and Uganda is no exception.[2] Women are disproportionately affected by HIV compared to males[2] 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

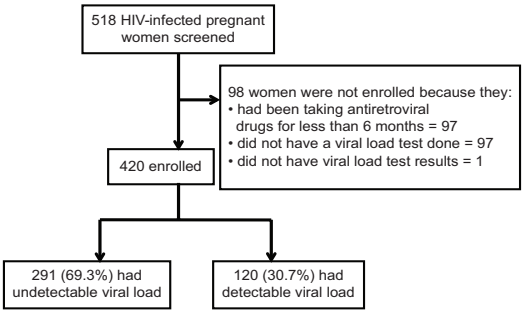


**Figure 1:** Study flow chart

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-1 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 HIV-infected 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 second-line 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

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 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 ≥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 cut-off of 50 copies/ml. Studies from South Africa[11,14,17] and Malawi[18] 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.

**Table 1a: Socio-demographic characteristics of HIV infected pregnant women receiving antenatal care at Lira Regional Referral 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 (%) |
| 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) | 11 (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 1 (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) |

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 Rwanda[24] 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 Uganda[22] and Malawi[25] reported a similar prevalence of virologic non-suppression among HIV infected pregnant women. The low prevalence of virological non-suppression 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 study participants Lira Regional Referral 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 | | | |
| 1 – 4 | 289 (68.8) | 203 (69.8) | 86 (66.7) |
| 5 – 9 | 131 (31.1) | 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) | 11 (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 Benin[27] found the opposite, that the predominant ethnicity of the study setting was more likely to have a detectable viral load. More qualitative studies are needed in our study context to understand reasons for this finding.

**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 |

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 Uganda[9] and the United States of America[28] 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 (≥50 copies/ml of HIV RNA in the blood)**

| Variables | Unadjusted OR (95% CI) | Adjusted OR (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 | 1 | 1 |
| Education status | | |
| 0 – 6 years | 1 | 1 |
| 7 – 10 years | 1.14 (0.72 – 1.8) | 1.21 (0.75 – 1.96) |
| 11 – 13 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 | 1 | 1 |
| Other | 1.77 (0.91 – 3.44) | 1.92 (1.05 – 3.90) |
| Person disclosed to | | |
| Spouse | 1 | 1 |
| 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 | 1 | 1 |
| 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 | 1 | 1 |
| ≥ 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 second-line ART regimen because of treatment failure of the first-line regimens which is mainly due to non-adherence.[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 follow-up 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 HIV-infected 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 target[33] 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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# III

PLOS ONE

RESEARCH ARTICLE

# Barriers and enablers of adherence to infant nevirapine prophylaxis against HIV 1 transmission among 6-week-old HIV exposed infants: A prospective cohort study in Northern Uganda

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**Citation:** Napyo A, Tylleskär T, Mukunya D, Tumuhamye J, Musaba MW, Ojok Arach AA, et al. (2020) Barriers and enablers of adherence to infant nevirapine prophylaxis against HIV 1 transmission among 6-week-old HIV exposed infants: A prospective cohort study in Northern Uganda. PLoS ONE 15(10): e0240529. https://doi.org/10.1371/journal.pone.0240529

**Editor:** Douglas F. Nixon, Cornell University Joan and Sanford I Weill Medical College, UNITED STATES

**Received:** August 9, 2020

**Accepted:** September 28, 2020

**Published:** October 15, 2020



**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** 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

## Abstract

### Background

Sub-optimal adherence to infant prophylaxis has been associated with mother-to-child-transmission of HIV. However, the factors associated have not been well characterised in different settings. This study describes barriers and enablers of adherence to infant prophylaxis among 6-week-old HIV exposed infants in Lira district, Northern Uganda.

### Methods

This prospective cohort study was conducted from 2018–2020 at the PMTCT clinic at Lira Regional Referral Hospital and included 472 mother-infant pairs. HIV-infected pregnant women were recruited, followed up at delivery and 6 weeks postpartum. We used a structured questionnaire to obtain data on socio-demographic, reproductive-related, HIV-related characteristics and adherence. Data were analysed using Stata to estimate adjusted risk ratios using Poisson regression models to ascertain barriers and enablers of adherence to infant nevirapine prophylaxis.

### Results

Barriers to infant adherence are maternal characteristics including: younger age (≤20 years adjusted risk ratio (ARR) = 1.55; 95% CI: 1.1–2.2), missing a viral load test during pregnancy (ARR: 1.4; 95% CI: 1.1–1.7) and not receiving nevirapine syrup for the baby after childbirth (ARR = 6.2; 95% CI: 5.1–7.6). Enablers were: having attained ≥14 years of schooling (ARR = 0.7; 95% CI: 0.5–0.9), taking a nevirapine-based regimen (ARR = 0.6; 95% CI: 0.4–0.9),

through the Survival Pluss Project at Makerere University (no. UGA-13-0030).

**Competing interests:** The authors declare that they have no competing interests.

**Abbreviations:** ARR, Adjusted risk ratio; ART, Antiretroviral therapy; CI, confidence interval; HEI, HIV exposed infant; HIV, Human Immunodeficiency Virus; LRRH, Lira Regional Referral Hospital; MTCT, Mother-to-child transmission of HIV; NVP, Nevirapine; PMTCT, Prevention of mother-to-child transmission of HIV.

long-term ART ($\geq$ 60 months ARR = 0.75; 95% CI: 0.6–0.9), accompanied by a husband to hospital during labour and childbirth (ARR = 0.5; 95% CI: 0.4–0.7) and labour starting at night (ARR = 0.7; 95% CI: 0.6–0.8).

## Conclusion and recommendations

Despite mothers receiving nevirapine syrup from the health workers for the infant, non-adherence rates still prevail at 14.8%. The health system needs to consider giving HIV infected pregnant women the nevirapine syrup before birth to avoid delays and non-adherence. There is need to pay particular attention to younger women and those who recently started ART.

## Introduction

HIV-1 exposed infants (HEI) can get infected with HIV from their mothers during pregnancy, childbirth or breastfeeding. Over 90% of paediatric HIV infections are through mother-to-child transmission of HIV-1 (MTCT) [1]. However, giving antiretroviral therapy to the mother and infant prophylaxis to the infant during breastfeeding are the major interventions in the prevention of mother-to-child transmission of HIV-1 (PMTCT) [2, 3].

Since 2013, the World Health Organisation (WHO) consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection [3] advocate lifelong antiretroviral therapy (ART) regardless of immune status for pregnant and breastfeeding mothers in addition to infant prophylaxis for the baby for 6–12 weeks. A longer duration of prophylaxis is recommended for high-risk infants born to an HIV infected mother that has a viral load (VL) greater than 1000 copies/ml [2, 3]. For a high-risk infant, the mother's VL test should be done at 12 weeks postpartum and only if $<$ 1000 copies/ml should the infant stop taking nevirapine (NVP). If the maternal VL is not suppressed by 12 weeks, the infant should continue taking NVP until the mother's VL is less than 1000 copies/ml or otherwise continue with NVP until four weeks after cessation of all breastfeeding [1]. These guidelines have been implemented in Uganda since 2012 [4]

For these interventions to yield impact in PMTCT, adequate adherence to both maternal ART and infant prophylaxis are a prerequisite [5]. Challenges in achieving optimal adherence can be programmatic, maternal- or infant-related. There are programmatic challenges with linkage of HEIs and their mothers from PMTCT to HIV care [6] and lack of clinic-based HIV counselling [7]. Maternal-related challenges include forgetfulness, poor adherence and social or cultural obligations [8]. Infant-related challenges are vomiting of the drug or the baby being sick [9]. Poor adherence to infant nevirapine prophylaxis may contribute to transmission of HIV hence identifying barriers to adherence is essential to eliminate MTCT.

Several studies have demonstrated an association between non-adherence to infant nevirapine prophylaxis and home deliveries, inadequate antenatal care, mother not receiving the nevirapine for her baby while at the hospital, misplacing of the baby's drug, lack of transport and the mother staying with in-laws [10, 11].

While there are numerous benefits of ART prophylaxis for PMTCT, there are still disparities in rates of MTCT due to differences in programme settings, systems, support requirements and context. Varying ART adherence rates in various contexts can also contribute to the disparities in MTCT rates. Most studies done on adherence to infant nevirapine prophylaxis have been qualitative and were done under previous treatment paradigms and cannot be compared to today's situation. Furthermore, different methods have been used to measure adherence to

infant NVP prophylaxis like relying on caregivers' report [12], measuring blood plasma concentrations of NVP therapeutic levels [9, 13] and electronic dose monitoring like medication event monitoring systems (MEMs) where bottle caps are fitted with a microchip that records the time and date of each bottle opening [14].

The goal set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) of getting to zero new HIV infections among children is far from being achieved in Uganda [1] since Uganda's MTCT rates of HIV have stagnated between 3–4% [15, 16] in the past decade. It is against this background that we studied barriers and enablers of adherence to infant nevirapine prophylaxis to optimise the PMTCT programme in Northern Uganda.

## Materials and methods

### Study design and setting

This prospective cohort study was conducted between August 2018 and January 2020 at the PMTCT clinic located within the Lira Regional Referral Hospital (LRRH). This clinic is an initiative of the Ugandan Ministry of Health where free HIV care and treatment are offered to HIV-infected pregnant women. These women have to attend several other clinics during pregnancy and after child birth such as: early infant diagnosis, postnatal, immunisation and family planning clinics. All these clinics are independent of each other and of the PMTCT clinic in terms of structural location. The PMTCT clinic receives about 30–50 HIV infected pregnant women daily. At this clinic, the women receive both their antenatal and routine HIV care until delivery. Approximately 600 HIV infected women deliver at LRRH annually. For delivery, women are free to choose any health facility or clinic. However, the nevirapine syrup for infant prophylaxis can only be provided at the clinic where the woman is registered for her HIV care. The reason for this is to assess, weigh and classify the baby as 'high risk' or 'not high risk' and to determine the dosage and duration of prophylaxis. It is rare for mothers to receive nevirapine syrup elsewhere. There are no stores of nevirapine syrup in the labour suite and maternity ward. Finally, when the baby is 6 weeks old, the mother-infant pair is transferred to the early infant diagnosis (EID) clinic for further management. Here, care may be extended, for instance with DNA PCR testing and viral load monitoring for the baby and others services as applicable.

### Participants and procedures

We consecutively enrolled HIV infected pregnant women who were receiving antenatal care at LRRH and with a gestational age of 20 weeks or more. After consent, women were interviewed on socio-demographic characteristics, HIV-related information like antiretroviral regimen, duration and a viral load test done during pregnancy. The interviews were conducted in *Lango* (the language predominantly spoken in the study setting) and/or English by trained study staff. The questionnaires were translated into *Lango* and back translated into English to minimize information and interpretation bias. The research assistants were trained, qualified midwives who had experience in conducting research, HIV counselling, providing antenatal care and taking off blood samples for viral load testing so as to shorten the waiting time of the mothers in the PMTCT clinic. To minimize loss to follow-up, information on telephone contacts and physical address were collected. The women were then followed up with a telephone interview around the time of delivery. At this point, women were interviewed on circumstances surrounding labour and delivery like time of onset of labour, type of delivery, place of delivery, person who supervised the delivery, maternal ART adherence, if the mother had received NVP syrup from the health worker at delivery and when the baby ingested the first prophylactic dose. At 6 weeks postpartum, mothers were

followed up and asked about the infant's adherence to nevirapine prophylaxis. A total of 472 mother-infant pairs were included in the final analysis, Fig 1. All study visits except the one around delivery were done at the PMTCT clinic as they coincided with the mothers' routine visits for ART care. The 6-week interview was done just before the mother was transferred to the EID clinic. We, therefore, never got the chance to check for HIV transmission rates at 6 weeks from the DNA PCR results and hence this variable is not included in our analysis.

## Sample size estimation

We calculated a sample size for detecting an unknown proportion of infants adhering to infant prophylaxis using OpenEpi (openepi.com). We assumed a 50% proportion, 80% power, 95% confidence interval (CI) and 5% precision. The total sample size for this study was 384 HEI. After adjusting for 10% non-response and another 10% to allow for enough degrees of freedom in the multivariable analysis, the final sample size was 464. We included 472 mother-infant pairs.

## Variables

ART duration was recorded in months and any ART duration of $\geq$ 60 months (5 years) [17] was classified as long term ART, else as short term ART. Viral load test results during

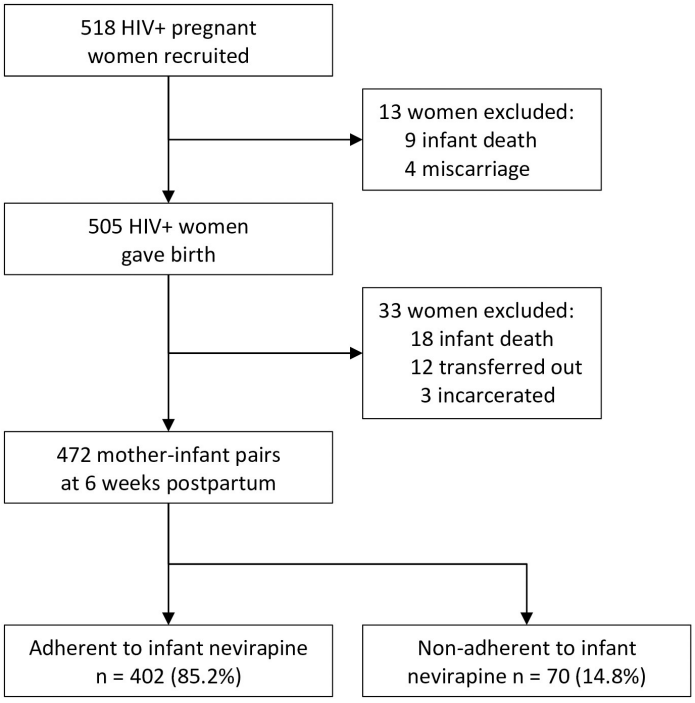


**Fig 1. Study profile.**

https://doi.org/10.1371/journal.pone.0240529.g001

pregnancy were categorised as "<50 copies/ml", "≥ 50 copies/ml" and "missing viral load". Viral loads <50 copies/ml were referred to as 'undetectable' and those ≥50 copies/ml as 'detectable'. The "missing viral load" was either due to having been on ART for less than 6 months or ineligibility for the annual viral load monitoring. Uganda ART guidelines do not include viral load monitoring at delivery. Women whose labour started between 06.00 hours to 18.59 hours were categorised as "day-time onset of labour" and else "night-time onset of labour". Women who delivered in any type of health care setting were all categorised as "clinic delivery" and otherwise as "non-clinic delivery". During the follow-up at the time of delivery, we also asked the mother if and when she had received the nevirapine syrup for the baby from a health worker and when the baby received the first dose. We estimated the expected date of delivery using the first day of the last normal menstrual period, and the research assistants called the mother at 7 days after the expected date of delivery. If the woman had not delivered yet, another telephone appointment was scheduled.

The outcome variable of interest was "non-adherence to infant nevirapine prophylaxis". At the 6-week visit, we asked the mother, "In the past week, how many days did you miss to give the baby the nevirapine syrup?" Infants that had missed 0–2 doses of nevirapine syrup were collectively categorised and labelled as "adhered" and those that had missed three or more doses were collectively categorised and labelled "non-adherent" [9]. We relied on the mother's recall for the measurement of infant adherence to NVP prophylaxis at 6 weeks postpartum [9, 14]. All infants included were brought to the PMTCT clinic by their mothers and so we never asked the mother if there is any other care giver that administered the nevirapine syrup to the baby other than the mother herself.

### Data analysis and management

Data was doubly entered into EpiData (www.epidata.dk, version 4.4.3.1) and exported for analysis to Stata version 14.0 (StataCorp, College Station, Texas, U.S.A.). Continuous data, if normally distributed, was summarised into means and standard deviations and if skewed, was summarised into medians with their corresponding interquartile ranges (IQR). Categorical variables were summarised into frequencies and percentages. The incidence of non-adherence to infant nevirapine prophylaxis was estimated and its confidence limits calculated using the exact method. Bivariable and multivariable analysis was done using Poisson regression models / analysis [18]. All variables that had a $p$-value $< 0.25$ at bivariable analysis and those of biological plausibility were collectively put into a multivariable model to control for confounding. We estimated unadjusted (RR) and adjusted risk ratios (ARR) with their corresponding 95% confidence intervals.

## Results

### Baseline characteristics

The mean age for the HIV positive pregnant women at baseline was 29.4 years (SD 5.4) (Table 1). Almost half of them were 30 years or more and had at least six years of schooling. The majority were unemployed and had disclosed their HIV status. More than half of them had taken ART for at least 5 years and had a viral load <50 copies/ml. All the women had someone accompanying them during labour and delivery, (Table 2). The majority had a spontaneous vaginal delivery in a hospital setting, were given nevirapine syrup by the health worker and were adherent to their ART.

**Table 1. Baseline characteristics of the HIV infected pregnant woman at enrolment.**

| Maternal characteristics | Total N = 472 n (%) | Adherent to infant NVP prophylaxis N = 402 (85.2%) n (%) | Non-adherent to infant NVP prophylaxis N = 70 (14.2%) n (%) |
|---|---|---|---|
| **Age** | | | |
| ≤ 20 years | 28 (5.9) | 20 (5) | 8 (11.4) |
| 21–29 years | 206 (43.6) | 171 (42.5) | 35 (50) |
| 30–39 years | 225 (47.7) | 198 (49.3) | 27 (38.6) |
| ≥ 40 years | 13 (2.8) | 13 (3.2) | 0 (0) |
| **Education** | | | |
| ≤ 6 years | 233 (49.4) | 195 (48.5) | 38 (54.3) |
| 7–13 years | 167 (35.4) | 141 (35.1) | 26 (37.1) |
| ≥ 14 years | 72 (15.2) | 66(16.4) | 6 (8.6) |
| **Marital status** | | | |
| Married | 441 (93.4) | 382 (95) | 59 (84.3) |
| Single | 31 (6.6) | 20 (5) | 11 (15.7) |
| **Employment status** | | | |
| Employed | 187 (39.6) | 161 (40) | 26 (37.1) |
| Unemployed | 285 (60.4) | 241 (60) | 44 (62.9) |
| **Religion** | | | |
| Christian | 454 (96.2) | 386 (96) | 68 (97) |
| Moslem | 18 (3.8) | 16(4) | 2 (3) |
| **Ethnic group** | | | |
| Lango | 430 (91.1) | 367 (91.3) | 63 (90) |
| Other | 42 (8.9) | 35 (8.7) | 7 (10) |
| **Parity** | | | |
| 0 to 4 | 337 (71.4) | 289 (71.9) | 48 (68.6) |
| 5 to 9 | 135 (28.6) | 113 (28.1) | 22 (31.4) |
| **Gestational age** | | | |
| 20–27 weeks | 244 (51.7) | 207 (51.5) | 37 (52.9) |
| 28–35 weeks | 162 (34.3) | 140 (34.8) | 22 (31.4) |
| ≥ 36 weeks | 66 (14.0) | 55 (13.7) | 11 (15.7) |
| **HIV disclosure** | | | |
| Disclosed | 457 (96.8) | 392 (97.5) | 65 (92.9) |
| Not disclosed | 15 (3.2) | 10 (2.5) | 5 (7.1) |
| **Antiretroviral regimen** | | | |
| Efavirenz-based | 423 (89.6) | 356 (88.6) | 67 (95.7) |
| Nevirapine-based | 41 (8.7) | 39 (9.7) | 2 (2.9) |
| Protease inhibitor-based | 8 (1.7) | 7 (1.7) | 1 (1.4) |
| **Antiretroviral treatment duration** | | | |
| Short-term (< 60 months) | 298 (63.1) | 243 (60.5) | 55 (78.6) |
| Long-term (≥ 60 months) | 174 (36.9) | 159 (39.6) | 15 (21.4) |
| **Viral load count** | | | |
| < 50 copies/ml | 264 (56) | 233 (58.1) | 31 (44.3) |
| ≥ 50 copies/ml | 119 (25.3) | 101 (25.2) | 18 (25.7) |
| Missing viral load | 88 (18.7) | 67 (16.7) | 21 (30) |

https://doi.org/10.1371/journal.pone.0240529.t001

**Table 2. Maternal characteristics at delivery.**

| Characteristics | Total N = 472 n (%) | Adherent to infant NVP prophylaxis N = 402 (85.2%) n (%) | Non-adherent to infant NVP Prophylaxis N = 70 (14.8%) n (%) |
|---|---|---|---|
| **Onset of labour** | | | |
| Day time | 251 (53.2) | 210 (52.2) | 41 (58.6) |
| Night time | 221 (46.8) | 192 (47.8) | 29 (41.4) |
| **Attendant during delivery** | | | |
| Mother | 89 (18.9) | 72 (17.9) | 17 (24.3) |
| Husband | 109 (23.1) | 102 (25.4) | 7 (10) |
| Mother in law | 76 (16.1) | 61 (15.2) | 15 (21.4) |
| Sibling | 51 (10.8) | 45 (11.2) | 6 (8.6) |
| Other | 147 (31.1) | 122 (30.3) | 25 (35.7) |
| **Type of delivery** | | | |
| Spontaneous vaginal delivery | 413 (87.5) | 350 (87.1) | 63 (90) |
| Caesarean section | 59 (12.5) | 52 (12.9) | 7 (10) |
| **Place of delivery** | | | |
| Clinic setting | 441 (93.4) | 379 (94.3) | 62 (88.7) |
| Non-clinic setting | 31 (6.6) | 23 (5.7) | 8 (11.4) |
| **Mother was given NVP syrup for baby at delivery** | | | |
| Given | 362 (76.7) | 341 (84.8) | 21 (30) |
| Not given | 110 (23.3) | 61 (15.2) | 49 (70) |
| **Maternal adherence to ART** | | | |
| Adhered | 329 (69.7) | 284 (70.7) | 45 (64.3) |
| Did not adhere | 143 (30.3) | 118 (29.3) | 25 (35.7) |

https://doi.org/10.1371/journal.pone.0240529.t002

### Non-adherence among infants at 6 weeks

Based on mothers' recall, 402 of the infants (85.2%, 95% confidence interval (CI): 81.6%–88.3%) missed between zero and two doses of their nevirapine prophylaxis in the 7 days prior to the interview. A total of 70 infants (14.8% 95%CI: 11.7%–18.4%) missed between 3 and 7 doses in the week preceding the interview (Fig 1).

### Barriers and enablers of adherence to infant nevirapine prophylaxis

Barriers to adherence to infant nevirapine prophylaxis were the following maternal characteristics: younger age (≤20 years ARR = 1.55; 95% CI: 1.1–2.2), having missed to have a viral load test done during pregnancy (missing viral load ARR: 1.4; 95% CI: 1.1–1.7) and not receiving nevirapine syrup for the baby after childbirth (ARR = 6.2; 95% CI: 5.1–7.6). Maternal characteristics that enabled infant nevirapine adherence were maternal characteristics that include: having attained 14 or more years of schooling (ARR = 0.7; 95% CI: 0.5–0.9), taking a nevirapine-based regimen (ARR = 0.6; 95% CI: 0.4–0.9), having taken ART for a longer period of time (long-term (≥ 60 months) ARR = 0.75; 95% CI: 0.6–0.9), accompanied by her husband to hospital during labour and childbirth (husband ARR = 0.5; 95% CI: 0.4–0.7) and having labour start during the night-time (ARR = 0.7; 95% CI: 0.6–0.8) (Table 3).

## Discussion

In our study, we found that non-adherence to infant nevirapine prophylaxis was high, 14.8%. We relied on the mother or caregiver's report in measuring adherence of the infant to

**Table 3. Barriers and enablers of adherence to infant to NVP prophylaxis among 6-week-old HIV exposed infants.**

| Variable | Unadjusted RR (95% CI) | Adjusted *RR (95%CI) |
|---|---|---|
| **Age** | | |
| ≤ 20 years | 1.3 (1.1–1.9) | **1.5 (1.1–2.2)** |
| 21–29 years | 1 | 1 |
| 30–39 years | 0.7 (0.6–0.9) | 1.1 (0.9–1.4) |
| ≥ 40 years | 0.1 (0.01–0.5) | 0.2 (0.03–1.3) |
| **Education** | | |
| ≤ 6 years | 1 | 1 |
| 7–13 years | 1.1 (0.9–1.3) | 0.9 (0.8–1.1) |
| ≥ 14 years | 0.7 (0.5–0.9) | **0.7 (0.5–0.9)** |
| **HIV status disclosure** | | |
| Disclosed | 1 | 1 |
| Not disclosed | 2.1 (1.4–3) | 1.3 (0.9–1.9) |
| **Antiretroviral regimen** | | |
| Efavirenz-based | 1 | 1 |
| Nevirapine-based | 0.4 (0.3–0.7) | **0.6 (0.4–0.9)** |
| Protease inhibitor-based | 1.01 (0.4–1.9) | 2.03 (0.98–4.2) |
| **ART duration** | | |
| Short term (<60 months) | 1 | 1 |
| Long term (≥ 60 months) | 0.6 (0.5–0.7) | **0.75 (0.6–0.9)** |
| **Viral load count** | | |
| <50 copies/ml | 1 | 1 |
| ≥ 50 copies/ml | 1.2 (0.9–1.5) | 1.1 (0.9–1.4) |
| Missing viral load | 1.9 (1.5–2.3) | **1.4 (1.1–1.7)** |
| **Time of onset of labour** | | |
| Day time | 1 | **1** |
| Night time | 0.8 (0.7–0.97) | **0.7 (0.6–0.8)** |
| **Attendant during labour and delivery** | | |
| Mother | 1 | 1 |
| Husband | 0.5 (0.4–0.7) | **0.5 (0.4–0.7)** |
| Mother-in-law | 0.8 (0.6–1.1) | 0.8 (0.6–1.1) |
| Sibling | 0.8 (0.6–1.1) | 0.8 (0.6–1.1) |
| Other | 0.9 (0.7–1.1) | 0.9 (0.7–1.2) |
| **Mother was given NVP syrup for baby at delivery** | | |
| Given | 1 | 1 |
| Not given | 6.3 (5.2–7.6) | **6.2 (5.1–7.6)** |
| **Maternal adherence to ART** | | |
| Adhered | 1 | 1 |
| Not adhered | 1.3 (1.1–1.6) | 1.1 (0.9–1.3) |

*__RR>1__ refers to barriers, *__RR<1__ refers to facilitators.

https://doi.org/10.1371/journal.pone.0240529.t003

nevirapine prophylaxis. Studies done in South Africa [9, 13, 19], have reported levels of non-adherence to infant nevirapine prophylaxis ranging from 12.3%–30% within which range the incidence of non-adherence in our study falls. The reported non-adherence rates vary across study contexts because different methods were used while measuring infant adherence. Studies that rely on self-reported or caregiver's report [9, 10] have reported higher levels of non-adherence compared to those that have relied on electronic dose monitoring [9] and plasma

concentration of therapeutic levels of nevirapine in the infant's blood [9, 13]. All these studies measure adherence to infant nevirapine prophylaxis at different time points; some at birth and the majority at 6 weeks while factoring in variable recall periods. As much as this scenario could explain the disparities in rates of non-adherence across the different studies and ours, it is also likely that actual differences in adherence rates do exist in the different study contexts. The high incidence of non-adherence to infant prophylaxis in our study could be explained by the fact that many non-adherent women actually did not receive nevirapine for the baby after delivery.

For the purpose of this discussion we shall focus on barriers and enablers to infant nevirapine adherence that are important for policy. The barriers to infant adherence included younger maternal age, missed viral load test during pregnancy and mother not receiving infant's nevirapine syrup after childbirth. Enablers to adherence included an HEI being born to a woman who: was well-educated ($\geq$14 years of schooling), was taking a nevirapine-based regimen, has been on long-term ART, had a night-time onset of labour and was attended to by the husband during childbirth.

Our study showed that infants born to younger women were less likely to be adherent to their prophylactic treatment. A number of studies have shown similar findings [5, 9, 12]. Most young mothers in our cohort have taken ART for a shorter duration (less than 6 months). This means that their interface with the healthcare system is limited and that they have not had time to receive adequate ART adherence counselling and subsequently less informed about the necessity to adhere to treatment and prophylaxis. This is supported by the fact that babies born to women on long term ART in our cohort were likely to be more adherent to prophylaxis than those born to women on shorter duration of ART. This finding further demonstrates that women who have been on ART for longer periods are aware of the benefits of adherence to ART compared to their counterparts that have been on ART for shorter periods of time due to their frequent and routine interface with the health care system. One study [20] also demonstrated that women who have taken ART for shorter periods were more likely to report side effects of ART and this affected their adherence to ART. While conducting ART adherence counselling, health workers need to pay attention to these younger mothers.

In our study, infants born to women who did not receive nevirapine syrup from the health worker for the baby were likely not to adhere to infant ART prophylaxis. The majority of the women in our cohort who never received nevirapine for the baby actually had a non-clinic delivery, mostly a home delivery. Studies done in Zambia [13], South Africa [19] and a systematic review for sub-Saharan Africa [12] have demonstrated the association between home delivery and non-adherence to infant prophylaxis. Home deliveries have also been associated with the mother not receiving the nevirapine syrup for the baby from the health worker at the time of delivery [10, 12]. Women who have delivered at home may not be able to return to the hospital to pick the infant's syrup for different reasons. Women who deliver outside the hospital are also less likely to receive counselling on the importance of their baby adhering to prophylaxis because they will deliver in the absence of a skilled birth attendant or health worker. Furthermore, HEIs born to women whose labour started in the night were more likely to adhere to nevirapine prophylaxis. Most women in our cohort are multiparous or of higher gravidity. The progress in labour for multiparous women is faster [14]. For women whose labour begins in the night are most likely to deliver during daytime which means they will be able to receive NVP syrup for the baby from the health worker at the PMTCT clinic. The PMTCT clinic is usually closed in the evening and night time in our study setting. Women who do not receive NVP for the baby are most likely not to administer it to the baby [12] and this contributes to non-adherence of the HEI to prophylaxis. An

alternative strategy could be to provide all HIV infected pregnant women with NVP syrup for the baby from the ANC prior to delivery.

Infants born to women who had not had a viral load test done during pregnancy were less likely to adhere to the infant prophylaxis. The main reason for this was because they had been on ART for less than six months [2]. Having had less time in health care, these women have not yet benefitted from the on-going and continuous ART counselling. Women who have taken ART for shorter periods of time remain a critical target for adherence counselling.

In our study, it was shown that infants born to educated mothers were more likely to adhere to their prophylaxis. Educated mothers are more likely to read and comprehend concepts of adherence taught to them during ART adherence counselling sessions and therefore are more likely to support their infants with adherence to prophylaxis. Some studies have shown no association between maternal education and infant adherence to nevirapine prophylaxis [8] while other studies have shown an association between lack of maternal education and low infant nevirapine adherence [10, 12] just like our study.

Women who were taking an NVP-based regimen were more likely to have infants that adhere to infant prophylaxis. In our cohort, women taking NVP-based regimens have taken ART for longer periods of time. The benefits of taking ART for longer durations have already been discussed in the earlier paragraphs.

Women who were accompanied to the hospital by their husbands for labour and delivery were more likely to have infants that were adherent to their prophylaxis. The husband plays a key role in decision making when it comes to newborn care [21]. Male involvement in PMTCT generally improves adherence to the whole PMTCT programme. Other studies have actually demonstrated that male involvement in maternal and child health services promotes adherence to infant nevirapine prophylaxis [12, 22]. This finding evidently shows that if PMTCT programs in our study context and those similar to it promoted male involvement, this would not only enhance adherence to infant prophylaxis but to also the entire PMTCT cascade of interventions.

### Strengths and limitations

Most studies that have been conducted on this subject have been qualitative in nature. With this prospective cohort study we could explore these associations.

We relied on the mother's or caregiver's report for measuring adherence. Measuring medication adherence while relying on self-reporting varies is influenced by how questions are phrased and the period of recall. Our adherence estimates are likely to be over-estimated due to the recall bias and social desirability imposed by the self-reporting [13, 14]. However, other studies have demonstrated correspondence between relying on self-reports and other measures of adherence [9, 23].

Most studies have been conducted in urban settings. Our study was done in a rural context and our findings may only be generalizable to contexts similar to it. The definitions of adherence adopted, the methods used to measure it and recall periods varied across different studies. Therefore, comparing findings across these studies was rather difficult. We did not measure the infant's adherence continuously from birth to six weeks of age considering the limitations of recall over such a long period of time. We also never included infant-related factors like infant refusal or illness that influence adherence to infant prophylaxis.

## Conclusion and recommendations

Despite many mothers receiving nevirapine syrup from the health workers for the infant, non-adherence rates still prevail. The barriers to adherence to infant NVP prophylaxis were in

order of importance: mother not receiving nevirapine syrup for the baby after delivery, young maternal age and having missed to have a viral load test during pregnancy. The health system needs to consider to give HIV infected pregnant women the infant nevirapine syrup before birth to avoid delays and non-adherence. There is also a need to pay particular attention to younger women and those who recently started ART.

## Supporting information

**S1 Data.**
(XLSX)

## Acknowledgments

We are grateful to Lira Regional Referral Hospital, the study participants and the research assistants for their contribution to this survey.

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# IV

GLOBAL HEALTH ACTION
2020, VOL. 13, 1833510
https://doi.org/10.1080/16549716.2020.1833510

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ORIGINAL ARTICLE

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# Exclusive breastfeeding among HIV exposed infants from birth to 14 weeks of life in Lira, Northern Uganda: a prospective cohort study

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**ABSTRACT**

**Background:** Breastfeeding is important for growth, development and survival of HIV exposed infants. Exclusive breastfeeding reduces the risk of morbidity, mortality and increases HIV free survival of infants. Evidence on risk factors for inappropriate breastfeeding in Northern Uganda is limited.

**Objective:** This study determined the risk factors for non-exclusivity of breastfeeding in the first 14 weeks of life.

**Methods:** This prospective cohort study was conducted among 466 mother-infant pairs between August 2018 and February 2020 in Lira district, Northern Uganda. HIV infected pregnant women were enrolled and followed up at delivery, 6- and 14- weeks postpartum. We used a structured questionnaire to obtain data on socio-demographic, reproductive-related, HIV-related characteristics and exclusive breastfeeding. Data were analysed using Stata version 14.0 (StataCorp, College Station, Texas, USA.). We estimated adjusted risk ratios using modified Poisson regression models.

**Results:** The proportion of HIV exposed infants that were exclusively breastfed reduced with increasing age. Risk factors for non-exclusive breastfeeding included infants being born to HIV infected women who: were in the highest socioeconomic strata (adjusted risk ratio = 1.5, 95%CI: 1.01– 2.1), whose delivery was supervised by a non-health worker (adjusted risk ratio = 1.6, 95%CI: 1.01– 2.7) and who had not adhered to their ART during pregnancy (adjusted risk ratio = 1.3, 95%CI: 1.01– 1.7).

**Conclusions:** HIV infected women: with highest socioeconomic status, whose delivery was not supervised by a health worker and who did not adhere to ART were less likely to practice exclusive breastfeeding. We recommend ART adherence and infant feeding counselling to be emphasised among HIV infected women who are at risk of having a home delivery, those with poor ART adherence and those of higher socioeconomic status. We also recommend integration of these services into other settings like homes, community and work places instead of limiting them to hospital settings.

**Abbreviations:** HIV: Human Immunodeficiency Virus; ART: Antiretroviral therapy; HEI: HIV exposed infant; PMTCT: Prevention of mother-to-child transmission of HIV; MTCT: Mother-to-child transmission of HIV; AFASS: Acceptable, Feasible, Affordable, Sustainable and Safe; LRRH: Lira regional referral hospital; CI: confidence interval; ARR: Adjusted risk ratio; SD: Standard deviation; PCA: Principal component analysis

**ARTICLE HISTORY**
Received 2 June 2020
Accepted 5 October 2020

**RESPONSIBLE EDITOR**
Stig Wall, Umeå University, Sweden

**KEYWORDS**
Breastfeeding; exclusive breastfeeding; HIV exposed infants; infant feeding; mixed feeding; Women living with HIV

## Background

Breastfeeding is important for growth, development and survival in children [1]. In HIV exposed infants (HEIs), exclusive breastfeeding is very important because they are more prone to diarrhoea, pneumonia, malnutrition and even death [2] compared to unexposed infants. Various studies have demonstrated the positive impact of breastfeeding on child survival. A number of studies have shown the benefits of breastfeeding which include: lowered risk of incidence and death from infections like diarrhoea and pneumonia [3,4] as well as reduced risk of hospitalisation [5]. Mixed feeding, when compared with exclusive breastfeeding, increases the risk of morbidity and HIV transmission by four fold [6,7] in addition to reducing HIV free survival among HEI [3]. Human breast milk contains various immunoglobulins, proteins, hormones, growth factors, lipids, carbohydrates and microbiota that play a very important role in the immunomodulation, immune-regulation as well as defence against pathogenic bacteria and viruses for the infant/neonate [8]

Guidelines from the World Health Organisation [1,9] and the Ugandan Ministry of Health [10] recommend that an HIV infected woman should breast feed her baby exclusively for the first 6 months and

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continue breastfeeding till the baby is 12–24 months of age while introducing appropriate complimentary foods. In cases where exclusive breastfeeding is not possible, exclusive replacement feeding is recommended provided it follows the AFASS criteria meaning it should be Acceptable, Feasible, Affordable, Sustainable and Safe. Women living with HIV who are lactating should take antiretroviral therapy (ART) regardless of their CD4 count and should be adherent to it [1]. ART helps to prevent HIV transmission during the phase of exclusive breastfeeding in the first 6 months of life and also during mixed feeding thereafter [11].

Barriers to breastfeeding include maternal factors like breast problems, home delivery [12], lack of safe water, cultural beliefs [13] and lack of counselling or support during continuation of infant feeding [6] as well as infant factors such as mouth ulcers [11]. Interventions such as counselling tend to improve exclusive breastfeeding rates [3], however, their implementation has to be broad based and should cover a wide range of settings such as homes, health facilities, communities and work places so as to yield a higher impact on breastfeeding.

Several studies have shown low rates of exclusive breastfeeding among HEI [6,11,12,14-16]. Risk factors for these low rates are not well understood and vary with in different contexts. The settings for these studies have been heterogeneous and tend to vary from country to country. Very few studies have been done in Uganda, particularly Northern Uganda. There is limited information on risk factors for inappropriate breastfeeding by HIV infected women in Lira, Northern Uganda. Therefore, our study aimed to determine the risk factors for non-exclusive breastfeeding in the first 14 weeks of life among HEIs.

## Methods

### Study design and setting

A prospective cohort study was done in Lira, Northern Uganda between August 2018 and February 2020 at the Prevention of Mother-to-Child Transmission (PMTCT) of HIV clinic in the Lira Regional Referral Hospital (LRRH). Lira is home to over 400,000 people who are predominantly Langi. It has a diversified economy characterised mainly by farming, brick making, boda boda (motorcycle) public transportation and pottery [17]. Northern Uganda, particularly Lira, has a very high antenatal HIV prevalence of 13.5% [18] which directly translates into a higher risk of mother-to-child transmission (MTCT) of HIV. The PMTCT clinic is an initiative of the Ugandan Ministry of Health where free HIV care and treatment is offered to HIV-infected pregnant and lactating women. Within this clinic, antenatal care is offered for HIV infected pregnant women every day of the week with the exception of weekends. On a daily basis, health education is given in group sessions only early in the morning to mothers who have come for antenatal care. Health education topics include infant feeding in the context of HIV, adherence to ART, viral load testing, maternal nutrition and malaria prevention.

### Participants and procedures

This study involved HIV infected women and their infants. At baseline, HIV infected pregnant women who were receiving antenatal care at LRRH with a gestational age of 20 weeks or more were consecutively enrolled onto the study and interviewed on socio-demographic and HIV-related information. A viral load test was done during any stage of pregnancy. The date of delivery was estimated using the palpation method, gestational wheel and first day of the last normal menstrual period. These women were then followed up with a telephone interview around the time of delivery. This follow-up visit was estimated at 7 days after the expected date of delivery. If the woman had not delivered yet, another telephone appointment was scheduled. At this point, women were interviewed on circumstances surrounding labour and delivery such as time of onset of labour, type of delivery, place of delivery, person who supervised the delivery, if the baby received any prelacteal feeds as well as maternal ART adherence. At 6 weeks postpartum, mothers were followed up with a face-to-face interview and asked about the infant's adherence to nevirapine prophylaxis and exclusivity of breastfeeding. When the infant was 14 weeks of age, women were also asked about exclusivity of breastfeeding through a face-to-face interview. We used a 7-day recall for and obtained information about exclusivity of breastfeeding at the different follow up points from when the infant was born to 14 weeks of age [19]. All study follow-up visits with the exception of delivery were done at the PMTCT clinic. The study visits were conveniently planned to coincide with the mothers' ART refills and the infants' immunisation schedule. We scheduled the study visits this way so that the mothers did not have to make extra visits to the clinic just for purposes of the study and in so doing we saved on extra transportation costs for the participants.

### 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 80% power, 95% confidence interval (CI) and a 5% precision. We also assumed that 70% of women [20] received EBF support and counselling at delivery and that 42.5% of women were not advised or counselled on exclusive breastfeeding during pregnancy [21]. We made these assumptions in order obtain the minimum sample size required to detect a difference between

exclusive breastfeeding and non-exclusive breastfeeding. The total sample size for this study was 418 HEI. After accounting for 10% non-response the final sample size was 464. We however, included 466 HEI.

### Measurement of variables

Prelacteal feeding was defined as the baby feeding on any liquid other than breast milk immediately after birth with the exception of medicines like nevirapine syrup. The mother was asked, 'After delivery, did you give the baby anything before giving him/her breast milk?' This was a 'yes' or 'no' response. We, however, did not ask which liquids had been given to the baby as pre-lacteal feeds. For both the 6-week and 14-week visits, the mother was asked, 'In the past week, have you given the baby any liquid or solid food other than the breast milk?' This was also a 'yes' or 'no' response. If the mother's response was 'yes', then she was asked, 'What food or liquid did you feed to the baby'. The baby was considered to be non-exclusively breastfed if the mother had reported giving prelacteal feeds at birth or if the mother had reported giving liquids or solid food other than breast milk at the 6-week and 14-week visits with the exception of medicines such as nevirapine or supplements like multivitamins.

We also measured maternal ART adherence during the follow-up at the time of delivery, we asked the mother, 'In the past week, did you miss taking any dose of your medication?' This was a 'yes' or 'no' response. If the mother answered 'yes' she was considered 'non-adherent'. We also asked who had assisted her during delivery and if she responded that it was a nurse, doctor, student nurse, clinical officer, midwife, all these responses were categorised into one group and labelled 'birth supervised by health worker'. If the response was 'mother-in-law, traditional birth attendant, or good samaritan' all these responses were categorised together and labelled 'birth supervised by non-health worker'

We created a composite index of wealth (socio-economic status) using principle component analysis (PCA). We used PCA on house ownership, availability of electricity in the house, source of drinking water and fuel used for cooking [22]. Scores were obtained and categorized into three groups which we refer to as strata ranging from the poorest to the least poor.

### Data analysis and management

Data were collected using pretested, structured questionnaires, doubly entered into Epi data (www.epidata.dk, version 4.4.3.1) and exported for analysis to Stata version 14.0 (StataCorp, College Station, Texas, USA.). Only mother-infant pairs with data at the three time points of follow-up were included in the analysis. Continuous data, if normally distributed, was summarised into means and standard deviations and if skewed, was summarised into medians with their corresponding interquartile ranges. Categorical variables were summarised into frequencies and percentages. The incidence of non-exclusivity of breastfeeding was estimated and its confidence limits calculated using the exact method. Bivariable and multivariable analysis was done using the modified Poisson regression model [23]. All variables that had a p value < 0.25 at bivariable level and those with biological plausibility were entered into the multivariable model. Variables that were independently associated with non-exclusivity of breastfeeding were determined using the confidence limits.

## Results

A total of 518 HIV infected women were enrolled on to the study and followed up till delivery at which point 505 women had given birth to their infants. These women then were followed up till 6 weeks postpartum at which point 472 women and their infants had the required data on exclusivity of breastfeeding. Complete information was obtained for 466 mothers by 14 weeks and these were included in our analysis. The reasons for loss to follow up of participants at subsequent visits are explained in the study flow chart (Figure 1)

### Characteristics of HIV infected pregnant women at baseline

Almost fifty per cent of the women were aged 30 years or more with a mean age of 29.5 years (Standard deviation (SD) 5.4). Most women were married, unemployed and had attained at least 6 years of education (Table 1).

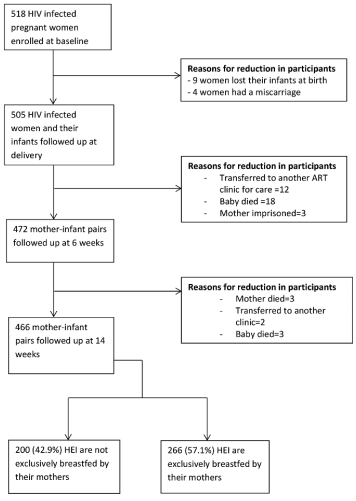


**Figure 1.** Study flow chart.

**Table 1.** Antenatal baseline characteristics for HIV infected women in the study in relation to breastfeeding at 14 weeks postpartum.

| | Total N = 466 n (%) | Exclusive breastfeeding at 14 weeks postpartum N = 266 n (%) | Not exclusive breastfeeding at 14 weeks postpartum N = 200 n (%) | P-value |
|---|---|---|---|---|
| **DURING PREGNANCY** | | | | |
| **Age** | | | | 0.5 |
| ≤ 20 years | 27 (5.8) | 13 (4.9) | 14 (7) | |
| 21– 29 years | 202 (43.3) | 120 (45.1) | 82 (41) | |
| ≥ 30 years | 237 (50.9) | 133 (50) | 104 (52) | |
| **Education status** | | | | 0.9 |
| ≤ 6 years | 229 (49.1) | 131 (49.3) | 98 (49) | |
| 7– 13 years | 166 (35.6) | 96 (36.1) | 70 (35) | |
| ≥ 14 years | 71 (15.3) | 39 (14.6) | 32 (16) | |
| **Marital status** | | | | 0.9 |
| Married | 435 (93.4) | 248 (93.2) | 187 (93.5) | |
| Single | 31 (6.6) | 18 (6.8) | 13 (6.5) | |
| **Employment status** | | | | 0.1 |
| Employed | 189 (40.6) | 100 (37.6) | 89 (44.5) | |
| Unemployed | 277 (59.4) | 166 (62.4) | 111 (55.5) | |
| **Religion** | | | | 0.04 |
| Christian | 448 (96.1) | 260 (97.7) | 188 (94) | |
| Moslem | 18 (3.9) | 6 (2.3) | 12 (6) | |
| **Ethnic belonging** | | | | 0.8 |
| Lango | 424 (90.9) | 243 (91.4) | 181 (90.5) | |
| Other | 42 (9.1) | 23 (8.6) | 19 (9.5) | |
| **Parity** | | | | 0.8 |
| 1 to 4 | 329 (70.6) | 189 (71.1) | 140 (70) | |
| 5 to 9 | 137 (29.4) | 77 (28.9) | 60 (30) | |
| **Gestational age** | | | | 0.3 |
| 20– 27 weeks | 243 (52.2) | 133 (50) | 110 (55) | |
| 28– 35 weeks | 158 (33.9) | 98 (36.8) | 60 (30) | |
| ≥ 36 weeks | 65 (13.9) | 35 (13.2) | 30 (15) | |
| **HIV disclosure** | | | | 0.8 |
| Disclosed | 451 (96.8) | 257 (96.6) | 194 (97) | |
| Not disclosed | 15 (3.2) | 9 (3.4) | 6 (3) | |
| **Socioeconomic strata** | | | | 0.06 |
| Lowest | 164 (35.2) | 105 (39.5) | 59 (29.5) | |
| Middle | 147 (31.5) | 82 (30.8) | 65 (32.5) | |
| Highest | 155 (33.3) | 79 (29.7) | 76 (38) | |
| **Antiretroviral regimen** | | | | 0.7 |
| Efavirenz-based | 420 (90.1) | 237 (89.1) | 183 (21.5) | |
| Nevirapine-based | 38 (8.2) | 24 (9.0) | 14 (7) | |
| Protease inhibitor-based | 8 (1.7) | 5 (1.9) | 3 (1.5) | |
| **Antiretroviral treatment duration** | | | | 0.08 |
| ≤ 6 months | 82 (17.6) | 46 (17.3) | 36 (18) | |
| 7– 30 months | 101 (21.7) | 50 (18.8) | 51 (25.5) | |
| 31– 119 months | 251 (53.8) | 146 (54.9) | 105 (52.5) | |
| ≥ 120 months | 32 (6.9) | 24 (9) | 8 (40) | |
| **Viral load count** | | | | 0.7 |
| <50 copies/ml | 264 (56.8) | 150 (56.6) | 114 (57) | |
| 50– 400 copies/ml | 76 (16.3) | 43 (16.2) | 33 (16.5) | |
| 401– 499 copies/ml | 12 (2.6) | 8 (3) | 4 (2.0) | |
| >1000 copies/ml | 27 (5.8) | 18 (6.8) | 9 (4.5) | |
| missing viral load | 86 (18.5) | 46 (17.4) | 40 (20.0) | |

More than half had been pregnant four times and were 20– 27 weeks of gestation at enrolment. Most of the women had disclosed their HIV status. A considerable proportion of them were taking an efavirenz-based regimen and more than half had a viral load less than 50 copies/ml.

### *Characteristics at birth and 6 weeks postpartum*

Most of the mothers had their labour start during the day time and had a spontaneous vaginal delivery (Table 2). Three quarters of them delivered in a hospital setting with most deliveries being supervised by a health worker. Almost a third of these women did not adhere to their antiretroviral treatment in the week preceding delivery. Thirty per cent of 6-week old infants missed receiving one or more doses of the nevirapine prophylaxis from their mother or caregiver.

### *Infant feeding practices at delivery, 6 and 14 weeks postpartum*

The proportion of infants that were exclusively breastfed reduced with increasing age of the infant (Figure 2). Incidence of pre-lacteal feeding at birth was 12.7% (95%CI: 9.8–16%) (Table 2). The incidence of non-exclusivity of breastfeeding at 6 weeks and 14 weeks

**Table 2.** Characteristics for HIV infected pregnant women and HIV exposed infants at the time of delivery and 6 weeks postpartum.

| | Total N = 466 n (%) | Exclusive breastfeeding at 14 weeks postpartum N = 266 n (%) | Mix feeding at 14 weeks postpartum N = 200 n (%) | P-value |
|---|---|---|---|---|
| **AT DELIVERY** | | | | |
| **Time of onset of labour** | | | | 0.5 |
| Day time | 243 (52.2) | 135 (50.8) | 108 (54) | |
| Night time | 223 (47.8) | 131 (49.2) | 92 (46) | |
| **Type of delivery** | | | | 0.06 |
| Spontaneous vaginal | 409 (87.8) | 240 (90.2) | 169 (84.5) | |
| Caesarean section | 57 (12.2) | 26 (9.8) | 31 (15.5) | |
| **Place of delivery** | | | | 0.3 |
| Hospital setting | 435 (93.4) | 251 (94.4) | 184 (92) | |
| Non hospital setting | 31 (6.6) | 15 (5.6) | 16 (8) | |
| **Person who supervised delivery** | | | | 0.05 |
| Health worker | 436 (93.6) | 254 (95.5) | 182 (91) | |
| Non health worker | 30 (6.4) | 12 (4.5) | 18 (9) | |
| **Infant given prelacteal feeds** | | | | 0.000 |
| Yes | 59 (12.7) | 0 (0) | 59 (29.5) | |
| No | 407 (87.3) | 266 (100) | 141 (70.5) | |
| **Maternal adherence to antiretroviral treatment** | | | | 0.06 |
| Adhered | 325 (69.9) | 195 (73.3) | 130 (65.3) | |
| Did not adhere | 140 (30.1) | 71 (26.7) | 69 (34.7) | |
| **AT 6 WEEKS POSTPARTUM** | | | | |
| **Infant adherence to nevirapine prophylaxis** | | | | 0.03 |
| Adhered | 317 (68.1) | 192 (72.2) | 125 (62.5) | |
| Did not adhere | 149 (30.1) | 74 (27.8) | 75 (37.5) | |
| **Infant exclusive breastfeeds at 6 weeks** | | | | 0.000 |
| Exclusively breastfed | 361 (77.5) | 266 (100) | 95 (47.5) | |
| Mixed feeding | 105 (22.5) | 0 (0) | 105 (52.5) | |

postpartum were 22.5% (95%CI: 18.8–26.6%) and 42.9% (95%CI: 38.3–47.5%) respectively (Table 3). By the time the infants were 14 weeks of age, almost half of them were not exclusively breastfeeding (Table 3).

### *Risk factors for non-exclusivity of breast feeding at 14 weeks of age*

Women who were in the highest socioeconomic strata were 50% more likely to give their infants liquids other than breast milk when compared to those in the lowest socioeconomic strata (Adjusted Risk ratio (ARR) = 1.5, 95%CI: 1.01– 2.1). Women whose delivery was supervised by a non-health worker were 60% more likely to practice mixed feeding when compared to those whose delivery had been supervised by a health worker (ARR = 1.6, 95%CI: 1.01– 2.7). Women who had not adhered to their ART during pregnancy were also likely to practice mixed feeding for their infants when compared to their adherent counterparts (ARR = 1.3, 95%CI: 1.01– 1.7) (Table 4).

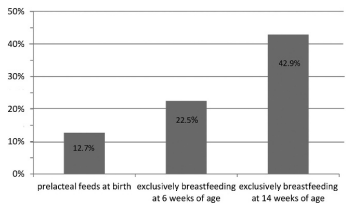


**Figure 2.** Infant feeding practices among HIV exposed infants by HIV infected lactating women.

**Table 3.** Feeds given to HIV exposed infants at 6 weeks and 14 weeks postpartum.

| | Feeds given to infants at 6 weeks postpartum (N = 466) | | Feeds given to infants at 14 weeks postpartum (N = 466) | |
|---|---|---|---|---|
| Type of infant's feed | **n** | **%** | **n** | **%** |
| Only breast milk | 361 | 77.5 | 266 | 57.1 |
| Honey | 55 | 11.8 | 44 | 9.4 |
| Water | 23 | 4.9 | 36 | 7.7 |
| Cow's milk | 13 | 2.8 | 70 | 15 |
| Soup | 6 | 1.3 | 17 | 3.7 |
| Porridge | 5 | 1.1 | 21 | 4.5 |
| Infant formula | 3 | 0.6 | | |
| Juice | | | 11 | 2.4 |
| Solid food | | | 1 | 0.2 |

**Table 4.** Risk factors for non-exclusivity of breastfeeding among HIV exposed infants at 14 weeks postpartum.

| | Unadjusted RR (95% CI) | Adjusted RR (95% CI) |
|---|---|---|
| **Age** | | |
| ≤ 20 years | 1.2 (0.7 – 2.1) | 1.1 (0.6 – 2) |
| 21 – 29 years | 0.9 (0.7 – 1.2) | 0.8 (0.6 – 1.2) |
| ≥ 30 years | 1 | 1 |
| **Education status** | | |
| ≤ 6 years | 1 | 1 |
| 7 – 13 years | 1.0 (0.7 – 1.3) | 0.9 (0.7 – 1.3) |
| ≥ 14 years | 1.1 (0.7 – 1.6) | 1.01 (0.7 – 1.5) |
| **Parity** | | |
| 0 to 4 | 1 | 1 |
| 5 to 9 | 1.01 (0.8 – 1.4) | 1.0 (0.7 – 1.4) |
| **Socioeconomic status** | | |
| Lowest | 1 | 1 |
| Middle | 1.2 (0.9 – 1.8) | 1.3 (0.9 – 1.8) |
| Top | 1.4 (0.9 – 1.9) | **1.5 (1.01 – 2.1)** |
| **Antiretroviral treatment duration** | | |
| ≤ 6 months | 1 | 1 |
| 7 – 30 months | 1.2 (0.8 – 1.8) | 1.27 (0.8 – 2) |
| 31 – 119 months | 0.9 (0.7 – 1.4) | 1.0 (0.7 – 1.6) |
| ≥ 120 months | 0.6 (0.3 – 1.2) | 0.6 (0.3 – 1.3) |
| **Person who supervised delivery** | | |
| Health worker | 1 | 1 |
| Non health worker | 1.4 (0.9 – 2.3) | **1.6 (1.01 – 2.7)** |
| **Maternal adherence to antiretroviral treatment** | | |
| Adhered | 1 | 1 |
| Did not adhere | 1.2 (0.9 – 1.7) | **1.3 (1.01 – 1.7)** |

## Discussion

The proportion of infants that were exclusively breastfed reduced with increasing age of the infant and by 14 weeks of age, almost half of the infants were not exclusively breastfeeding. We found a low incidence of EBF among 14 week-old HEIs probably because their mothers perceive that their breast milk is so insufficient that it will not satisfy the baby and so resort to other foods as feeding options for the infant such as cow's milk, water and porridge [21]. Cultural beliefs surrounding breastfeeding also influence infant feeding practices, for example, believing that giving the baby honey will protect them against false teeth and colic pain [24]. Giving the baby prelacteal feeds also contributed to the incidence of non-EBF. Studies from South Africa [6] and Nigeria [14] report a similar trend in exclusive breastfeeding among HIV exposed infants as they grow older. Some systematic reviews [12,16] and observational studies [11,15] have reported rates similar to that in our study. However one study from Tanzania [25] reported a higher prevalence of exclusive breastfeeding than our study. These disparities could be explained by the fact that all these studies included infants of varying ages and were done in different sociocultural contexts.

It was common for mothers to give their infants prelacteal feeds after delivery. Women are most likely to give their babies prelacteal feeds because of sore breasts, perceived insufficient milk flow immediately after delivery, social and cultural issues like discarding of colostrum [21]. Several studies of HEI infants [11] demonstrate that mothers give infants these feeds due to insufficient breast milk shortly after delivery, because of breast problems or maternal death. One study from Northern Uganda, a context similar to our study, showed that lactating women discard colostrum shortly after delivery because they culturally perceive it to be dirty and harmful to the baby [21]. This could possibly explain why infants in our cohort were given prelacteal feeds. An infant missing out on colostrum misses out on the essential benefits like building up of their immune system and lining of the infant's gut to keep pathogens at bay. This is a potential risk for mother-to-child transmission of HIV and development of opportunistic infections.

In our cohort, women of the highest socioeconomic status were more likely not to exclusively breastfeed their infants when compared to those in the lowest socioeconomic strata. One study [26] demonstrated an association between socioeconomic status and exclusive breast feeding. Most women in the top most socioeconomic strata in our cohort were actually employed and probably had to return to work shortly after delivery because of work-related demands and pressures. Furthermore, because of work-related demands these women are more likely not to receive adequate antenatal care and infant feeding counselling and this could explain the finding in our study. In our study setting, infant feeding counselling has also not been integrated with workplace environments. Therefore, women with busy work schedules are less likely to receive infant feeding counselling.

Women whose delivery was supervised by a non-health worker were less likely to exclusively breastfeed and were likely to have had a home delivery. Having a home delivery deprives the mother of interfacing with the health worker and healthcare there by losing out on the benefits of counselling and support for exclusive breastfeeding. Some systematic reviews [3,12,16] and observational studies [11,15,21] showed that women who attended antenatal care clinics, those that delivered in a hospital and those that had infant adherence counselling were more likely to practice exclusive breastfeeding. In a hospital setting, there is on-going infant feeding training for the healthcare worker and infant feeding counselling for the mother. Another study from Northern Uganda [24] found that health workers were key decision makers when it came to breastfeeding. These findings from various studies clearly explain why a mother whose delivery is not supervised by a health worker is most likely not to exclusively breastfeed her infant. In light of this, it is important that infant feeding counselling is introduced in a combination of settings and not only at health facilities: such as at the facility, work place, community and home settings.

Our study demonstrated that women who had not adhered to ART during pregnancy were also likely not to exclusively breastfeed their infants. Being non-adherent to ART is an aftermath of not interfacing routinely with the healthcare system [27]. Therefore, these women will not achieve the benefits of this routine interaction with the healthcare system like continued counselling on infant feeding. Women who are non-adherent to ART will hence most likely not be adherent to infant feeding guidelines and will not exclusively breastfeed their infants. Non-adherence to ART will lead to higher viral loads and advanced HIV disease which poses a high risk for transmission of HIV from a mother to her baby during breastfeeding. Few studies have examined antiretroviral adherence during pregnancy and its association with infant feeding practices. However, pregnancy in itself has been associated with low ART adherence [28]. Drug-related factors such as side effects and pill burden as well as physiological changes during pregnancy are barriers to ART adherence [29]. More qualitative studies should be done to shed more light on the association between ART adherence and breastfeeding.

### *Strengths and limitations*

This study had some strength. The fact that this is a prospective cohort study has helped to establish causality between various covariates and non-exclusivity of breastfeeding. Most studies that have been conducted on this subject matter have been cross-sectional in nature and only show associations. Showing causality for inappropriate infant feeding paves the way to the designing of interventions to promote exclusive breastfeeding. We also measured exclusive breastfeeding continuously from birth and also relied on a 7-day recall which is likely to avoid exaggeration of the incidence of exclusive breastfeeding in our cohort. To minimize loss to follow-up, we documented the telephone contacts and residential mapping of each participant. Instances where we could not reach the participant on phone, we made a home visit and this resulted into a high completion rate of 94%.

Our study had some limitations. This study was done among HIV infected women attending a public health facility therefore our findings may not be generalizable to women attending clinics that are private-for-profit and private-not-for profit. We measured exclusive breastfeeding at 6 and 14 weeks using a 7-day recall of the mother or care giver. This can potentially be a source for recall bias.

## Conclusion

The proportion of exclusively breastfed HEI reduced with increase in the infant's age. HIV infected women with highest socioeconomic status, those whose delivery was not supervised by a health worker and those that who did not adhere to antiretroviral treatment were likely not to exclusively breastfeed their infants. We recommend ART adherence and infant feeding counselling to be emphasised and integrated in a diverse settings such as homes, work places, communities and health facilities.

## Acknowledgments

We are grateful to Lira regional referral hospital, the study participants and the research assistants for their contribution to this survey.

## Author contributions

Conception and design of work – AN, JKT, GN, PW and TT; Drafting of work, data acquisition, analysis and interpretation – AN, JKT, TT, GN and DM; Funding acquisition JKT, GN, PW and TT; Methodology, AN, JKT and TT; Project administration, JKT, GN, PW and TT; Resources, JKT, GN, PW and TT; Supervision, JKT, GN, PW and TT; Writing – original draft, AN; Writing – review & editing, final approval of version to be approved – AN, JKT, DM, GN, PW and TT. Accountable for all aspects of the work - AN, JKT, DM, GN, PW

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Ethics and consent

Approval to conduct the study was granted by the Makerere University School of Medicine Research and Ethics Committee SOMREC: Ethical approval number: REC REF No. 2017-004;

Date of approval: 10 January 2018; the Uganda National Council for Science and Technology: Ethical approval number: HS222ES; Date of approval: 24 September 2018; and the Norwegian Regional Committee for Medical and Health Research Ethics in the West (Ethical approval number: 2017/2489/REK vest; Date of approval: 26 January 2018) Administrative clearance was granted by the Lira district health office and LRRH. Service providers/counselors 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 penalized or denied standard healthcare Confidentiality and privacy of all data collected were observed during the course of the study through restricted access.

## Funding information

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).

## Paper context

Exclusive breastfeeding reduces the risk of morbidity, mortality and increases HIV-free survival of infants. Evidence on risk factors for inappropriate breastfeeding in Northern Uganda is limited. We therefore aimed to study risk factors for non-exclusivity of breastfeeding among HIV-exposed infants. Findings from this study have identified high-risk women for inappropriate breastfeeding. These women can now be targeted for counselling during the implementation of infant feeding policies in the context of HIV.

## Data availability

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

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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS


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ISBN: 9788230863626 (print)
9788230866269 (PDF)