
Out of the

Division of Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich (LMU), Germany

# Retention-in-Care, Adherence and Treatment outcomes in a cohort of HIV-positive pregnant and breastfeeding women enrolled in a pilot project implementing "Option B+" in Cameroon.

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submitted by

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I hereby declare, that the submitted thesis entitled

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**Keywords**

Preventing mother-to-child transmission, Option B+, Retention-in-care, Adherence, Cameroon

**Abstract**

**Introduction**

Retention-in-care and adherence to lifelong antiretroviral therapy (ART) are major requirements to successfully optimise treatment benefits. We assessed linkage and retention-in-care with adherence and determinants of poor adherence along the PMTCT cascade in HIV-positive pregnant and breastfeeding women initiating option B+ in Cameroon.

**Materials and Methods**

We prospectively determined uptake of HIV testing and counselling (HTC), uptake of ART, retention-in-care and adherence after Option B+ initiation between October 2013 and December 2014 in pregnant and breastfeeding women from five sites within the Kumba Health District. Retention-in-care was assessed over at least 12 months follow-up and estimated by Kaplan Meier analysis. Adherence at 12 months was determined for women retained in care using a composite adherence score. During follow-up, tracing outcomes and reasons for discontinuing treatment were documented and adherence measured.

**Results**

Uptake of HTC in 5,813 women with unknown HIV status was 98.5% and ART uptake in women eligible to start Option B+ was 96.8%. We enrolled 268 women initiating lifelong ART in the follow-up. Overall, 65 (24.3%) discontinued treatment, either defined by loss to follow-up 29(44.6%) or actively stopped treatment 36(55.8%). Retention-in-care was 88.0% and 81.1% at 6 and 12 months, respectively. Discontinuation was significantly associated in multivariate analysis with small sites and high staff turnover [aOR 2.5 (95% CI 1.6, 3.9), $p < 0.001$]. At 12 months 88.6% of women retained in care had good treatment adherence. After adjusting for confounders, younger age, attending a Pentecostal church, low level of education and employment in the informal sector significantly predicted poor adherence.

**Conclusion**

Twelve months retention-in-care and adherence for women retained were 81.1% and 88.6% respectively. Retention-in-care was lowest at small facilities with a high staff turnover while adherence was poor for younger, women with low level of education, attending Pentecostal churches and employed in the informal sector.

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| | |
|---|---|
| 3TC | Lamivudine |
| ABC | Abacavir |
| ACTG | AIDS Clinical Trial Group |
| AIDS | Acquired Immune Deficiency Virus |
| ANC | Antenatal care |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral |
| AZT | Zidovudine |
| CAM | Composite adherence measure |
| CAS | Composite adherence score |
| CBCHS | Cameroon Baptist Convention Health Services |
| CCR5 | Chemokine Receptor 5 |
| CD4 | Cluster Designation 4 |
| CDC | United States Center for Disease Control and Prevention |
| CHAI | Clinton Health Access Initiative |
| CI | Confidence Interval |
| CNLS | National AIDS Control Committee |
| CRF | Circulating recombinant forms |
| CTL | Cytotoxic CD8+ T-lymphocytes |
| CTX | Contrimoxazole |

| | |
|---|---|
| CXCR4 | Chemokine Receptor 4 |
| DBS | Dried Blood Spot |
| ddI | Didanosine |
| DHS | District Health Service |
| DNA | Deoxyribonucleic Acid |
| DOT | Direct Observed Therapy |
| EBV | Epstein-Barr virus |
| EDM | Electronic Drug Monitoring |
| EFV | Efavirenz |
| EGPAF | Elizaberth Glasier Pediatric AIDS Foundation |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| FTC | Emtricitabine |
| GALT | Gut associated lymphoid tissues |
| GHSS | Global Health Systems Solutions |
| HAART | Highly Active Antiretroviral Therapy |
| HEI | HIV exposed infant |
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leucocyte antigen |
| HPTN | HIV Prevention Trials Network |

| | |
|---|---|
| HR | Hazard Ratio |
| HTC | HIV testing and counselling |
| IDU | Intravenous drug use |
| IDV | Indinavir |
| INS | National Institute of Statistics |
| INSPIRE | INtegrating and Scaling-up PMTCT through Implementation REsearch |
| IWC | Infant welfare clinic |
| LMIC | Low and middle income country |
| LMP | Last Menstrual Period |
| LOD | Lower limit of detection |
| LTFU | Loss to follow up |
| MEMS | Medication Electronic Monitoring System |
| MOPH | Ministry of Public Health |
| MSM | Men sex men |
| MTCT | Mother-to-child transmission |
| NFV | Nelfinavir |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| NRTI | Nucleoside Reverse Transcriptase Inhibitor |
| NtRTI | Nucleotide Reverse Transcriptase Inhibitor |
| OR | Odd Ratio |

| | |
|---|---|
| PAM | Pharmacy adherence measure |
| PC | Pill count |
| PCR | Polymerase Chain Reaction |
| PE | Peer educator |
| PEPFAR | President Emergency Plan For AIDS Relief |
| PI | Protease Inhibitor |
| PLHIV | People living with HIV |
| PMTCT | Prevention of Mother-To-Child Transmission |
| POC | Point of care |
| RNA | Ribonucleic Acid |
| sdNVP | Single dose Nevirapine |
| SMS | Short Message Service |
| SQV | Saquinavir |
| STI | Sexually Transmitted Infections |
| TB | Tuberculosis |
| TDF | Tenofovir |
| TELE | Tenofovir, lamivudine, efavirenz |
| ULQ | Upper limit of quantification |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| UNICEF | United Nation Children Emergency Fund |
| VAS | Visual analogue scale |
| VL | Viral load |
| WHO | World Health Organisation |

## 1. Introduction

### 1.1 Background

Prevention of mother-to-child transmission (PMTCT) services have been part and parcel of most national HIV control programmes though their implementation has varied greatly across countries and over time. New HIV infection among children and maternal and child deaths have significantly dropped in high-income countries but the milestones so far reached in low- and middle-income countries leave much to be desired (UNAIDS, 2014b).
If HIV-positive pregnant women in Africa have access to quality, life-saving antiretroviral drugs for their health or as prophylaxis to prevent HIV transmission during pregnancy, delivery and breastfeeding, HIV transmission can be reduced to less than 5% (UNAIDS, 2015; UNICEF, 2012). A randomized control trial of pregnant and breastfeeding women on highly active antiretroviral therapy (HAART) in Botswana produced a rate of mother-to-child-transmission (MTCT) monitored at 6 months after birth of 1.1% (Shapiro *et al*., 2010).

In 2011 the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched an ambitious programme to eliminate new HIV infections among children while keeping their mothers alive (UNAIDS, 2014b). This was known as the global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive, which covered all low- and middle-income countries but with special focus on 22 countries with the highest number of pregnant women living with HIV. These countries which later on became known as the priority countries of the global plan are all found in sub-Saharan Africa but for India. More global and national commitments are needed in sub-Saharan African countries with over 90% of pregnant women living with HIV in need of comprehensive PMTCT services (UNAIDS, 2014b).

The Global Plan over-arching goals states, “Global goal 1: Reduce the number of new HIV infections among children by 90% and Global goal 2: Reduce the number of AIDS-related maternal deaths by 50%” (UNAIDS, 2014b).

At the end of 2015 despite all the concerted efforts put in place by the World Health Organisation (WHO) in consultation with partner organisations these goals were far from being met (UNAIDS, 2016a). A lot has been done to come up with the most efficacious treatment regimen for HIV-positive pregnant women and their babies (WHO, 2013). However, these efforts towards universal expansion of ART coverage with the most effective regimens have been constrained by limited resources. These efforts were progressively put in place and in 2010, the WHO recommended two PMTCT options for HIV-positive pregnant and breastfeeding women not eligible for lifelong ART based on clinical and/or immunologic criteria as follows:

- The first option (Option A) includes maternal Zidovudine (AZT) from 14 weeks of pregnancy, plus single-dose Nevirapine plus Zidovudine and Lamivudine (AZT/3TC) during labour and delivery and one week of AZT/3TC postpartum with Nevirapine syrup for the infant from birth till cessation of breastfeeding.
- The second option (Option B) introduced the use of triple ARVs (based on recommended first-line ART) to the mother from 14 weeks of pregnancy through labour, delivery and until cessation of breastfeeding. (WHO, 2010)

By 2011, UNAIDS estimated that only 57% of HIV-infected pregnant women in low and middle-income countries received the WHO–recommended PMTCT regimens and that same year, an estimated 300,000 infants acquired HIV infection from their mothers in sub-Saharan Africa (WHO, 2011).

In 2011, the Malawian Ministry of Health, after evaluating its ARV coverage in PMTCT and recognising the challenges with CD4+ T-cell based testing required to implement the WHO recommendation, decided to adopt a pragmatic and ambitious public health approach to improve the low PMTCT ART coverage in Malawi known as “Option B+”(CDC, 2013). With Option B+ all HIV-infected pregnant and breastfeeding women are immediately initiated on lifelong ART, regardless of clinical stage or CD4+ T-cell count. Option B+ has come to eliminate the previous complex PMTCT algorithms, which relied on CD4 testing and ART

start and stop with each pregnancy with Option B, thus simplifying the PMTCT process, with expected important health and social benefits for HIV-infected women, their HIV-exposed infants, and their HIV-uninfected sex partners (Ahmed, Kim, & Abrams, 2013; M. S. Cohen et al., 2011; Schouten et al., 2011).

The WHO/UNAIDS recommendations of 2011 aimed at a final MTCT of 5% or less in breastfeeding populations and 2% or less in non-breastfeeding populations (UNAIDS, 2014b). Reaching these objectives in the low resource countries had been daunting and required extra efforts and more commitment from the national governments. Many African countries adopted one or the other of the WHO recommendations and their choices were more or less driven by cost and logistics and not the efficacy of the regimen. It was for this reason that most of the countries including Cameroon opted for the less costly option A. However, it soon became clear that this option was more complicated and less cost-effective in the long run (Gopalappa, Stover, Shaffer, & Mahy, 2014). In 2013 the WHO issued the first consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in which it recommended immediate ART for all HIV-positive pregnant and breastfeeding women irrespective of clinical stage or CD4+ T-cell count (WHO, 2013). In 2016, WHO further expanded the eligibility criteria and now recommended test and treat for all but with special emphasis on pregnant women, children and key populations (WHO, 2016).

Although early results from Malawi and elsewhere indicate an important increase in ART initiation for the target population and cost effectiveness of Option B+ (Fasawe *et al*., 2013; Gopalappa *et al*., 2014; VanDeusen, Paintsil, Agyarko-Poku, & Long, 2015), important concerns still remain on safety, ethical issues including preferences for treatment options, sub-optimal adherence and retention, with the possibility of increased postpartum transmission and HIV drug resistance development (Coutsoudis *et al.*, 2013; Ngarina *et al.*, 2014).

## 1.2 Problem Statement

Since the launch of the Global plan by UNAIDS in 2011, the number of new HIV infections among children has declined by 60% between 2009 (year of baseline) and 2015 in the 21 Global Plan priority countries compared to 13% decline between 2000 and 2008 (UNAIDS, 2016a). This marked decline in MTCT is due to the increasing access by HIV-positive pregnant women to lifelong antiretroviral therapy especially with the introduction of Option B+ (CDC, 2013; WHO, 2013, 2016) which has been progressively implemented in most of the Global plan priority countries. Twelve of these countries had already achieved or were close to achieving full national implementation.

According to the 2016 Global plan progress report, ARV coverage increased from 37% in 2009 to 80% at the end of 2015 in the Global plan priority countries. On the other hand the same report showed that MTCT in 2014 was 4.7% at six weeks but this rose to 8.9% at the end of breastfeeding (UNAIDS, 2016a). This strongly indicated that most of the new infections occurred during the breastfeeding period which is more than twice the new infections during pregnancy, labour and delivery (Ngoma *et al.*, 2015). This residual transmission is highly blamed on the reduced adherence and retention-in-care during the breastfeeding period due to the poor systems available to follow-up mothers postpartum thus leaving the infants vulnerable to acquiring infection (Ebuy, Yebyo, & Alemayehu, 2014; Tenthani *et al.*, 2014; Tweya *et al.*, 2014). In a South African study looking at barriers to retention in Option B+ care among postpartum women, the participants highlighted as experienced barriers the lack of money, work conflict and negative treatment from health care workers as the main reasons for dropping out of care. However, when the women were interviewed on what they perceived as barriers for other women to HIV care after delivery they said the mothers care more about the baby's health than their own, women were irresponsible or ignorant, negative staff treatment, denial and lack of disclosure of status (Clouse *et al.*, 2014).This showed how important it is to take the woman's perspective into consideration when planning care for them and their exposed infants, especially during the postpartum period.

In Cameroon, a sentinel survey amongst pregnant women aged 15-49 years in 2011 put the HIV sero-prevalence at 7.8%, ranging from 4.3% in the Far North Region to 11.9% in the Centre Region (Billong *et al.*, 2015). The South West Region was at 10.6% a rate much higher than the national prevalence of 4.3% (INS, 2011). The mother-to-child transmission rate still stood at 25% in 2013 (UNAIDS, 2014b). With this high HIV prevalence in pregnancy, high MTCT rate and the low coverage of ART (66%) for pregnant and breastfeeding HIV-positive women (UNAIDS, 2015), in August 2012 and following the WHO programmatic updates (WHO, 2012c) the government of Cameroon decided to initiate a pilot project to implement Option B+ in two health districts in the country. This move was also motivated by the potential advantages of Option B+ from the Malawi's experience which greatly simplify and integrate PMTCT and ART services avoiding stopping and re-starting ARVs while preventing MTCT in future pregnancies (CDC, 2013).

However, there has been a significant improvement in the ARV coverage for HIV-positive pregnant women rising from 66% in 2014 to 82% in 2015 with a six week MTCT of 5.2% and a final transmission rate at 12.6% (UNAIDS, 2016b). The pilot project which is still on-going, started in October 2013 and the roll out of Option B+ in the country became effective since December 2015.

Moreover, the above data indicates that achieving and maintaining this low transmission rate requires high coverage across the entire PMTCT cascade including; high antenatal attendance, high HIV testing and counselling rates, ART coverage above 90% and strong systems to support lifelong adherence to ART and retention-in-care for mothers postpartum (UNAIDS, 2015). Considering the fact that with Option B+ healthy patients are going to start treatment there are concerns that these patients, especially those with CD4+ T-cells > 350 cell/$mm^3$, may not be adequately retained in care and their adherence to treatment may be suboptimal (Grimsrud *et al.*, 2016).

### 1.3 Rationale and significance of the study

Cameroon with a 6-8 week MTCT rate at 5.2% and a final transmission rate at 12.6% (UNAIDS, 2016a) still points to the fact that many of the residual HIV infections in infants are still occurring during the breastfeeding period. There is thus, an urgent need to support pregnant and breastfeeding women so that they are retained in care and adhere to antiretroviral therapy throughout the risk periods of pregnancy and breastfeeding. The impact of both low retention-in-care and poor adherence to ART is most evident when one focuses at the final MTCT rates (Jean B Nachega et al., 2012; Ngoma et al., 2015). Following early implementation of treatment under Option B+ in Cameroon, adherence and retention-in-care have not been determined. Considering that adherence and retention-in-care following this new treatment option could be country specific and could vary with the approach used in measurement, we therefore decided to carry out this study to determine retention-in-care, adherence and treatment outcomes for HIV-positive pregnant and breastfeeding women initiating Option B+ in Cameroon.

This study which was carried out alongside the pilot project and the eventual scale up of Option B+ in Cameroon was also an opportunity to better characterise the determinants of adherence and treatment discontinuation. To better evaluate retention-in-care and to properly assess adherence to lifelong ART for these women, the HIV testing and counselling uptake and the ART uptake of women attending the antenatal care and infant welfare services in the Kumba health district were first established. We measured adherence with a composite adherence score comprising of an indirect objective measure (pharmacy refill) and two indirect subjective measures (4-day patient self-report and 30-day visual analogue scale). The results of this pioneer study will assist the national programme in developing strategies to achieve optimal retention-in-care and improve adherence, which are very important determinants of treatment success as Option B+ is progressively being implemented in Cameroon.

## 1.4 Objective

The overall objective of this study was to evaluate retention-in-care and adherence among HIV-positive pregnant and breastfeeding women initiating lifelong antiretroviral therapy in the context of PMTCT Option B+ in the South West Region of Cameroon.

## 1.5 Hypothesis

Retention-in-care and adherence to lifelong ART for HIV-positive pregnant and breastfeeding women initiating treatment with a CD4+ T-cell count >350 cell/µL is much lower than for those initiating therapy for their own health i.e. with CD4+ T-cell count ≤ 350 cell/ µL.

### Null hypothesis

There is no observed difference in retention-in-care and adherence between HIV-positive pregnant and breastfeeding women initiating lifelong antiretroviral therapy with a CD4**+** T-cell count >350 cell/ µL when compared with those initiating therapy for their own health (CD4**+** T-cell count ≤ 350 cell/ µL).

## 1.6 Research Questions

1. What is the HIV testing and counselling uptake and ART uptake in pregnant and breastfeeding women attending antenatal care (ANC) and infant welfare (IWC) services in Kumba Health District, Cameroon?
2. What is the difference in the rate of retention-in-care on lifelong antiretroviral therapy for HIV-positive pregnant and breastfeeding women who initiate Option B+ with CD4**+** T-cell count ≤ 350cell/ µL compared to those with CD4**+** T-cell count >350cell/ µL at 6 and 12 months?
3. What is the difference in the rate of adherence to lifelong antiretroviral therapy for HIV-positive pregnant and breastfeeding women initiating Option B+ with CD4**+** T-cell

count ≤ 350cell/ µL compared to those with CD4**+** T-cell count >350cell/ µL at 6 and 12 months?

4. How does adherence measured with a composite adherence score (CAS) predict viral suppression in HIV-positive pregnant and breastfeeding women initiating Option B+ in Cameroon?

5. What are the important predictors of suboptimal adherence in pregnant and breastfeeding women initiating option B+ in Cameroon and retained in care?

6. What are the reasons for discontinuation of lifelong antiretroviral therapy in pregnant and breastfeeding mothers initiating Option B+ in Cameroon?

7. What is the testing (PCR) uptake and HIV-free survival at 2 months (6-8 weeks) for exposed babies of women on Option B+ in Cameroon?

8. What is the maternal mortality (all causes included) and adverse pregnancy outcomes (pre-term delivery, low birth weight, abortions etc.) observed with Option B+?

## 2. Review of literature

### 2.1 Overview of the global HIV and AIDS epidemic

UNAIDS estimated that at the end of 2015, a total of 36.7 million persons were living with HIV (PLHIV) infection worldwide, as compared with 29.1 million in 2001 with 25.8 million (70%) of these living in sub-Saharan Africa (UNAIDS, 2016b). Though the greatest impact of the HIV/AIDS epidemic with heterosexual transmission is today in sub-Saharan Africa, it originated in men who have sex with men (MSM) in the United States and Western Europe (De Cock, Jaffe, & Curran, 2012). The peculiarities of this epidemic include the disproportionate burden borne by females, especially in sub-Saharan Africa, where more than 70% of infected females reside (Simon, Ho, & Karim, 2006). In 2015, two million persons were newly infected and 1.2 million died a decline of 47.8% from 2005, when the number of AIDS deaths peaked at 2.3 million. Sixty six per cent (790,000) of the deaths among PLHIV in 2014 occurred in sub-Saharan Africa (UNAIDS, 2016b). Similarly, the number of new infections among neonates and infants in the global plan countries has decreased from 270,000 in 2009 to 110,000 in 2015 as a result of improved PMTCT interventions (UNAIDS, 2016a). However, these global figures tend to hide a wide diversity amongst regions and countries.

The prevalence of HIV infection among adults according to continent and country varies greatly with sub-Saharan Africa continuing to be the most affected continent, followed by Eastern Europe and the Caribbean. Nigeria is a special case among the global plan countries with 41,000 newly infected children in 2015, a number equivalent to the next eight countries of the global plan combined. Without Nigeria the remaining 20 countries of the global plan had a 69% reduction in new HIV infections among children by the end of 2015 (UNAIDS, 2016a).

Although all regions of the world are affected by this pandemic, southern Africa is now fully confirmed as the epicentre of the global HIV/AIDS epidemic. One-third of the global

HIV infection and about half of the world's HIV-associated tuberculosis are found in nine southern Africa countries which account for less than 2% of the world's population (De Cock *et al.,* 2012). This high HIV prevalence has frequently been associated with lack of male circumcision and high rates of sexually transmitted infections such as HSV-2 infection (Bailey et al., 2007; Buvé et al., 2001; Gray et al., 2007). Even within a country, the prevalence of HIV infection varies widely according to region and risk group as is the case in Cameroon and several other countries within the sub-region (INS, 2011). As of December 2015, 17 million people living with HIV globally were accessing antiretroviral therapy, up from 15.8 million in June 2015 and 7.5 million in 2010 greatly surpassing the UNAIDS target of 15 million by 2015 (UNAIDS, 2016b). In 2015 there was a dramatic improvement of children access to treatment globally up from 21% to 49%, slightly surpassing adult treatment access which stood at 46% (UNAIDS, 2016b).

### 2.2 Epidemiology of HIV infection in Cameroon

Cameroon has an HIV prevalence of 4.3% representing one of the most affected countries in central Africa region (INS, 2011). Across the country the women are disproportionately more infected than the men (Figure 2.1) and this has contributed to the high mother-to-child transmission rate. The main risk groups in the country include; commercial sex workers, men who have sex with men, truck drivers, fishermen, and military personnel (CNLS, 2014). The sero-prevalence amongst pregnant women aged 15-49 years is 7.8% and this varies greatly across the different regions (Billong *et al.*, 2015). The ARV coverage for pregnant women in Cameroon rose from 36% in 2009 to 82% in 2015. This was accompanied by a significant drop in mother-to-child transmission with an early (6-8 weeks) transmission rate of 5.2% and a final transmission at the end of all breastfeeding of 12.6% dropping from 8% and 22% in 2014 respectively (UNAIDS, 2016a). It should be noted that since May, 2007, Cameroon instituted a free ART policy for all patients living with HIV and eligible for ART. This included children and pregnant and breastfeeding mothers. However, adherence and retention-in-care and treatment for HIV-positive pregnant and breastfeeding women remains a serious public health concern as most

women enrolled in care drop out very early leaving their infants at risk of HIV infection (Ngoma *et al.*, 2015; UNAIDS, 2016a).

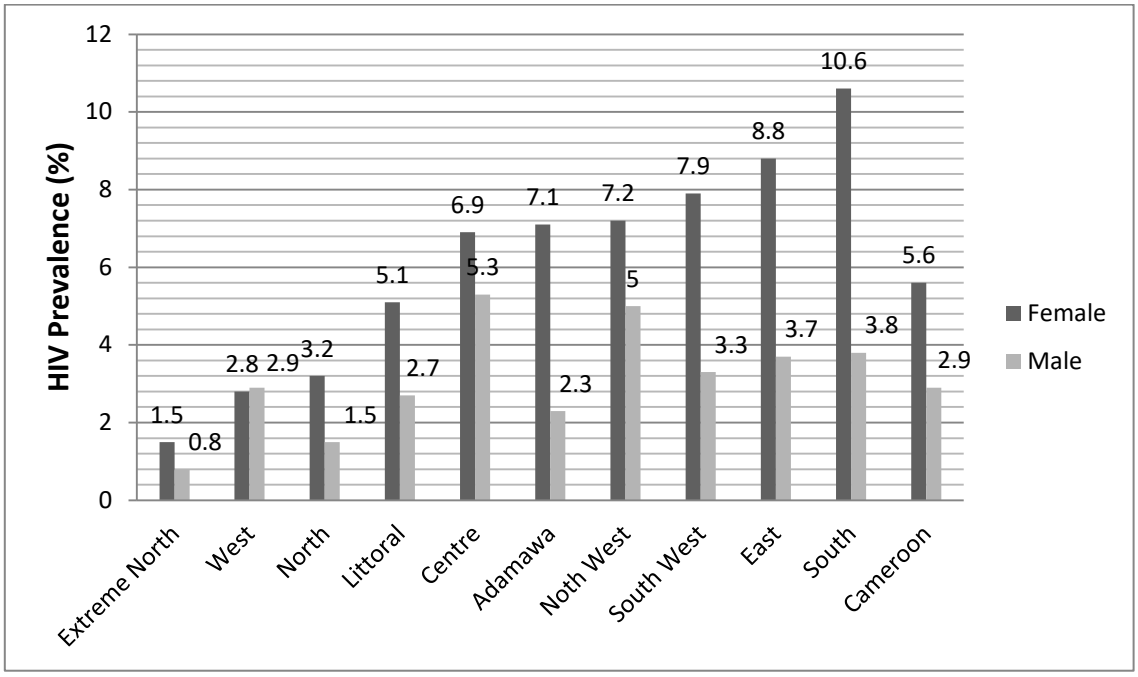


**Figure 2.1:** *National HIV Prevalence in Cameroon by regions and by sex (men and women aged 15-49 years)*

*(Adopted from EDS-MICS 2011)*

The HIV prevalence in Cameroon varies greatly by region ranging from 1.2% in the extreme north to 7.2% in the south region (Figure 2.2). The urban areas especially the big cities are more affected than the rural areas (INS, 2011).

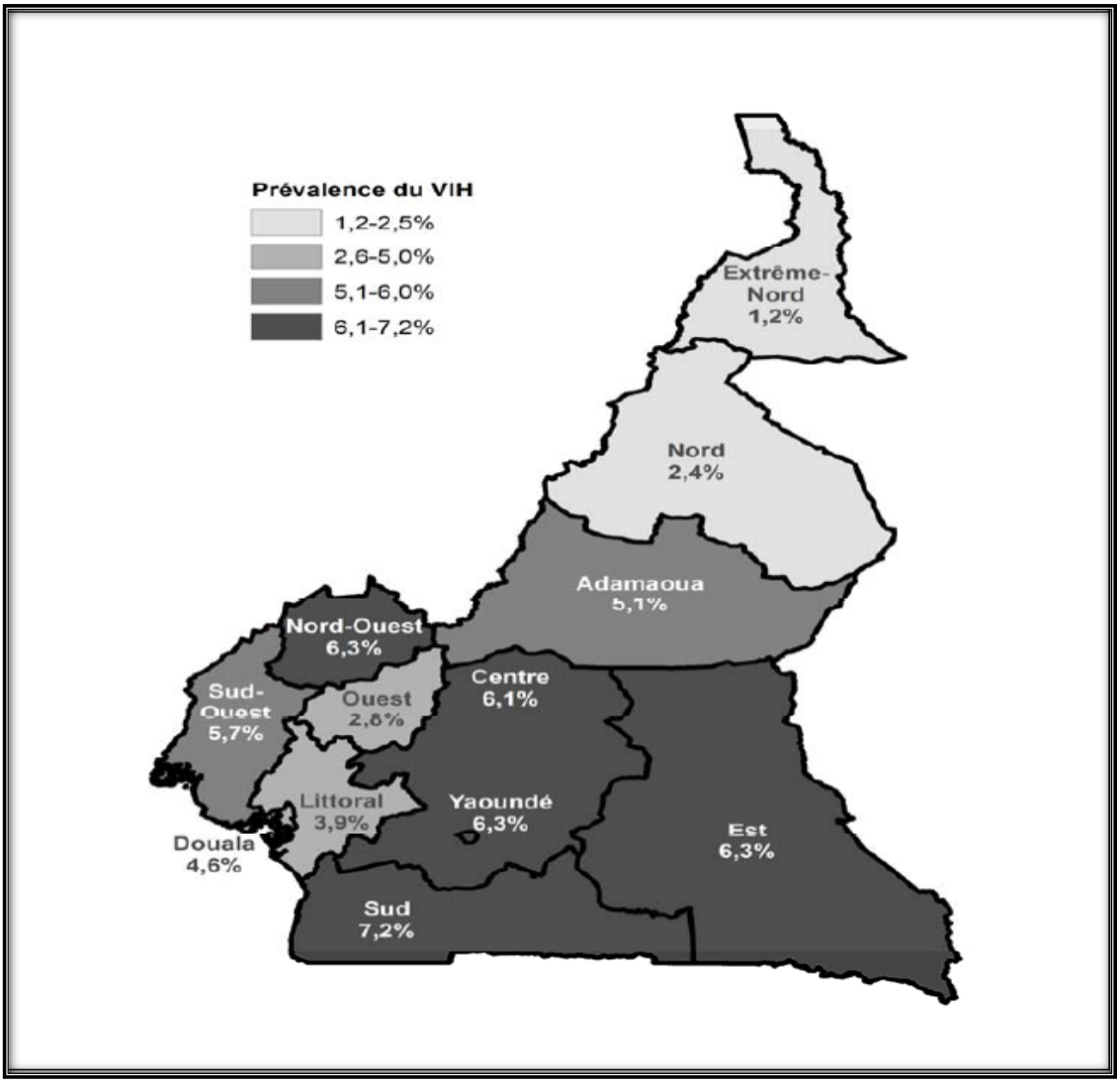


**Figure 2.2:** *National HIV Prevalence in Cameroon by regions (men and women aged 15-49 years)*

*(Adopted from EDS-MICS 2011).*

### 2.3 History of the PMTCT programme in Cameroon

With an estimated population of 21,700,000 people living in Cameroon in 2013, 660,000 were living with HIV. There were approximately 9,500 new HIV infections in 2014 among pregnant women, with only 40% of these women receiving ARV treatment or prophylaxis (CNLS, 2015). The Prevention of Mother-to-Child Transmission of HIV (PMTCT) programme in Cameroon started in its pilot phase in the year 2000 in the Centre, North-West and

Littoral Provinces (now regions). In 2000, the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) supported the first five PMTCT health facilities in Cameroon in partnership with the Cameroon Baptist Convention Health Services (CBCHS). It witnessed an extension in 2002 in the West and South West regions. It gained ground from July 2003 covering the rest of the regions. The PMTCT programme was officially launched in 2003. The nationwide scale up of PMTCT services started in 2003 with all the regional and district hospitals and by 2006 PMTCT services were present in all health districts nationwide following the district approach. Single-dose Nevirapine (sdNVP) was used for the period 2001 to 2012 though Cameroon introduced AZT combination prophylaxis in 2006 with AZT being initiated at 28 weeks of pregnancy, followed by sdNVP and AZT/3TC during labour and AZT/3TC tail for a week. This was progressively rolled out with the gradual removal of sdNVP. Infants received NVP syrup at birth for a week or more depending on duration of exposure of the mother to ARVs before pregnancy. This was guided by the 2006 PMTCT national guidelines.

These guidelines were updated in 2011 following the WHO 2010 guidelines introducing Options A and B as PMTCT options. Cameroon just like most African countries opted for Option A whereby the pregnant women started AZT prophylaxis at 14 weeks up to delivery, then sdNVP with AZT/3TC during labour with an AZT/3TC tail for a week while those eligible for treatment were referred for triple therapy for their own health. The babies then received NVP prophylaxis until complete cessation of breastfeeding. In August 2012, following the April 2012 WHO programmatic updates that recognized the potential advantages and the need to take into consideration the new Option B+ approach introduced by Malawi within a public health perspective in resource-limited settings (WHO, 2012 2b), Cameroon decided to adopt Option B+. However, it was not until October 2013 that Option B+ was piloted in the country in two health districts, Bamenda and Kumba of the North West and South West regions respectively with funding from President Emergency Plan for AIDS Relief (PEPFAR). Full scale up of Option B+ in Cameroon was only effective as from December, 2015 with the production of a consolidated national

guideline for treating and preventing HIV infection (CNLS, 2015) and a ministerial circular letter authorising all sites to systematically start all HIV-positive pregnant and breastfeeding women on tenofovir, lamivudine, efavirenz (TELE) irrespective of their disease clinical classification or CD4+ T-cell count.

## 2.4 HIV Transmission, pathogenesis, disease progression and natural history

### 2.4.1 HIV transmission

HIV is transmitted through three main routes, namely; the sexual route, through blood and blood products and from mother-to-child. HIV Transmission depends on the infectiousness of the source person and the susceptibility of the exposed one. Infectivity varies during the course of illness and is not constant between individuals. Transmission of HIV is dependent on a large number of behavioural and biologic factors. Some of the many variables that influence the probability of HIV transmission include the genetic background of the potential host, the size and infectiousness of the inoculum, and the local environment in which the exposure occurs (Dean, Carrington, & Winkler, 1996). Factors that result in physical disruption of the exposed mucosa, such as the use of vaginal desiccants or the presence of genital ulcer disease and other sexually transmitted infections, can enhance viral transmission (Pantaleo *et al.*, 1998). Based on its genetic make-up, the HIV-1 virus which is responsible for the world's pandemic is divided into four groups namely; M (main), N (new), O (outlier) and P. While HIV-2 has groups A-H. The M group which constitutes the major group has nine subtypes and the subtype C is dominant representing about 55-60%. Transmission also depends on the virus strain. HIV-1 is more easily transmitted than HIV-2 which is found principally in West Africa. More than 70 circulating recombinant forms (CRFs) have also been identified and can easily be transmitted.

#### 2.4.1.1 Sexual transmission

Sexual transmission occurs through the contact of genital secretions of an infected person with the disrupted rectal, genital, or oral mucous membranes of an uninfected person. The size of the inoculum and the integrity of these membranes are important determinant factors in sexual transmission. The risk for transmitting HIV through unprotected anal intercourse is greater than the risk from vaginal intercourse or oral sex (Rothenberg, Scarlett, del Rio, Reznik, & O'Daniels, 1998).

#### 2.4.1.2 Blood and blood products

This transmission route was recognised as early as 1983 as the HIV infection was found to spread among intravenous drug users (IDU), recipients of blood and blood products like haemophiliacs and through occupational exposure in health care settings (De Cock *et al.*, 2012). A major risk factor for HIV infection is the sharing and reusing syringes contaminated with HIV-infected blood. World Health Organisation estimates that approximately 2.5% of all HIV infections in sub-Saharan Africa are transmitted through unsafe healthcare injections (WHO, 2008). Before the advent of the HIV epidemic a majority of the world's population did not have access to safe blood and most HIV infections may have occurred through transfusion of infected blood and use of blood products (De Cock *et al.*, 2012).

#### 2.4.1.3 Perinatal or Mother-to-child transmission (MTCT)

More than 90% of children living with HIV got infected through mother-to-child transmission. The transmission of the virus from an infected mother to the child can occur in utero during the last weeks of pregnancy, during childbirth and through breastfeeding. However, most transmission occurs during labour and delivery when the baby comes in direct contact with maternal blood and secretions. Many factors influence vertical transmission varying from pregnancy, through delivery and breastfeeding. The table below summarises the risk factors involved in MTCT. In the absence of any intervention

mother-to-child transmission ranges from 25-40% (WHO, 2006). The most important risk factor that cuts across all time points is the maternal viral load.

**Table 2.1:** Risk factors of Mother-to-child transmission of HIV

| Time point of HIV transmission and risk factors associated | | |
|---|---|---|
| **Pregnancy** | **Labour and delivery** | **Breastfeeding** |
| - High maternal viral load (new infection or advanced AIDS) | - High maternal viral load (new infection or advanced AIDS) | - High maternal viral load (new infection or advanced AIDS) |
| - Sexually Transmitted Infections (STIs) | - Rupture of membranes for more than 4 hours | - Prolonged breastfeeding |
| - Viral, bacterial, or parasitic placental infection | - Invasive delivery procedures that increase contact with mother's infected blood or body fluids (e.g. episiotomy, foetal scalp monitoring)<br>- Prolonged labour | - Mixed feeding, particularly during the first 6 months of life (e.g. food or fluids in addition to breast milk) |
| - Poor maternal nutritional status | - First infant in multiple birth | - Breast abscesses, nipple fissures, mastitis |
| - Chorioamnionitis (from an untreated STI or other infection) | - Preterm delivery | - Poor maternal nutritional status |
| | - Low birth weight | - Oral disease in the baby (e.g. oral thrush or sores) |

**Adapted from WHO, 2006**

### 2.4.2 Pathogenesis

The pathogenesis of HIV infection is a complex, multi-factorial process involving viral and host factors. The net degree of virus replication *in vivo* reflects a balance of factors that positively or negatively regulate virus expression. In turn, the amount of virus replication appears to be intimately related to the rate of CD4+ T-cell depletion that occurs, and thus to the rate of disease progression. The clinical features of HIV infection vary depending on the stage of disease. In the acute and early stages of the disease, symptoms resulting from immune hyper-activation predominate. However, with the inexorable depletion of CD4+ T-cells that characterizes disease progression, overt cellular immunodeficiency and its

many complications develop (Camaur & Trono, 1996). The CD4+ T-cell count is an excellent long term marker of the degree of immunodeficiency and determines the immediate risk of opportunistic infections and other AIDS-related complications (Masur *et al.,* 1989). The plasma viral load is the most valuable short term prognosticator of HIV infection that is currently available. Viral load not only predicts disease progression independent of the CD4+ T-cell count, but also actually predicts the trajectory of the CD4+ T-cell count (Mellors *et al*., 1997).

#### 2.4.2.1 Acute Infection

Although more than half of primary HIV infections are accompanied by symptoms, most of these infections are not recognized in the acute setting (T. Schacker, Collier, Hughes, Shea, & Corey, 1996). The differential diagnosis of primary HIV infection is extremely broad, given the variable presentations associated with the syndrome and the ubiquity of the observed signs and symptoms. Fever, rash, pharyngitis, and lymphadenopathy are common during primary HIV infection, as they are in many "flulike" and "mononucleosis-like" illnesses (Niu, Stein, & Schnittman, 1993). Myalgias, arthralgias, diarrhoea, nausea, vomiting, headache, hepatosplenomegaly, weight loss, thrush, and neurologic symptoms also may occur. Among patients who develop symptoms during primary HIV infection, the mean duration of symptoms is 3 weeks (Kinloch-de Loës *et al*., 1993). Plasma HIV RNA levels vary widely in primary HIV infection, from thousands to millions copies per millilitre (T. W. Schacker, Hughes, Shea, Coombs, & Corey, 1998). The peak level of HIV RNA (viral set point) may have prognostic value, and persistently high levels after 4 to 6 months add to the predictive power towards more rapid progression of disease (Mellors *et al*., 1995).

#### 2.4.2.2 Early-Stage Disease

The natural history of HIV infection includes a long period of clinical latency between the time of primary infection and the development of symptoms indicative of advanced immune deficiency. In the tropics, this period has an average duration of 4 – 5 years or

less. Generalized lymphadenopathy and some degree of fatigue are characteristic of this period of clinical latency. As the CD4+ T-cell count falls below 500 cells/ µL symptoms and syndromes indicative of depressed cell-mediated immunity in HIV infection that are not AIDS defining generally begin to appear. Examples include recurrent vulvovaginal candidiasis, multi-dermatomal herpes zoster, pelvic inflammatory disease, oral hairy leukoplakia associated with Epstein-Barr virus (EBV), cervical dysplasia (usually associated with human papillomavirus infection), constitutional symptoms such as unexplained fever or diarrhoea lasting more than 1 month, idiopathic thrombocytopenic purpura, and peripheral neuropathy (Buehler & Berkelman, 1990).

#### 2.4.2.3 Late-Stage Disease - AIDS

As the CD4+ T-cell count decreases below the level of approximately 200 cells/ µL, the loss of integrity of cell-mediated immune responses allows ubiquitous environmental organisms with limited virulence (e.g., *Pneumocystis jiroveci* and *Mycobacterium avium*) to become life-threatening pathogens. Conditions indicative of severely depressed cell mediated immunity due to HIV infection constitute the CDC surveillance case definition of AIDS (Buehler & Berkelman, 1990).

#### 2.4.2.4 Determinants of Disease Progression

Several host and virologic factors determine the extremely variable rates of disease progression that are observed among HIV-infected individuals (Dalmau *et al*., 2009). A small percentage of HIV-infected individuals experience no evidence of disease progression over a prolonged period. These long-term non-progressors provide clues regarding factors associated with disease progression. The ability of certain HLA molecules to present immune-dominant viral epitopes efficiently to generate cell-mediated immune responses may explain an association with slow disease progression. Conversely, other HLA haplotypes (HLA-B35) may preclude an effective cell-mediated antiviral response and may therefore be associated with more rapid disease progression (Carrington *et al*., 1999).

Genetic polymorphisms in the HIV co-receptors and their ligands may also significantly affect the course of HIV disease progression. Individuals who are homozygous for a 32-base pair deleting mutation within the CCR5 gene (CCR5-Δ32) are afforded a high degree of protection against HIV infection, whereas HIV-infected heterozygotes are partially protected against disease progression (Carter & Saunders, 2007). Genetic polymorphisms in the chemokine–chemokine receptor axis genes represent only one of 15 possible mechanisms responsible for some resistance to HIV infection or delayed disease progression. Levels of CCR5 expression exhibit considerable inter-individual variability and these levels correlate with infectivity of cells with R5 strains of HIV in vitro (Wu *et al*., 1997). Studies of long-term non-progressors and exposed-uninfected individuals indicate important roles for CTL, CD8+T-cell suppressor factors, CD4+ T-helper responses, neutralizing antibody responses, and mucosal humoral immune responses in protecting against HIV infection or disease progression (Pantaleo *et al.*, 1994).

### 2.4.3 Natural course of HIV infection

The natural course of any disease describes the evolution of the disease in an individual from the moment of infection to death without any medical intervention. This has been possible to observe directly in HIV infected patients since the first therapies were only available about seven years after the first cases were described in 1981. Figure 2.3 shows the natural course of HIV infection, how the immune system interacts with the virus until the late disease and how this can affect disease progression and HIV transmission in the population. Viral replication is highest at early infection and at the late stage of the disease. This is particularly important in mother-to-child transmission as a woman who gets infected during the pregnancy runs a higher risk of MTCT than a woman who got pregnant with her HIV infection (WHO, 2006).

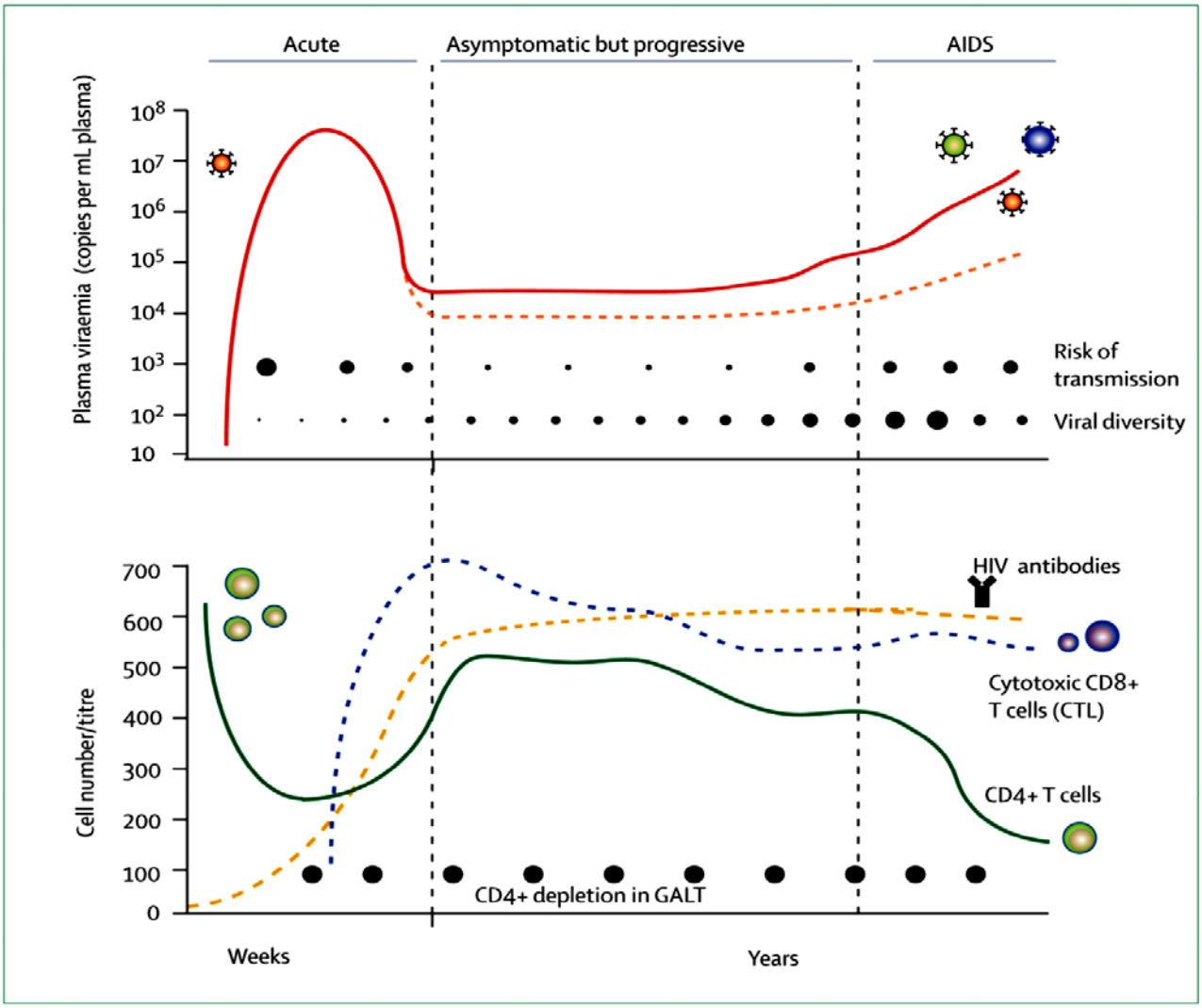


**Figure 2.3:** *The course of HIV-1 infection defined by the level of viral replication*

*(Adopted from Simon et al., 2006):*

*Plasma viraemia (top) and dynamic changes of the CD4+ T-lymphocyte compartments (bottom). Primary infection is characterised by high plasma viraemia (red line, top), low CD4 cells (green line, bottom), and absence of HIV-1 specific antibodies (orange line, bottom). Viraemia drops as cytotoxic CD8+ T-lymphocytes (CTL) develop (blue line, bottom) and an individual viral-load set point is reached during chronic infection. Viral set points differ greatly among individuals (e.g., red dotted line, top) and predict disease progression. Viral diversity increases throughout the disease (closed circles, top). The risk of transmission is highest in the first weeks when viraemia peaks (closed circles, top) and during late disease. GALT=gut-associated lymphoid tissues. (p.27)*

## 2.5 Management of HIV infection

In 2014, WHO and UNAIDS set an ambitious treatment target to help end the AIDS epidemic by 2030. The 90-90-90 target by 2020 i.e. 90% of people living with HIV should know their status, 90% of people with diagnosed HIV infection should be initiated and maintained on a sustained ARV treatment and 90% of those on ARV treatment should attain viral suppression will guide the AIDS agenda beyond 2015 (UNAIDS, 2014a). This target is far from being met especially in sub-Saharan African countries where a lot of people still do not know their HIV status and access to viral load monitoring is still limited (Piot *et al*., 2015).

With the recent adoption of test and treat for all, WHO has proposed a general package for care for people living with HIV in order to reduce new HIV transmission, to prevent illness and to improve the quality of life of PLHIV. This care package could vary depending on the epidemic type, population affected, prevalence of co-infections, other comorbidities and general health conditions (WHO, 2016). In this care package that cuts across the continuum of care, WHO recommends a package of 13 prevention interventions that will help guide the management of adults and adolescents living with HIV in resources constrained settings: "(1) Psychosocial counselling and support; (2) disclosure and partner notification; (3) cotrimoxazole prophylaxis (CTX); (4) TB counselling, screening and preventive therapy; (5) preventing common fungal infections; (6) treatment of STIs and supporting reproductive health needs, including prevention of and screening for cervical cancer; (7) preventing malaria (CTX, bed-nets and particularly preventing malaria among pregnant women); (8) the use of vaccines for the prevention of pneumococcal disease, influenza, hepatitis B and yellow fever; (9) provision of adequate nutrition; (10) family planning services; (11) prevention of mother-to-child HIV transmission; (12) needle and syringe programmes for people who inject drugs; and (13) water, sanitation and hygiene". This comprehensive package of care will require enough human and material resources to be implemented at all service delivery points in resource limited settings.

### 2.5.1 Diagnosis

Since lentiviral infections are persistent, antiviral antibodies are present throughout the lifetime of the infected host. Detection of antiviral antibodies is thus the most widely used method for determining the presence of viral infection. However, diagnosis could also be done using antigens, or both, and many commercial kits are now available. The serological test that are readily available today can be done on plasma, serum, whole blood or saliva by health care workers with little laboratory expertise following minimal training with same day results possible (Simon *et al.,* 2006). Serological diagnosis of HIV entails the use of first and second-generation assays of HIV antibodies, which employ whole virus lysate and recombinant proteins respectively. Third generation assays employ a mixture of recombinant antigens from the core (gag), pol (polymerase) and env (envelope) products of HIV-1 and HIV-2, and it is most widely used (McMillan *et al.,* 2002).

Serologic test are limited in that they cannot diagnose early infection and are not suitable for diagnosis of HIV infection in children younger than 18 months. The use of dried blood spot (DBS) specimen has resolved some of the challenges associated with transportation and storage of samples needed for virological assessments especially for early infant diagnosis and more recently for viral load testing (WHO, 2013).

It is recommended that for surveillance studies in settings with HIV prevalence ≤ 10%, two testing strategies should be used (WHO, 2013). Most national programmes have developed testing algorithms for HIV antibody testing for disease surveillance, diagnosis or blood transfusion identifying the different tests to be used depending on the test sensitivity and specificity. Most of the testing algorithms perform serial testing with the first test being highly sensitive and the second test being highly specific (CNLS, 2015).

### 2.5.2 Clinical staging

Measurement of CD4+ T-cells and viraemia is required for disease staging and patient follow-up especially during treatment with ARVs. Treatment failure and therapeutic drug monitoring for treatment success should be monitored with plasma viral load. CD4+ T-cells count measures the degree of immunodeficiency and is, therefore, used to assess the

stage of infection. CD4+ T-cell counts together with clinical manifestations (e.g., occurrence of opportunistic infections) are key criteria for HIV disease classification.

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2007 (WHO, 2007). Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS based on specific clinical conditions or symptoms (Table 2.2). Even with the coming in of test and treat for all, disease staging should follow a confirmed HIV infection prior to initiation of treatment as this will serve as a baseline for better follow-up of the patient while on ART.

**Table 2.2:** WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

| **WHO clinical stage** | **Clinical conditions or symptoms** |
|---|---|
| Primary HIV infection | Asymptomatic |
| | Acute retroviral syndrome |
| Clinical Stage 1 | Asymptomatic |
| | Persistent generalized lymphadenopathy |
| Clinical Stage 2 | Moderate unexplained weight loss (<10% of presumed or measured body weight) |
| | Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) |
| | Herpes zoster |
| | Angular cheilitis |
| | Recurrent oral ulceration |
| | Papular pruritic eruptions |
| | Seborrheic dermatitis |
| | Fungal nail infections |
| Clinical stage 3 | Unexplained severe weight loss (>10% of presumed or measured body weight) |
| | Unexplained chronic diarrhoea for >1 month |
| | Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) |
| | Persistent oral candidiasis (thrush) |
| | Oral hairy leukoplakia |
| | Pulmonary tuberculosis (current) |
| | Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) |
| | Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis |
| | Unexplained anaemia (haemoglobin <8 g/dL) |
| | Neutropenia (neutrophils <500 cells/mL) |
| | Chronic thrombocytopenia (platelets <50,000 cells/mL) |
| Clinical Stage 4 | HIV wasting syndrome, |

| | |
|---|---|
| | *Pneumocystis jirovecii* pneumonia (PCP) |
| | Recurrent severe bacterial pneumonia |
| | Chronic herpes simplex infection (oro-labial, genital, or anorectal site for >1 month or visceral herpes at any site) |
| | Oesophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) |
| | Extrapulmonary tuberculosis |
| | Kaposi sarcoma |
| | Cytomegalovirus infection (retinitis or infection of other organs) |
| | Central nervous system toxoplasmosis |
| | HIV encephalopathy |
| | Cryptococcosis, extrapulmonary (including meningitis) |
| | Disseminated nontuberculosis mycobacteria infection |
| | Progressive multifocal leukoencephalopathy |
| | Candida of the trachea, bronchi, or lungs |
| | Chronic cryptosporidiosis (with diarrhoea) |
| | Chronic isosporiasis |
| | Cryptococcosis, extrapulmonary (including meningitis) |
| | Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) |
| | Recurrent nontyphoidal *Salmonella* bacteraemia |
| | Lymphoma (cerebral or B-cell non-Hodgkin) |
| | Invasive cervical carcinoma |
| | Atypical disseminated leishmaniasis |
| | Symptomatic HIV-associated nephropathy |
| | Symptomatic HIV-associated cardiomyopathy |
| | Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis) |

**Adopted from WHO, 2007**

### 2.5.3 Management of opportunistic infections

When the immune system becomes severely damaged following HIV infection the patients start developing opportunistic infections. The risk of contracting some opportunistic infections varies in line with the degree of destruction of the immune system. Mycotic skin and mucous membrane infections or herpes zoster develop as a result of minor damage. In Africa most patients will also develop tuberculosis (TB) at this stage even though TB usually develops in patients with late stage disease. TB is the most common opportunistic infection and the major cause of mortality in people living with HIV (Simon *et al*., 2006; WHO, 2007). Most TB infections in these patients are due to endogenous reactivation but the risk of acquiring a new infection after infection with HIV is twenty times higher than in HIV-negative individuals and extra-pulmonary forms of TB are more prevalent. Other opportunistic diseases such as Kaposi sarcoma, pneumocystis jiroveci pneumonia, cerebral toxoplasmosis, cytomegalovirus virus retinitis or lymphomas are diagnosed when the immune system is severely compromised, usually when the CD4+ T-cell count is less than 200 cells per microliter.

Without treatment most of these opportunistic infections will further damage the immune system resulting in very high viral load and increase the risk of mother-to-child transmission. Adequately diagnosing and treating a major opportunistic infection takes priority over antiretroviral therapy but optimal timing of antiretroviral therapy in all patients and especially in pregnant women where ART remains an emergency is very important (WHO, 2016). Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4+ T-cell counts < 350 cells/mL unlike in children and adolescents whereby prophylaxis should be provided irrespective of clinical or immunologic condition (WHO, 2016).

### 2.5.4 Antiretroviral therapy

Antiretroviral therapy (ART) refers to the use of a combination of three or more antiretroviral drugs for treating HIV infection. Lifelong ART is now recommended for all patients diagnosed with HIV irrespective of the immunological or clinical condition of the patient (WHO, 2016). However, test and treat does not exclude adequate adherence counselling and assessment of patients for treatment preparedness or willingness to initiate ART. Of nearly 22,000 women who started ART under option B+ in Malawi 17% were lost to follow-up six months after ART initiation. Loss to follow-up was highest among women who began ART at large clinics on the day they were diagnosed with HIV (Tenthani *et al.*, 2014). This further emphasizes the need to have the client adequately prepared and mindful of the implications of lifelong ART. This decision might be overwhelming and complex to take immediately after HIV diagnosis. World Health Organisation suggest that it is good practice to make a lot of efforts to reduce the time between HIV diagnosis and ART initiation based on the assessment of the person's readiness to start? If the person decides not to start ART immediately, counselling should continue and the advantages of early initiation adequately explained to the client and ART can be proposed at subsequent clinical visits (WHO, 2016). WHO further call on national programmes, to strike the balance between starting pregnant and breastfeeding women without delay and ensuring that women are adequately prepared, have accepted lifelong ART and have access to support systems, including peer support, to promote treatment adherence and retention-in-care (WHO, 2016).

#### 2.5.4.1 Classification of antiretroviral drugs

Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life cycle that the drug inhibits (Figure 2.4).

- Entry inhibitors (or fusion inhibitors); Examples are Maraviroc and enfuvirtide.
- CCR5 receptor antagonists. Most strains of HIV use the CCR5 receptors as ligands to attach to T-cells receptors.

- Nucleoside reverse transcriptase inhibitors (NRTI) and nucleotide reverse transcriptase inhibitors (NtRTI). Examples include zidovudine (AZT), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC), didanosine (ddl), abacavir (ABC) and tenofovir (TDF).
- Non-Nucleoside reverse transcriptase inhibitors (NNRTI). Examples include nevirapine (NVP) and efavirenz (EFV).
- Protease inhibitors (PIs). Examples include saquinavir (SQV), indinavir (IDV), Lopinavir (LPv) and nelfinavir (NFV).
- Integrase inhibitors inhibit the enzyme integrase, Example,raltegravir.
- Maturation inhibitors

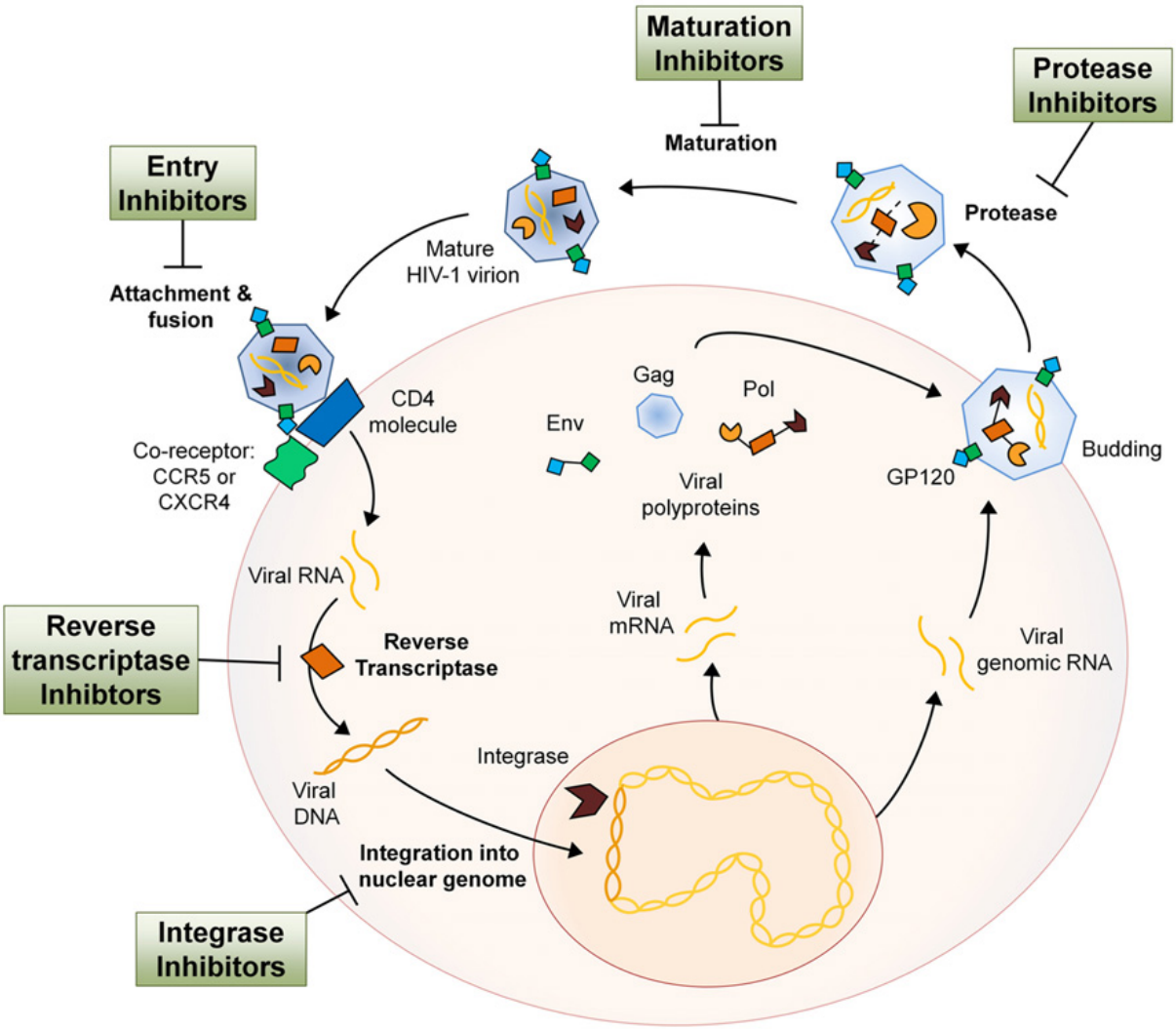


**Figure 2. 4:** *Different classes of antiretroviral drugs and their point of action along the lifecycle of HIV infection*

*(www.frontiersin.org, Retrieved 29th July, 2016).*

### 2.5.4.2 Antiretroviral drugs and regimens used in PMTCT

Antiretroviral use in pregnancy has changed considerably overtime and most of the regimen selection procedures have been driven by fear of the safety for the infant while providing optimal efficacy to reduce mother-to-child transmission. Prevention-of-mother-to-child programmes started by offering short course ARV or single doses of ARV drugs to the mother and her infant in the first few days of life. There was a major shift in 2003 and later on updated in 2006 when the WHO guidelines recommended, "pregnant women living with HIV be assessed for treatment eligibility and those considered eligible should be offered lifelong combination ART for their own health, while those who were not eligible should receive short courses of ARV for PMTCT". These eligibility criteria have changed overtime with a lot of improvement in the PMTCT treatment options (WHO, 2006).

In 2010 WHO adopted Options A and B as PMTCT options, this was later on revised in 2012 with impelling evidence from Malawi who started an ambitious public health approach which they called Option B+ whereby all pregnant and breastfeeding women were immediately put on treatment following HIV diagnosis irrespective of their clinical or immunological status. In 2013 the first WHO consolidated guidelines was published recommending Option B+ as the preferred PMTCT option for all pregnant and breastfeeding mothers (WHO, 2010, 2012c).

Option B+ has been seen to have the highest impact in settings with high HIV prevalence, high fertility and long duration of breastfeeding. Universal ART for all pregnant and breastfeeding women would reduce the incidence of HIV and prevent HIV transmission in both current and future pregnancies (WHO, 2014). The table below summarize these PMTCT options that were adopted in the WHO 2013 consolidated guidelines.

**Table 2.3:** Programme options for ART for PMTCT

<table>
<tr><th>National PMTCT programme option</th><th colspan="2">Pregnant and breastfeeding women with HIV</th><th colspan="2">HIV-exposed infants</th></tr>
<tr><td rowspan="2">Use lifelong ART for all pregnant and breastfeeding women (“Option B+”)</td><td colspan="2">Regardless of WHO clinical stage or CDC4 cell count</td><td>Breastfeeding</td><td>Replacement feeding</td></tr>
<tr><td colspan="2">Initiate ART and maintain after delivery and cessation of breastfeeding</td><td rowspan="3">6 weeks of infant prophylaxis with once-daily NVP</td><td rowspan="3">4-6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)</td></tr>
<tr><td rowspan="2">Use lifelong ART only for pregnant and breastfeeding women eligible for treatment (“Option B”)</td><td>Eligible for treatment [a]</td><td>Not eligible for treatment [a]</td></tr>
<tr><td>Initiate ART and maintain after delivery and cessation of breastfeeding [b]</td><td>Initiate ART and stop after delivery and cessation of breastfeeding [b c]</td></tr>
</table>

Adapted from WHO, 2013

**Table legend**

[a] *CD4 count ≤ 500cells/mm3 or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.*

[b] *Patients who develop clinical or laboratory criteria indicating failure of ART during pregnancy or the breastfeeding should be assessed for 2nd line treatment.*

[c] *In case of breastfeeding stop ART one week after cessation of breastfeeding. In case of replacement feeding stop ART after delivery.*

Later on in 2015 with the growing evidence of the importance for treating all patients living with HIV regardless of CD4+ T-cell count or WHO clinical staging, PMTCT has gradually moved away from the aforementioned options to lifelong ART treatment for all pregnant and breastfeeding women living with HIV. This is the current recommendation in the WHO 2016 consolidated guidelines. Cohen and colleagues in the HPTN 052 randomized controlled trial showed that ART is highly effective at preventing the heterosexual transmission of HIV if viral suppression is achieved and maintained (Cohen *et al.*, 2015).

One very important potential benefit of universal ART for all is that it normalizes HIV treatment in addition to prioritising pregnant and breastfeeding women thus reducing the likelihood of women dropping out of care on or before the end of the transmission risk period. Overall, the health benefits of universal ART for pregnant and breastfeeding

women outweigh potential harm, but women should not be coerced to start treatment unless they are ready to do so. However, a right based approach can offer women the opportunity to make informed decisions thus can result in better acceptability and improved health outcomes (WHO, 2016).

### 2.5.5 Combination HIV prevention

HIV prevention programmes today are centred around combination HIV prevention as current evidence shows that no single, stand-alone HIV prevention intervention offers the most appropriate results. It is unlikely that a single deployed intervention, even a vaccine (Vermund, 1998) will halt or even reverse the epidemic. However, a growing number of behavioral, structural and biomedical (Bailey *et al.*, 2007; Cohen *et al.*, 2015; Gray *et al*., 2007; Halperin *et al*., 2011; Millett, Flores, Marks, Reed, & Herbst, 2008; Wilson & Halperin, 2008) HIV prevention strategies appear promising in providing some protection against infection. WHO reiterates that combination prevention programmes use a mix of biomedical, behavioural and structural interventions to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest possible impact on reducing new infections (WHO, 2016). Some authors have compared combination prevention to combination ART: 'Combination ART reduces HIV replication by attacking the virus at multiple points of its life cycle, leading to multiple therapeutic targets for treatment, and yielding dramatic clinical benefits. Similarly, combination HIV prevention is likely to be most effective when different points in the "transmission cycle" are impeded, combining strategies to reduce infectiousness of HIV-positive persons with strategies that reduce HIV susceptibility in the uninfected' (Cremin *et al.*, 2013). Synergistic effects are therefore obtained when combination prevention strategies are used.

Proven interventions adopted from WHO, 2016 guidelines to be included in a combination HIV prevention programme includes:

- Condoms both male and female and condom compatible lubricants
- Treatment as prevention (early ART for infected patients)
- Pre-exposure prophylaxis (PrEP)

- Post-exposure prophylaxis (PEP)
- Voluntary male medical circumcision
- Needles and syringe substitution for injection drug users
- Opioid substitution therapy for injection drug users
- Blood transfusion safety
- Targeted information and education
- Structural and supportive interventions.

It is important to focus on high impact strategies but too much emphasis on a particular preventive intervention may just be sending out an erroneous message to the population. For example male circumcision is only partly preventive and to be effective it must be combined with other measures like condom use, otherwise some men and women will understand if circumcised then unprotected sex is risk-free (Merson *et al.*, 2008). The other major challenge with HIV prevention is the difficulty of scaling up some behavioural strategies. An intervention like partner reduction (Wilson & Halperin, 2008) though important in generalised epidemics, but it is not a clearly defined intervention like blood transfusion that can be easily scaled up. The "know your epidemic" approach (Wilson & Halperin, 2008) involves understanding determinants of local HIV prevalence and incidence to identify population targets with the highest rate of recent HIV infections, and to maximize the prevention benefits achieved. However, the need to know one's epidemic should not impedes action, if local epidemiologic data are not good enough for better decision making (Kurth, Celum, Baeten, Vermund, & Wasserheit, 2011).

Different settings and populations will require different combinations of interventions. The best HIV prevention impact comes from offering a package of interventions carefully selected to suit the epidemic setting and the population.

## 2.6 Retention-in-care and treatment

Following HIV diagnosis, prompt engagement to care and subsequent retention-in-care is imperative to allow access to treatment, requiring uninterrupted receipt and excellent adherence to achieve and sustain an undetectable plasma viral load (VL) (Fox & Rosen, 2010; Rosen & Fox, 2011). Recognising the clinical and programmatic importance of retention-in-care, there is yet no standard measure for retention-in-care. Comparatively to linkage to care which is a dichotomous event, measuring retention is more complex as it includes multiple visits, scheduled at varying time intervals, and occurring across time (Mugavero *et al*., 2012).

In 2011 in its meeting on "*Retention in HIV programmes: Defining the challenges and identifying solutions*", WHO attempted defining retention in HIV care as "the continuous engagement from diagnosis in a package of prevention, treatment, support and care services". However, there was no common consensus as with the definitions of LTFU and adherence to care. Retention-in-care was defined from the moment of initial engagement in care, when a person with HIV is successfully linked to services, to assessment for eligibility, initiation on ART and retention in lifelong ART care (WHO, 2012b). Retention just like adherence is critical to reduce HIV-related morbidity and mortality, reduce the incidence of new infections in children and adults, and reduce development of ART drug resistance. In the context of Option B+ in which the client is initiated on treatment as an emergency and as such needs to be progressively and adequately prepared for lifelong therapy retention-in-care is thus critical. Implicit to the concept of retention-in-care is the sense of continuity and receipt of care at relevant time points. Early drop outs from treatment will seriously affect the outcome of the client and increase the risk of morbidity and mortality in the mother but also the risk of MTCT of HIV.

World Health Organisation divides the continuum of care into four steps, thereby defining points at which patient attrition occurs. This division is very essential to identify points on the continuum of care where programmes need to reinforce strategies to reduce LTFU and subsequently improve retention in care. It is noteworthy that the highest rates of

LTFU occur between testing and enrollment (Tayler-Smith et al., 2010) and up to 80% of patients diagnosed with HIV infection may be LTFU between testing and initiation of ART (Rosen & Fox, 2011). This is summarized in Figure 2.5.

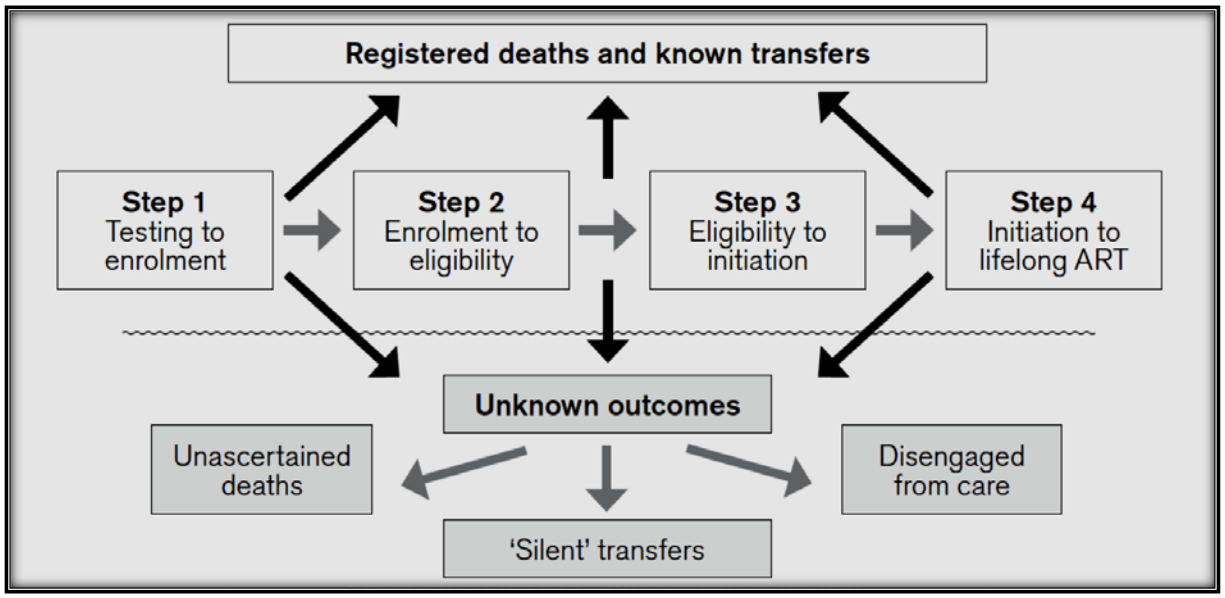


**Figure 2.5:** *The 4 steps along the continuum of HIV care and treatment*

*(Adopted from WHO, 2012).*

*"Patient loss may occur at all 4 steps along this continuum.* ***Step 1*** *– HIV testing to enrolment into care services;* ***Step 2*** *– enrolment in care to ART eligibility (may be very short if person has WHO clinical stage 3 or 4 or a low CD4, or may be years for someone with a high CD4 count);* ***Step 3*** *– eligibility to initiation of ART;* ***Step 4*** *-initiation to lifelong ART". (WHO, 2012b)*

With the incremental expansion of ART eligibility to include all pregnant women and discordant couples irrespective of CD4+ T-cell count, raising the T-CD4+ cell eligibility threshold to less than 500cells/ µL and other co-morbidities like TB and hepatitis B and C (Delva *et al*., 2012; WHO, 2013), the continuum of care will progressively be shortened and the several points of LTFU are expected to reduce. In 2016, WHO has endorsed test and treat for all thus normalizing HIV treatment but also removing all the steps that were initially required to get a patient eligible before initiating ART treatment (WHO, 2016).

Adequately assessing retention in care will depend so much on the definition of lost to follow-up and disengagement from care. Unfortunately there is little consensus on this

and we still find varying definitions of LTFU in the literature. WHO defines LTFU on ART as "patients receiving ART and not seen at the clinic, or pharmacy, 90 days after the date of their last missed appointment or last missed drug pick-up and who are not known to have transferred out or died" (WHO, 2012b). However, in a systematic review of 111 countries *Chi et al.* concluded that a universal definition of LTFU of 180 days produced the least misclassification (Chi *et al*., 2011). Even though WHO has proposed a definition for retention-in-care there are still a lot variations as to how retention has been defined and measured with no particular gold standard (Mugavero *et al*., 2012). In a study defining and analysing retention in care among pregnant and breastfeeding women, Rollins and colleagues comment, “Equating attendance of HIV-infected mothers clinic at 12-month postpartum with full retention in PMTCT over this period fails to capture patterns of attendance and care received by mothers and children and risk introducing error and bias. Thus providing only an aggregate rate of attendance as a proxy for retention in care fails to identify gaps in health services where interventions to improve retention along the PMTCT cascade are most needed”. These authors are thus emphasising that failing to capture missed visits, or inconsistent clinic attendance falter the continuity aspect of retention-in-care. They therefore, proposed a framework for defining retention-in-care (Table 2.5) which takes into account the number of scheduled clinic visits and the attendance rate (N. C. Rollins et al., 2014). The INtegrating and Scaling-up PMTCT through Implementation REsearch (INSPIRE) initiative aimed at evaluating interventions to improve retention in care among pregnant and lactating women also used varied definition of retention. These projects that were carried out in three countries also used different definitions of retention-in-care each on its part trying to integrate attendance at a given point in time with some elements to elucidate the pattern of attendance to capture continuity (Mangwiro et al., 2014; N. Rollins et al., 2014; N. C. Rollins et al., 2014).

**Table 2.4**: Framework for Defining Retention-in-care

| Term | Definition | Comment |
|---|---|---|
| **Attendance (assessed at a single point)** | Attends clinic at stated time point ± 2 week | Equates with programmatic definition of retention-in care. Need to standardize breadth of window around time point. This would be reported as a stand-alone estimate, separate from retention-in-care |
| **Retention-in-care, for example, assessed at 12-month postpartum** | | |
| – **Full** | Attends at stated time, for example, 12 month (±2 week) and at least 80% of scheduled visits. | The proportions of follow-up visits that constitute full or partial retention-in-care should be standardized and should reflect a meaningful high or mid-range of continuity of care. Consensus is needed for the thresholds of the proportion of scheduled visit to be attended. |
| – **Partial** | Attends at stated time, for example, 12 month (±2 week) but for only 30%–80% of scheduled visits | Could also consider if woman does not attend at stated time but does attend the prior scheduled visit and more than half of other scheduled visits |
| **Not retained in care or failed** | Attends,30% of scheduled visits | |
| **LTFU** | Status/whereabouts not | |

| | |
|---|---|
| | known at the end of the study period |
| **Death** | Woman confirmed to have died at any time after enrolment |

Adopted from Rollins *et al.,* 2014

## 2.7 Adherence to HIV and AIDS care and treatment

Adherence to ART for HIV infection is important for plasma viral load suppression. This is key to treatment success as it reduces both morbidity and mortality but most especially improves the quality of life and reduces HIV drug resistance development (Bangsberg, 2008; Mills et al., 2006; Paterson et al., 2000). With an effective treatment regimen that fully suppresses viral replication, non-adherence is the only most important factor that leads to viral resistance. Unfortunately, health care workers are incapable of easily identifying patients who may or may not easily adhere to their treatment. It is therefore, important to perform formal adherence measurements in the course of treatment to provide an opportunity to identify who may require adherence support measures and take appropriate action.

Many tools have been developed over the years to assess HAART adherence. However, there is yet no gold standard on how to measure adherence (Oyugi *et al*., 2004). An ideal adherence measurement tool should be reliable, valid and logistically practical, without constraining either the participant or staff administering it (Simoni *et al*., 2006). However, in clinical settings, some authors think measures must be efficient, practical, and inexpensive, and precision may be less important than accurately identifying patients in need of interventions (Berg & Arnsten, 2006). The available methods have been categorized as either direct or indirect (L. Miller & R. Hays, 2000; Turner, 2002). Direct methods such as biological assays of active drug, metabolite or other markers in blood, urine, or other body fluids and directly observed treatment (DOT) confirms active drug ingestion. Indirect methods, which do not measure the level of the drug in the individual, include self-reports and visual analogue scale (VAS), clinician assessment, medical chart reviews, clinic attendance, pill counts (PC- announced and un announced), pharmacy refill records, medication or drug possession ratio, electronic drug monitoring (EDM) or medication even monitoring system (MEMS) and therapeutic impact such as HIV-1 viral load (VL), CD4+ T lymphocyte count, WHO staging of disease progression and mortality. Other publications go ahead to categorize the indirect methods into subjective and

objective depending on how the information is obtained (L. G. Miller & R. D. Hays, 2000; Paterson, Potoski, & Capitano, 2002; Steel, Nwokike, & Joshi, 2007). One of the most widely used indirect subjective measures of adherence is the self-report due to its practicality. These assessment methods have their advantages and disadvantages. In all, antiretroviral adherence is crucially important in resource limited settings where second line medication options are limited and third line regimens are virtually non-existent. Sub-optimal adherence must be timely and accurately identified and managed prior to the development of drug resistance.

### 2.7.1 Direct methods of adherence measures

#### 2.7.1.1 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) which involves measuring drug levels in the blood may fail to account for the variability of pharmacokinetic factors of medications and individuals and may be invasive. Their routine use in monitoring adherence for patients on treatment is limited to the protease inhibitor classes. In nucleoside reverse transcriptase inhibitors (NRTI), blood levels may not directly infer levels inside HIV-infected cells. This approach is expensive limiting its use in developing countries. Biomarkers can be used to monitor adherence by adding secondary non-toxic medicines to indicate the presence of the primary medicine initially taken. Factors other than adherence may affect drug levels, such as drug-drug interactions and diet. Also, serum drug levels only reflect adherence over the past 24 hours, and patients who are aware of a planned visit may ingest medication in anticipation of the test.

#### 2.7.1.2. Directly observed therapy

Direct observed therapy (DOT) method which has been widely used in TB treatment allows health care workers or supervisors directly administer medicines to patients. This method confirms adherence since the health care worker or supervisor observes the patient taking the medicine. Direct observation is objective and practical only in single-

dose therapy, intermittent administration and hospitalized patients. DOT has been used with success in settings of great privation like prisons with inmates (Farmer *et al*., 2001). Unfortunately its application in HIV may be limited since it is a chronic condition and treatment is life-long. Some see it as stigmatising, paternalistic and deprives the patient of his privacy. Due to cost and lack of the necessary logistics, direct methods of adherence assessment are seldom used in low resource settings.

### 2.7.2 Indirect methods of adherence measures

#### 2.7.2.1 Self-report adherence

This is one of the most widely used methods of adherence assessment for patients on HAART both in clinical and research settings. This personal interview or written questionnaire has many advantages among which are, low cost and flexibility in terms of mode of administration (Wagner & Miller, 2004). Additionally, the specificity of self-report measures is high, .i.e. patients' acknowledgement of non-adherence is generally credible (Bangsberg, Hecht, Clague, et al., 2001). With its flexibility, barriers and facilitators to adherence can be assessed with self-reports but are completely inaccessible with other adherence assessment methodologies (Simoni *et al*., 2006). In a meta-analysis the authors found that despite significant study heterogeneity, the pooled association between self-reported ART adherence and patient vireamia was statistically significant, adjusted OR = 2.31, 95% CI = 1.99, 2.68 (Nieuwkerk & Oort, 2005). However, Nieuwkerk and Oort in their study commented, “Patients early in their experience with HAART are more inclined to complete self-reports carefully. With time, patients may become accustomed to the self-report instruments and may learn that there are advantages to reporting higher adherence which makes it easier for them to complete the forms and could spare time that may be allocated to counselling about adherence based on their responses” (Nieuwkerk & Oort, 2005).

On the contrary, self-report is susceptible to recall bias, inaccurate memory and potentially to social desirability bias. Self-report may produce estimates of adherence that are 10-20% higher than those from electronic drug monitoring (Arnsten *et al.,* 2001;

Wagner & Miller, 2004). Overestimated adherence rates can result in patient misclassification and may lead to inaccurate targeting of adherence-improving interventions or delays in addressing adherence problems. Some guidelines now exit to greatly reduce social desirability bias. Using self-administered questionnaire with open-ended and forced choice items, introducing the topic with a preamble acknowledging the challenges and difficulty of attaining perfect adherence, wording items in such a way that non-adherence is presented as expected and accepted (Vinten, 1998; Wagner & Miller, 2004).

Reasons for non-adherence are then assessed specifying a time frame, focusing on recent behaviour, aiding recall when possible, attaching reports to salient events, embedding threatening with non-threatening items, using authority to justify and normalize the behaviour and ending with a reliability check of the accuracy of responses (L. Miller & R. Hays, 2000). Patients do report more accurately over briefer time periods. The recall period for self-report assessments varies with different studies ranging from three to seven days (Golin *et al.*, 2002; Reynolds *et al.*, 2007; Steel *et al.,* 2007; Wagner & Miller, 2004). However, the consensus is to have shorter recall periods to reduce recall bias though some authors hold that the seven day recall or having questions about adherence over the weekends were very important since adherence is problematic during weekends (Reynolds *et al.*, 2007). Interestingly, despite the shortcomings of self-reported adherence it remains one of the most widely used adherence measure both in clinical and research settings.

#### 2.7.2.2 Linear Visual Analogue Scale (VAS)

VAS is an instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot be easily measured directly. It is also considered as a subjective assessment of adherence which assesses adherence over a month prior to the assessment date. To measure adherence, the patient is asked to place a mark somewhere along a line from 0 to 10 that best describes their adherence to the

prescribed ARVs. VAS is a simple tool for uncovering adherence and has the potential for use for both clinical and research purposes in resource-constrained settings. The reliability and validity of the VAS has been demonstrated (Giordano, Guzman, Clark, Charlebois, & Bangsberg, 2004). This instrument which has been used to assess medication adherence for several years is based on the work of Walsh (Walsh, Mandalia, & Gazzard, 2002).

#### 2.7.2.3 Pharmacy Adherence Measures

Pharmacy refill or pill pickup records for measuring adherence to ART, pharmacy adherence measures (PAMs), are adherence estimates calculated using dates of prescription refills and/or pill counts performed during routine clinic visits (Bangsberg, 2008). PAMs which are not affected by recall or social desirability bias are objective and may be calculated from information routinely available in medical and pharmacy records (Meyer *et al*., 2011; Simoni *et al*., 2006).

In a systematic review of studies assessing adherence using PAMS the authors found that studies conducted in Low and middle income countries (LMICs) generally assessed ART-naive populations receiving nonnucleoside reverse transcriptase inhibitor (NNRTI) containing regimens and demonstrated that PAMs were predictive of either virological failure or virological suppression (Meyer *et al.*, 2011). PAMs may however, overestimate actual pill taking if individuals discard or share pills and, therefore, estimate maximum possible adherence.

On the other hand the most commonly used PAMs in clinical settings are pill count (PC) and patients may find this unacceptably intrusive or paternalistic which may eventually harm the physician-patient relationship. The patient may also forget to bring their pill bottles to scheduled visits and it is time consuming. Despite these limitations, in settings with limited routine viral load monitoring, PAMs can play an important role in monitoring individual and population-level adherence to ART. The table below identifies three broad categories of PAMs.

**Table 2.5:** Pharmacy-Based Adherence Measure (PAMs) Categories

| PAM category | Definition | Formulae |
|---|---|---|
| **Medication or drug possession ratio (MPR)** | Measures the amount of time an individual is in possession of >1 ARV or prescriptions for the ARVs as a proportion of the time between 2 ARV pick-ups or prescriptions | Number of days ARV prescribed or dispensed/number of days in the interval. |
| **Pill count** | Measures the quantity of ARV pills an individual has used between 2 ARV pickups as a proportion of the number of pills dispensed or as a proportion of time between pick-ups | 1. (Number of ARV pills dispensed – number of ARV pills returned)/number of ARV pills dispensed.<br>2. (Number of days ARV pills dispensed – number of days ARV pills returned)/ number of days in the interval. |
| **Pill pickup** | Measures whether an individual picks up all or a majority of their prescribed ARVs and expresses the adherence estimate in a dichotomous fashion (some measures require that ARVs be picked up on or before the date the previous ARV supply finishes). | 1. Where ‘‘Adherent’’ = (ARV refills picked up/ARV refills prescribed)> predefined value<br>2. Where ‘‘Adherent’’= (ARV refills picked up prior to previous refill finishing/ARV refills prescribed)> predefined value. |

Adopted from Meyer *et al.,* 2011

### 2. 7.2.4 Medication Event Monitoring System (MEMS)

Medication Event Monitoring System (MEMS) is considered by many to be the current state-of-the art method of assessing adherence, as its results strongly predict clinical outcome (Arnsten et al., 2001; Bangsberg, Hecht, Charlebois, Chesney, & Moss, 2001). Although commonly employed, the electronic medication monitor has several potential limitations.

It requires that (1) all medications are stored in the electronic monitor container, (2) only the correct numbers of pills are taken out with each dose, (3) the container is only opened during dosing, and (4) the monitor is closed after each dose (Bangsberg, Hecht, Charlebois, et al., 2001). Unfortunately, though readily available and has been used for decades in developed countries, MEMS caps are not easily available in developing countries except in few research settings (Steel *et al*., 2007).

### 2.7.3 Composite Adherence Measure (CAM)

Several studies have shown that pharmacy refill and pill count adherences are lower than self-reported adherence and higher than adherence measured by MEMS (Arnsten *et al.*, 2001; Chalker *et al.*, 2010; Liu *et al.*, 2001). It is therefore, evident that no single method provides the gold standard needed to assess adherence. Employing a technique that combines information from several measures will thus reduce the error that would be introduced by using a single method. (Berg & Arnsten, 2006; Steel *et al.*, 2007).

The first composite adherence score was produced and used in 2001 by Lui *et al.* The composite score produced method was higher than EDM and lower than both pill counts and self-reports. Compared to each individual adherence measure that made up this composite score, the score was the most highly correlated with virologic response (Liu *et al*., 2001). In another review the authors thought this might not be routinely required in clinical settings where viral loads and other biological markers are often readily available and funds for additional assessments are limited (Simoni *et al.*, 2006). In a summary measure of adherence using the 4 items of the AIDS Clinical Trial Group (ACTG) Adherence Questionnaire, the scored adherence was found to be strongly associated with plasma HIV RNA outcome and compared favourably with adherence estimates based on discrete medication event monitoring systems (MEMS) indices (Reynolds *et al.*, 2007). A validated multi-method tool has been in used in South Africa to monitor patient adherence in routine clinical care (Steel *et al.*, 2007). Several authors are unanimous on the use of a multiple adherence measures to better predict treatment outcome but there is yet no

consensus on how many measures to combine, how best to combine them and even how many time points to include. (Bangsberg, 2008). This could continue to vary overtime and with different settings as treatment protocols changes towards single dose regimens in order to improve adherence.

## 3. Methods

### 3.1 Study design and settings

This prospective cohort study investigated linkage to care including the uptake of HIV test and counselling (HTC) procedures, uptake of maternal ART, and retention to HIV care and treatment after initiation of Option B+ procedures with a targeted follow-up period of at least 12 months. The study was carried out in five health facilities (District Hospital Kumba, Presbyterian General Hospital Kumba, Kumba Town Urban Integrated Health Centre, Catholic Health Center Fiango and Ntam Integrated Health Centre Kumba) located within the Kumba Health District, South West Region, Cameroon, offering antenatal care (ANC), postnatal and infant welfare services. These facilities were selected based on high coverage, specifically receiving well over 90% of the pregnant women seeking ANC in the health district. Facilities were classified as large if they had a median monthly first ANC attendance of over 70 women and as small if the median monthly first ANC uptake was below 70 women.

These sites were among the ten sites that were selected to pilot Option B+ in this region with its staff being the first to be trained in Option B+ procedures and task shifting in the country. At the initiation of the pilot project staffs from all five health facilities were trained on Option B+ procedures and task shifting and the numbers of trained staff varied according to the volume of the site. Between 4 and 8 staff were trained per site. Task shifting allows midwives and nurses to prescribe and follow-up HIV-positive clients on ART. Facilities that lost more than 75% of their trained PMTCT staff within 6 months of the pilot project were classified as having a high staff turnover and those who lost between 50% and 75% of their trained PMTCT staff were considered as having a moderate staff turnover.

Alongside the clinical staff, a team of peer educators were trained to implement community follow-up of clients and especially tracking cases of women missing their clinic appointments and getting them back to care.

### 3.2 Description of the PMTCT programme in the South West Region, Cameroon

The PMTCT programme in the South West Region, Cameroon has been scaled up to cover the entire region since October 2011 by the Cameroon Baptist Convention Health Services (CBCHS) with funds from the United States' President's Emergency Plan For AIDS Relief (PEPFAR) working together with the Ministry of Public Health (MOPH), the Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) and the Clinton Health Access Initiative (CHAI) through its HIV-Free South West project. Kumba health district in the South West was the first in the country alongside the Bamenda health district in the North West to pilot option B+ in the country since October of 2013. Option B+ is now fully rolled out in the region since the beginning of 2016.

In the South West region, the pilot project took place in 10 health facilities of the Kumba health district including public, private and faith based health facilities. Within the PMTCT programme the MOPH provides most of the HIV test kits and the PEPFAR project provides just a buffer stock to avoid any stock outs. MOPH equally provides the ARVs required by the HIV-positive pregnant and breastfeeding mothers and their exposed babies alongside cotrimoxazole prophylaxis for the mother-baby pairs. CHAI on its part provides the region for this project with point of care (POC) CD4 machines. It has also strengthened laboratory capacity in collection and shipment of dried blood spot (DBS) samples for PCR testing from the entire region to the reference Laboratory in Mutengene. This was further reinforced in 2013 with the introduction of the 'bikers for health'. These are bike riders trained and provided with bikes to transport DBS samples and PMTCT reports from the various health facilities to the health district and in turn transport PMTCT commodities and utilities back to the health facilities. This has gone a long way to overcome one of the main challenges which is poor road infrastructure in the region. CHAI has also put in place at all district health services PCR SMS printers which are connected by internet to the reference laboratory to reduce the turnaround time in PCR result delivery. Another PEPFAR implementing partner also based in the region, Global Health Systems Solutions (GHSS) which is working very closely with the US Centre for Disease Control and Prevention (CDC)

is monitoring the main laboratories in the region for quality assurance in HIV rapid testing. In 2013, their services were expanded to include the 10 health facility laboratories that were included in the pilot project. This observational study was therefore carried out within this programmatic set up so that the results will reflect a real programme situation and will therefore help to inform policies in the rolled out of Option B+ in Cameroon.

### 3.3 Study population

The study population included all pregnant and breastfeeding women attending ANC, postnatal or infant welfare clinic (IWC) services for their first visit from the five selected health facilities of the Kumba Health District.

#### 3. 3.1 Inclusion criteria

- HIV-positive pregnant and breastfeeding women irrespective of age attending ANC, postnatal and infant welfare clinics (IWC) in 5 selected health facilities of the Kumba health district who gave their informed consent. However, adolescents and women under 21 years needed parental or guardian consent.

- Resident in the Kumba Health District and available for follow-up for the planned study duration.

#### 3.3.2 Exclusion criteria

- HIV-positive pregnant and breastfeeding women already on highly active antiretroviral therapy,

- Resident outside the Kumba health district area. This was to give all study participants the same opportunity to be followed up by peer educators through home visits and phone calls,

- Women who had any history of a medical or psychiatric disorder by interview and physical examination according to standard practices, which in the judgment of the treating physician or attending midwife/nurse, would interfere with or serve as a

contraindication to adherence to the study protocol or ability to give informed consent.

### 3.4 Ethical considerations

Ethical clearance for this study was obtained from the Institutional Review Board (IRB) of the University of Buea and administrative authorization from the Regional Delegation of Public Health of the South West Region to carry out research in the health district and health facilities within the region. Ethical waiver was obtained from the ethical review board of the Medical Research School of the Ludwig-Maximilians-Universität München. The attending midwife or designee ensured that before a pregnant or breastfeeding woman agreed to participate in the study, she understood its purpose, the procedure and any risks or benefits associated with the study by either providing her with the study information sheet or reading out and explaining the information sheet in case participant could not read or write. The woman was given enough time to study the informed consent form and had a chance to ask questions about the study. All women were informed that participation in the study was voluntary. A woman was free to decide not to take part in the study or stop being in the study at any time without it having any adverse consequences on the medical care she received at the moment or in the future or that of her baby or other relations. Individual written consents were obtained from each woman. Women who could not read had the consent form read to them by a study staff and they could give their informed consent by using their thumb prints. The informed consent carried only initials and the study code of the study participant for reasons of confidentiality. A copy of the signed informed consent form was then given to the woman to keep. All the tests required were routine in the study area for the follow-up of HIV positive-pregnant or breastfeeding women and their baby-pairs and the follow-up of PLHIV on antiretroviral therapy. However, the viral load at 12 months or soon after on ART was paid for entirely by the project. ARV treatment or cotrimoxazole prophylaxis for all study participants in this study was given free of charge.

### 3.5 Sample size consideration

To calculate the sample size we considered the primary hypothesis of a lower adherence in pregnant and breastfeeding women placed on life-long ART with a CD4+ T-cell count >350 cell/µL when compared to women who were placed on life-long ART based on CD4+T-cell count ≤350 cells/µL. Adherence to lifelong ART for PLHIV in Cameroon since the advent of free antiretroviral therapy in May, 2007 ranged between 80% and 95% (Mahy *et al*., 2011; Mbopi-Kéou, Djomassi, & Monebenimp, 2012; Mbuagbaw *et al*., 2012) for patients eligible for HAART. In a systematic review of adherence during and after pregnancy the authors estimated the pooled adherence in women with CD4+ T-cell count <350 cell/µL at 72% (Jean B Nachega et al., 2012). However, because we could not find any reference to adherence in women beginning ARVs at a CD4+ T-cell counts >350cells/µL we hypothesized that adherence in these women would be 15% lower. A study of ANC HIV-positive attendees in two semi-urban clinics in Buea, Cameroon predominantly (82.4%) had CD4+ T-cell >350 cells/µL (Takow et *al.*, 2013). We thus assumed that two-thirds of our patients would have CD4+ T-cell >350 cells/µL and one-third a CD4+ T-cell ≤350 cells/µL. The sample size was calculated using the G*-Power 3 calculator (Faul, Erdfelder, Lang, & Buchner, 2007) considering a power of 80% at a significance level of 5% to be able to identify this difference. We obtained a total minimum sample size of 236 with an attrition rate of 10% (CD4+ T-cell count >350 cells/µL =157 and CD4+ T-cell count ≤350 cells/µL = 79).

### 3.6 Study procedures

Women at first ANC registration visits underwent a group education session including HIV counselling messages, followed by 'opt-out' provider-initiated HIV antibody rapid testing, and individual post-test counselling for women assessed with an unknown HIV status. In the delivery room women with unknown HIV status were also counselled and provided HIV testing. HIV testing and counselling uptake was assessed and defined as the proportion of pregnant women received at first ANC or in the labour room who got newly

tested for HIV of all women seen with an unknown HIV status from the five participating sites.

Psychosocial and adherence support for women diagnosed HIV-positive were provided on ART initiation and followed-up by peer educators (PE). New ANC and labour cases were registered, an ARV follow-up card was opened for every HIV-positive woman initiating lifelong ART, and tracing information was documented by PE following individual consent. In addition, HIV infected breastfeeding mothers who were not yet on ART were recruited at the health facility's affiliated infant welfare clinics (IWC).

HIV-infected pregnant or breastfeeding women were started on lifelong ART based on a fixed dose combination of tenofovir, lamivudine and efavirenz (TELE) regardless of their clinical or immunological status in accordance with WHO and national guidelines (CNLS, 2015; WHO, 2013). Those who had initially started Option A were switched to Option B+ if they consented. In women with new HIV diagnosis, ART was initiated on the same day of diagnosis. To determine ART uptake we included all consenting pregnant and breastfeeding women from the five sites newly diagnosed HIV-positive including those who switched from option A to B+ and those known HIV-positive but were not yet on ART. Baseline socio-demographics, clinical and laboratory information were collected on study specific questionnaires and case report forms. Participants were then seen monthly for follow-up during ARV dispensing visits managed at ANC and IWC post-delivery by trained nurses or midwives. Clinic refill appointments were programmed during the first two weeks of the month. After the third week, clients who had not shown up for their scheduled visit were considered having missed their appointment and the PE immediately embarked on their search if consent to be traced by phone calls and /or home visits was available. Tracing outcomes were recorded as: (i) lost to follow up (LTFU) if the search went on for more than 90 days and the client was not reachable; (ii) transferred to another ART clinic if the client was reachable and confirmed to receive ART from another clinic and this was then verified by the PE; (iii) stopped treatment if the client was reachable but decided not to come back to care, in which case the reasons for stopping

treatment were noted; (iv) death. Women who were LTFU and those who had stopped treatment were considered having discontinued treatment. The date of treatment discontinuation was set at the date of the last missed appointment. Patients who were dead or transferred out were censored at the date of death or transfer. All women were followed up from ART initiation to the date of outcome of interest or censored at the 31st December 2015 date of database closure for women enrolled in the study.

All HIV exposed infants (HEI) after deliveries were enrolled and an HEI follow-up card was opened for them. During routine IWC, HEI were routinely followed up and DBS samples for DNA- PCR collected at 6-8 weeks. These samples were then transported to the district health service by 'bikers for health' for onward shipment to the reference laboratory. If HEIs were negative on the first PCR and remained asymptomatic they got an HIV antibody rapid test at 9 months and only children with positive antibody test at 9 months were eligible for a second PCR or else they had a confirmatory HIV antibody rapid test at 18 months after cessation of all breastfeeding. All the HEI were systematically put on cotrimoxazole prophylaxis as from 6 weeks of age until confirmation of their HIV status. For those whose PCR results came back positive, they were maintained on cotrimoxazole prophylaxis and were immediately transferred to the nearby HIV/AIDS management unit for initiation and follow-up on ART treatment. Babies born in the cohort were followed up till May 31st 2016 date of database closure for the exposed infants and those with complete 18 months follow up had their HIV antibody rapid test done.

### 3.7 Definition of outcomes

#### 3.7.1 Primary outcomes

Our primary outcomes were retention-in-care and adherence to lifelong ART at 6 and 12 months post ART initiation.

##### 3.7.1.1 Retention in care

Retention-in-care was defined as the proportion of women who had started on lifelong Option B+ ART and attended clinic visits at month 6 or 12, or any stated time prior to database closure or who were transferred out but known to continue ART following tracing information. Since we assessed treatment discontinuation i.e. LTFU or intentionally stopping ART and then used this as a continuous function to estimate retention in care in a time series analysis we are confident that our estimates will capture the continuity aspect of retention in care.

##### 3.7.1.2 ART adherence

Adherence was measured using three measures which were then combined into a composite adherence score and the overall adherence at 6 or 12 months was defined as the composite scores at 6 or 12 months. Previous studies have shown that available adherence measures have limitations, raising questions about how best to measure drug taking behaviour (Liu *et al*., 2001; Steel *et al*., 2007); consequently we decided to use a composite adherence score to more objectively measure adherence in our cohort.

#### 3.7.2 Secondary outcomes

Our secondary outcomes included HIV testing and counselling (HTC) uptake, ART uptake, treatment discontinuation, reasons for discontinuation, risk factors of treatment discontinuation, 12 months virologic suppression, HIV free survival at 6-8 weeks and maternal mortality and adverse pregnancy outcomes (abortions, still birth, preterm delivery and low birth weight). Maternal viral load was measured at 12 months post ART

initiation or soon after. The overall early HIV-free survival in the exposed babies was assessed at 6-8 weeks using the DNA-PCR following national guidelines and outcome compared to mothers composite adherence score at 12 months. For children who attained 18 months in the cohort prior to database closure for exposed babies, a final HIV-free survival was assessed using an HIV antibody rapid test after cessation of all breastfeeding. We collected additional data on service delivery, staffing, facility type and size.

#### 3.7.2.1 HIV testing and counselling uptake

HTC uptake was defined as the proportion of pregnant women received at first ANC or in the labour room who got newly tested for HIV of all women assessed with an unknown HIV status.

#### 3.7.2.2 ART uptake

ART uptake was defined as the proportion of HIV infected pregnant or breastfeeding women who were ART-naïve or on previous Option A starting on lifelong ART for Option B+.

#### 3.7.2.3 Treatment discontinuation rate

This was defined in this study as the proportion of women LTFU without any further information following 90 days tracing procedures and those who had intentionally stopped treatment of all women initiating lifelong ART. The date of treatment discontinuation was set at the date of the last missed appointment.

#### 3.7.2.4 Virologic suppression

A patient's viral load was considered suppressed if the plasma viral load collected at least 12 months after ART initiation was less than 1,000 copies/ µL on a single measurement (CNLS, 2015; WHO, 2016).

#### 3.7.2.5 Abortions

Abortions were defined as any pregnancy terminating on or before 28 weeks of gestation.

#### 3.7.2.6 Preterm delivery

Any baby born alive before 37 weeks of pregnancy are completed was considered preterm (WHO, 2012a).

#### 3.7.2.7 Low birth weight

Low birth weight was defined as any baby born alive with a body weight less than 2,500 grams irrespective of the gestational age.

### 3.8 Data collection procedure

A rigorous process was put in place to assure the quality of the data collected through trainings, supervision and continuous mentoring of the data collection staff monthly on the field by the principal investigator.

#### 3.8.1 Training and pretesting of questionnaire

We found that at all participating health facilities, the same staff were involved in antenatal care, delivery room, postnatal care and infant welfare services. The number of staff varied from one facility to the other depending on the work load. We thus selected between two and four staff from each participating facility and they were given a two days training. A total of 15 nurses and midwives were trained on the objectives of the study, the data collection tools and interviewing techniques especially in assessing adherence. The second day of the training was dedicated to the piloting of the questionnaire and this culminated in a debriefing session at the end of the day. The questionnaire was pre-tested with 15 participants at the district hospital Kumba with staff taking turns to administer the different sections of the questionnaire. Analysis of the piloted questionnaires and the inputs from the debriefing session led to some modifications before the production of the final version of the questionnaire and study forms.

#### 3.8.2 Monthly supervision

The principal investigator (PI) carried out monthly supervisory visits to all the five facilities to ensure the quality of data collection and to also motivate the staff. At each visit the PI cross-checked all filled visits to assure completeness and accuracy and also updated his monitoring spread sheet. With the help of this spread sheet the PI was able by phone calls to remind a facility as to when a patient's appointment was due. This greatly helped to assure accuracy and data completeness.

### 3.9 Construction, use and interpretation of the composite adherence score (CAS)

Steel and colleagues combined four items in the composite score they validated for South Africa including; Pill count, Pill instruction test, Visual analogue scale and a self-report.

This was necessary to account for the different types of pills that constituted the dose and the number of times medication had to be taken a day (Steel *et al*., 2007). In this study all women who initiated Option B+ in the pilot project were all on a single fixed dose combination therapy with tenofovir, lamivudine and efavirenz (TELE). We opted to use a composite adherence measure to reduce the errors associated with using a single adherence measuring tool. Since we had just a single once daily regimen which did not have any food or water restrictions, we did not need the pill instruction test and our adherence score was simply built on three elements including; Pill pick up from pharmacy refill records, a self-report questionnaire with 4 items and a 30-day visual analogue scale. We included the pharmacy refill record because till date in Cameroon ARVs are sourced and distributed by only one body through approved ARV treatment centres and Option B+ sites free of charge. We did not also include the pill count because of its demonstrated shortcomings (Berg & Arnsten, 2006).

Adherence was first estimated by each measure and classified into three categories as high, moderate and low before finally combing the results of the three measures into the CAS.

Six months after initiation of lifelong ART, the pharmacy refill records for each woman in care were reviewed by the study staff and the total refills documented using the ART cohort register. This was double-checked by cross-checking with the woman's personal clinic record and the peer educator's appointment log book to rule out any missing information resulting from incomplete filling of the ART register. Adherence was then estimated as follows;

- if the woman had picked up all her refills for six months she was scored as highly adherent,
- if she had missed one refill she was scored as moderately adherent and
- if she had missed more than one refill her adherence was scored as poor.

A face-to-face 4-day self-report questionnaire was then administered at the sixth month visit. The questions were usually prefaced by normalizing language in order to reduce

social desirability bias (Vinten, 1998; Wagner & Miller, 2004). The normalizing language we used was adopted from Steel and colleagues who developed and tested a multi-method tool in South Africa (Steel *et al.*, 2007). This was piloted and adapted to our setting before use. The version we used read thus:

*"I understand that most people taking antiretroviral medication (anti-HIV drugs) find it very difficult to take their medication regularly and may miss some doses. So I will not be surprised if you have had this happen to you. It is important for me to understand how you are really doing with your medicine. Don't worry about telling me if you don't always take all your doses. I need to know what is really happening, not what you think I want to hear".*

The interviewer then administered the four closed ended questions formulated such that right answer should be a no to avoid participants giving the spontaneous answer of 'yes' to save face when found in front of service providers. The table below has the four closed-ended questions that were used to evaluate self-reported adherence.

**Table 3.1:** The four self-report questions

| **Self-reported adherence** | | |
|---|---|---|
| 1 | Do you sometimes find it difficult to remember to take your medicine? | 0=No, 1=Yes |
| 2 | When you feel better, do you sometimes stop taking your medicine? | 0=No, 1=Yes |
| 3 | Thinking back over the past 4 days, have you missed any of your doses? | 0=No, 1=Yes |
| 4 | Sometimes if you feel worse when you take the medicine, do you stop taking it? | 0=No, 1=Yes |

(Adapted from Steel *et al.,* 2007)

Adherence in this case referred to the week before the interview took place. Self-reported adherence was then estimated as follows;

- if the woman responded no to all four questions she was scored as highly adherent
- if she responded yes to one question she was scored as moderately adherent and
- if she responded yes to two or more questions her adherence was scored as poor.

The last aspect of the adherence evaluation was done using the linear visual analogue scale (VAS) to evaluate one month adherence. This was always prefaced by normalising language as was the case in self-report above. The woman was then presented with the visual analogue scale on an enlarged plasticised chart with a pen and providing her with the following explanation.

*"Now I would like to ask you to estimate how much of your prescribed ARV you took in the last month. A mark at the left end where there is a number zero (0) means you had taken no medications. A mark in the middle where you see the number five (5) means you had taken about half of your medications and a mark on the right end where you can see the number ten (10) means you had taken every single dose of your medications. Please put a*

*mark on this line somewhere between 0 and 10 to describe your best guess about how much of your prescribed medication you took in the last month".*

The woman was then expected to put a mark along the scale as shown on the diagram below.

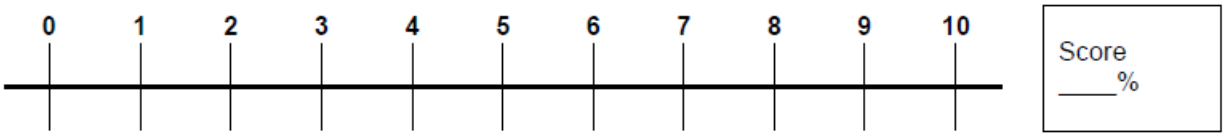


**Figure 3.1***: Visual Analogue Scale.*

*The above figure is based on the work of Walsh, 0% means the client has taken no drug, 50% means the client has taken about half of his/her drug, and 100% means the client has taken every single dose of his/her drug (Walsh et al., 2002).*

The midwife then transformed her best guess into a percentage and put in the score box beside. Adherence in this case referred to the month before the interview took place. Adherence was then estimated as follows;

- if the woman scored 90% or above her adherence was high
- if she scored between 70% and 90% her adherence was scored as moderate and
- if she scored below 70% her adherence was scored poor.

Since all our respondents used the whole numbers to score themselves all adherence rates were estimated as percentages of the whole numbers thus making the above a discrete rather than a continuous scale.

The results from the three different assessment measures were then transcribed and combined into a composite score table by the coders and the composite adherence score interpreted as explained below. Scores of adherence ranged between 1 and 3 such that 3=high (perfect adherence), 2 = moderate adherence and 1= poor (non-adherence).

**Table 3.2**: Interpreting the composite adherence score (CAS)

| **Adherence measure** | **SCORE** | | |
|---|---|---|---|
| **Pharmacy Refill** | Had 6 refills (3) | Missed 1 refill (2) | Missed 2 or more refills (1) |
| **Self-Report** | No to all questions (3) | Yes to 1 question (2) | Yes to 2 or more questions (1) |
| **VAS** | 90% or more (3) | 70 & 80% (2) | Less than 70% (1) |
| **Overall Adherence** | **High** | **Moderate** | **Low** |

(Adapted from Steel *et al.,* 2007)

Instead of just interpreting the composite adherence score by reading down the columns and across the table from left to right as Steel and colleagues did in South Africa (Steel *et al*., 2007), we used the sum of all possible combinations that could occur to determine CAS. However, if all the results appeared in the same column then the overall adherence was taken as that of that column. But this was not always the case in many situations as for the same woman her scores could spread across all adherence categories. Table 3.3 shows how all the different possible combination of scores were combined to come up with the final composite adherence score of each patient.

**Table 3.3:** All possible combinations of the three adherence measures of the CAS

| **Adherence tool** | **Score** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Medication refill** | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 2 | 2 | 1 |
| **Self-Report** | 3 | 3 | 3 | 2 | 2 | 2 | 1 | 2 | 1 | 1 |
| **VAS** | 3 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 |
| **Total score** | 9 | 8 | 7 | 7 | 6 | 6 | 5 | 5 | 4 | 3 |
| **CAS** | **High** | **Moderate** | | | | | **low** | | | |

Considering the fact that most studies have shown that moderate to high adherence is adequate for virological suppression with new treatment regimens (Bangsberg, 2006;

Kitahata et al., 2004) and given the results of the viral suppression at 12 months for our study participants we further regrouped the adherence into two categories such that high and moderate adherence was reported as good adherence and low reported as poor adherence. This was then used to dichotomise the adherence measure to determine the predictors of adherence in our cohort.

### 3.10 Viral load

#### 3.10.1 Viral load sample collection, processing and transportation

Once a study participant attained one year or soon after on antiretroviral therapy a whole blood sample was collected for viral load. For each eligible participant, venous blood (10 ml) was collected into 10ml ethylenediamine-tetra-acetate (EDTA) vaccutainer tube by a trained qualified phlebotomist. The sample was immediately centrifuged and 2 ml of plasma aliquoted into properly labelled cryovials and stored at -20 degrees at the District Hospital Laboratory Kumba. Samples were always collected in duplicates to compensate for possible manipulation errors.

The samples were then transported at the end of each week in an appropriate cold box to Buea. While in Buea, the samples were stored at -80 degrees at the Laboratory for Emerging Infectious Diseases of the Faculty of Science of the University of Buea. The samples were finally transported in a dry shipper with liquid nitrogen to the Chantal Biya International Research Centre (CIRCB), Yaoundé for viral load analysis. Before transporting the samples, the reference laboratory was informed in advance and staff kept on standby to receive the samples on arrival.

### 3.10.2 Sample analysis and interpretation

Plasma viral load was determined using the automated HIV-RNA Abbott Real Ti*m*e HIV-1 *m*2000™ System which is made up of Abbott *m*2000*sp* (RNA extraction) and Abbott *m*2000*rt* systems (Abbott Molecular Inc. Des Plaines, Illinois, USA) according to manufacturer's instructions. The Abbott RealTime HIV-1 assay is an invitro reverse transcription-polymerase chain reaction (RT-PCR) assay for the quantification of Human Immunodeficiency Virus type 1 (HIV-1) on the automated m2000 System in human plasma from HIV-1 infected individuals over the range of 40 to 10,000,000 copies/µL. The upper limit of quantification (ULQ) for the Abbott Real Ti*m*e HIV-1 assay was 10million copies/µL, and the lower limit of quantification (LLQ) was equivalent to the lower limit of detection (LOD) i.e. 40 copies/µL for the 0.6 µL sample volume procedure. Viral load values <40 copies/µL were considered undetectable. According to the 2016 WHO guidelines, adequate viral response is defined as viral load <1000 copies/µL (WHO, 2016). However, between 40-999 copies/µL this can be explained by a blip (intermittent low-level viraemia). Two persistent viral loads of ≥1000 copies/µL after ≥6 months of ART after adequate adherence enhancement defines virologic failure and the patient should be considered for switching to a second line regimen. The Abbott RealTime HIV-1 assay is intended for use in conjunction with clinical presentation and other laboratory markers for disease prognosis and for use as an aid in assessing viral response to antiretroviral treatment as measured by changes in plasma HIV-1 RNA levels. The Abbott Real Ti*m*e HIV-1 assay uses the automated extraction and detection m2000 system platform. This fully automated system has a reporting capacity of 93 patient results per an 8-h day and has been fully validated against other real time assays.

### 3.11 Statistical Analysis

Data were collected on study specific questionnaires and case report forms, entered into an Excel spread sheet and corrected for inconsistencies before extraction for analysis. Data were analysed using the IBM Statistical Package for Social Sciences (version 19, IBM SPSS Inc., Chicago IL, USA). For retention in care, descriptive statistics were reported for the baseline characteristics based on the retention status of the study participants. In a time to event analysis, observation time began from the date of ART initiation and ended at either, treatment discontinuation (stop treatment or lost to follow-up), transferred out, death or censored at the date of May 31, 2016 date of database closure. The Kaplan–Meier methods were used to assess treatment discontinuation and estimate retention-in-care at 6 and 12 months post-ART initiation and beyond. Cox proportional hazards model was used to compare different predictors of retention-in-care. Odds ratios (OR) and 95% confidence intervals (CI) that assessed the likelihood that study participants of specific demographic characteristics as well as in specific facility type would discontinue treatment or adhere to treatment were generated using the generalized estimating equation within the generalized linear model that accounted for potential correlation with clusters within facilities. Variables with marginal association ($p < 0.100$) and those proven to predict retention-in-care and adherence on lifelong ART were included in the multivariate analyses. Spearman correlation was used to compare the different adherence measures and to compare adherence at 6 and 12 months after ART initiation. Unadjusted odd ratios (OR) and adjusted OR were reported, including the 95% confidence intervals and an alpha level of $<0.05$ was used to define significance.

## 4. Results

### 4.1 Baseline characteristics, uptake of HTC and ART

Between October 2013 and December 2014, a total of 5,966 pregnant or breastfeeding women were attended to and assessed for HIV status at ANC/IWC of the five health facilities of the Kumba Health District. A total of 5,813 (97.4%) with an unknown HIV status received HIV testing and counselling (HTC) as applicable. One hundred and nineteen (2.0%) women were already on ART and excluded from the study, while 30 (0.5%) others had initiated Option A and 4 (0.1%) were known positive but were not yet on treatment. HTC uptake was 98.5% and 251 women were newly diagnosed HIV-positive giving a prevalence of 4.4%. Reasons why 90 (2.6%) women did not receive HTC were not assessed. In total, 285 pregnant and breastfeeding women who were either newly HIV diagnosed, ART naïve or previously receiving Option A regimen were eligible for Option B+. Of those 276 women were started on lifelong ART and 9 actively rejected ART initiation with a resultant ART uptake of 96.8%. Overall, 268 (94.0%) women initiating lifelong ART following Option B+ guidelines were included into the study, 8 (2.8%) women were not included as they were coming from other districts (Figure 4.1).

On inclusion, study participants were interviewed on their last menstrual period (LMP) at ANC initiation irrespective of their pregnancy status; 18 (6.8%) women reported staring ANC in the first trimester of their pregnancy, 180 (66.6%) in the second trimester and 62 (23.6%) in the third trimester (Figure 4.2). Two hundred and fifty three (94.4%) women initiated ART during pregnancy or labour and 15 (5.6%) started ART after delivery during breastfeeding.

All women were followed-up until December 31$^{st}$, 2015 with a median follow-up of 16.9 (IQR 11.1-23.3) months. Babies born in the cohort were followed up until May 31$^{st}$, 2016 date of database closure for the exposed infants and those with complete 18 months follow up had their HIV antibody rapid test done to determine their final HIV status.

Patients' status, site affiliation, baseline socio-demographic and HIV characteristics are provided in Table 4.1. In brief, 234 (87.3%) women were newly HIV diagnosed, the median age at ART initiation was 27 (IQR 24-31) years. The median CD4+ T-cell count at treatment initiation was 376 cells/mL (IQR 244 - 544.8) and 115 (43.0%) women had a CD4+ T-cell count less than 350 cells/mL. ART was started in 234 (87.3%) ART naïve women and in four others (1.5%) who had been exposed to ARV during previous pregnancies. Thirty (11.2%) women who had already received Option A during their current pregnancy were also switched to Option B+( Figure 4.1).

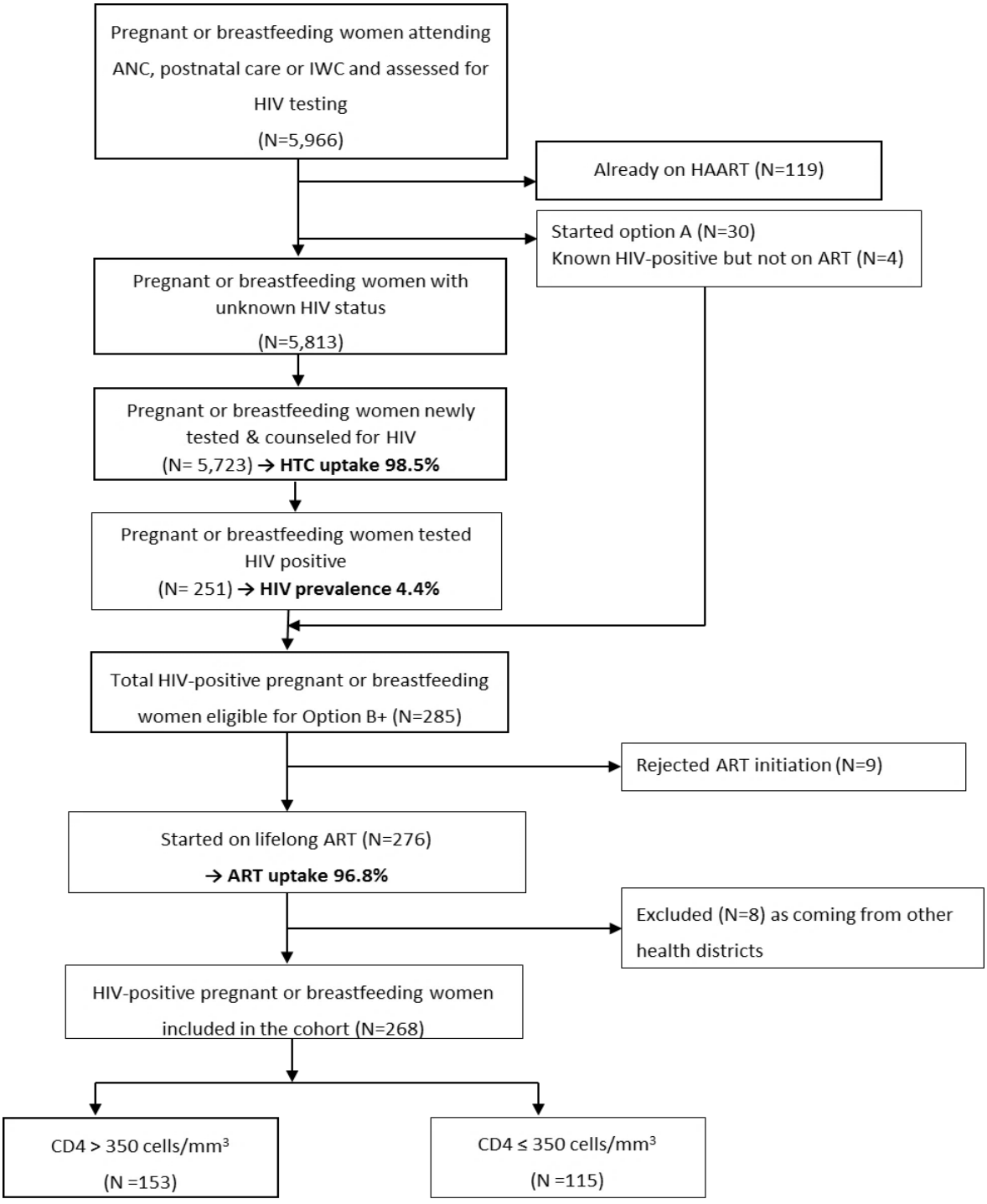


**Figure 4.1:** *Flow chart of study participants*

*Figure shows how women attending ANC and IWC services from the five participating facilities were assessed for HIV status, counselled and tested for those with unknown status and how positive cases were eligible for Option B+ and enrolled into the study.*

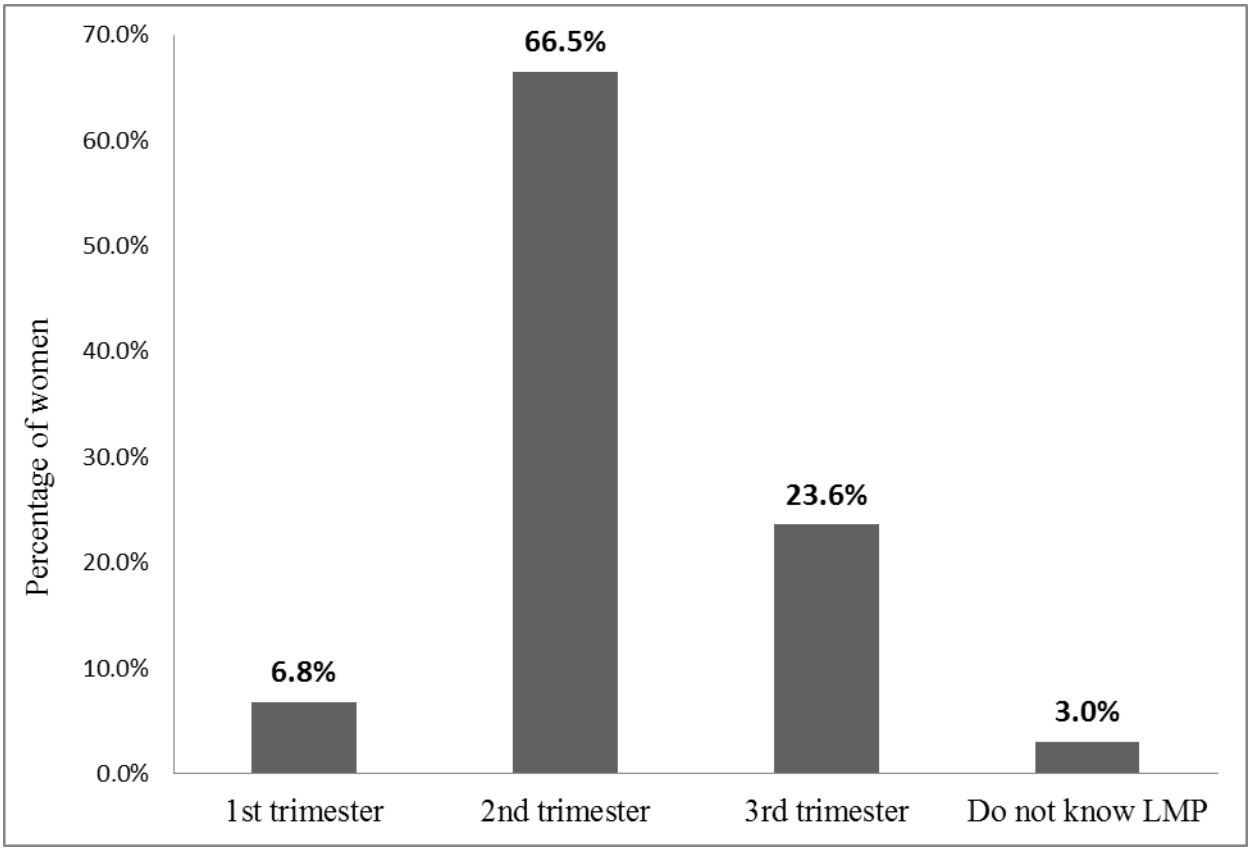


**Figure 4.2***: Distribution of women initiating Option B+ in Kumba health district by gestational age at ANC enrollment.*

About three quarters of the women started ANC before 28 weeks of pregnancy, providing a good opportunity to initiate ARV before delivery.

**Table 4.1:** Socio-demographic and clinical characteristics of women who started lifelong ART for PMTCT Option B+ in Kumba Health District, South West Region, Cameroon between October 2013 and December 2014 .

| Variable | Total Population N=268 | Women retained in care N=182 (67.9%) | Women who discontinued treatment N= 65 (24.3%) | Transferred to another ART clinic or died N=21 (7.8%) |
|---|---|---|---|---|
| **Age at ART initiation, median (IQR)** | 27 (24-31) | 28 (24.75-32) | 26 (23-30) | 29 (21-31.5) |
| 15-24 years | 76 (28.4) | 47 (25.8) | 22 (33.8) | 7 (33.3) |
| 25 years and above | 192 (71.6) | 135 (74.2) | 43 (66.2) | 14 (67.7) |
| **Educational Level** | | | | |
| None | 5 (1.9) | 5 (2.7) | 0 (0.0) | 0 (0.0) |
| Primary | 147 (54.9) | 93 (51.1) | 41 (63.1) | 13 (61.9) |
| Secondary and above | 116 (43.3) | 84 (46.2) | 24 (36.9) | 8 (38.1) |
| **Marital Status** | | | | |
| Single | 60 (22.4) | 43 (23.6) | 12 (18.5) | 5 (23.8) |
| Married | 171 (63.8) | 116 (63.7) | 43 (66.2) | 12 (57.1) |
| Others (divorced, widow) | 37 (13.8) | 23 (12.6) | 10 (15.4) | 4 (19.1) |
| **Number of children** | | | | |
| None | 65 (24.3) | 45 (24.7) | 15 (23.0) | 5 (23.8) |
| 1 – 2 | 139 (51.9) | 91 (50.0) | 38 (58.5) | 10 (47.6) |
| 3+ | 64 (23.9) | 46 (25.3) | 12 (18.5) | 6 (28.6) |
| **Cell phone possession** | | | | |
| Yes | 24 (9.0) | 16 (8.8) | 6 (9.2) | 2 (9.5) |
| No | 244 (91.0) | 166 (91.2) | 59 (90.8) | 19 (90.5) |
| **Religious affiliation** | | | | |
| Traditional Christian churches (Catholic, Presbyterian and Baptist) | 163 (60.8) | 109 (59.9) | 38 (58.5) | 16 (76.2) |
| Pentecostals | 100 (37.3) | 69 (37.9) | 26 (40.0) | 5 (23.8) |
| Muslim | 5 (1.9) | 4 (2.2) | 1 (1.5) | 0 (0.0) |
| **Occupation** | | | | |
| Unemployed | 137 (51.1) | 96 (52.7) | 29 (44.6) | 12 (57.1) |
| Employed (formal public sector) | 14 (5.2) | 10 (5.5) | 3 (4.6) | 1 (4.8) |

| | | | | |
|---|---|---|---|---|
| Employed (informal sector) or others | 117 (43.7) | 76 (41.8) | 33 (50.8) | 8 (38.1) |
| **HIV status** | | | | |
| Known HIV positive, not on ART | 4 (1.5) | 3 (1.6) | 1 (1.5) | 0 (0.0) |
| Known HIV positive, already started on AZT (Option A) | 30 (11.2) | 20 (11.0) | 8 (12.3) | 2 (9.5) |
| New HIV diagnosis | 234 (87.3) | 159 (97.8) | 56 (86.2) | 19 (90.5) |
| Missing | 34 (12.7) | 11 (6.2) | | 4 (19.0) |
| **Timing of ART initiation** | | | | |
| Breast feeding | 15 (5.6) | 8 (4.4) | 7 (10.8) | 0 (0.0) |
| Antenatal Care (ANC or labour) | 253 (94.4) | 174 (95.6) | 58 (89.2) | 21 (100) |
| **ARV use at initiation** | | | | |
| Previously exposed to ART prophylaxis | 33 (12.3) | 20 (11.0) | 11 (16.9) | 2 (9.5) |
| ART naïve | 235 (87.7) | 162 (89.0) | 54 (83.1) | 19 (90.5) |
| **CD4 cell count on initiation, median (IQR)** | 376 (244-544.8) | 368 (210-578.5) | 381 (277.8-604.5) | 372(241-500) |
| >350 cells/µL | 153 (57.1) | 104 (57.1) | 37 (56.9) | 12 (57.1) |
| ≤350 cells/µL | 115 (42.9) | 78 (42.9) | 28 (43.1) | 9 (42.9) |
| **WHO stage** | | | | |
| WHO stage 1 | 226 (84.3) | 157 (86.3) | 52 (80.0) | 17 (81.0) |
| WHO stage 2 | 35 (13.1) | 20 (11.0) | 12 (18.5) | 3 (14.3) |
| WHO stage 3 | 7 (2.6) | 5 (2.7) | 1 (1.5) | 1 (4.8) |
| **Health Facility Type** | | | | |
| Small sites with high staff turnover | 49 (18.3) | 24 (13.2) | 19 (29.2) | 6 (28.6) |
| Larger sites with moderate staff turnover | 219 (86.8) | 158 (86.8) | 46 (70.8) | 15 (71.4) |

*Data are in numbers and percentages [n (%)], unless stated otherwise*

Socio-demographic and clinical characteristics of women who were retained in care, discontinued treatment, died or transferred out to other clinics.

### 4.2 Retention in care and factors related with treatment discontinuation

Of the 268 women included in the study, 86 (32.0%) did not complete study procedures. Overall, 19 (7.1%) were self-transferred to other ART clinics for whom no further treatment information was available, 2 (0.7%) died and 65 (24.3%) women discontinued antiretroviral Option B+ therapy. Socio-demographic and HIV characteristics of women

who were retained in care, discontinued treatment, self-referred or died are shown in Table 4.1. At months 6, 32 (13.0%) women had discontinued treatment, of those 14 (43.8%) did not return for any refill appointment, and 24 (75.0%) had discontinued treatment within 3 months of ART initiation. Twenty (8.1%) women discontinued treatment between months 6 and 12, and cumulatively 52 (21.1%) women had discontinued treatment by month 12 of ART initiation. Numbers and percentages of women with treatment discontinuation by time and site are shown in Table 4.2. Treatment discontinuation at 12 months varied across the five sites ranging from 12.0% to 36.4% and the two smaller sites with a high staff turnover recorded the highest discontinuation rates (Table 4.2). Age presented as a significant predictor of treatment discontinuation in the clustering adjusted linear model [OR (95% CI) = 1.5 (1.1, 2.0), p = 0.020] with younger women more likely to discontinue their treatment but this significance was lost in the multivariate analysis.

Comparing treatment discontinuation before and after delivery it came out clear as can be seen on the Kaplan Meier curves (Figure 4.3) that women were three times more likely to discontinue their treatment after delivery than before delivery and this difference was statistically significant in a Cox proportional hazard model [HR (95% CI); 3.0 (1.7, 5.2), p = 0.012)].

Overall retention-in-care was estimated at 6 and 12 months after ART initiation using a time-to-event analysis to efficiently use all available data from each woman in the cohort. Including all 268 women in the Kaplan Meier analysis, 88.0% of women were still in care at 6 months and 81.1% were still in care at 12 months after ART initiation (Figure 4.4). Retention-in-care was significantly lower in women attending a small facility with a high staff turnover (83.0% and 68.3% at months 6 and 12, respectively) when compared to those attending a larger facility with a moderate staff turnover (89.2% and 84.1% at months 6 and 12, respectively) see Figure 4.7. Follow-up information on retention-in-care beyond 12 months was available for 201 women until 18 months and 185 women until 24

months with observed retention rates of 74.2% and 73.3%, respectively. In the Cox proportional hazard model adjusting for baseline age, CD4 count at initiation, educational level, marital status and timing of ART initiation low scale facility type with high staff turn-over were identified as a significant predictor for discontinuation of Option B+ procedures [HR (95% CI) = 2.0 (1.2,3.4), p = 0.012].This was confirmed in the clusters adjusted generalized estimating equation within the generalized linear model that adjusted for age, education level, marital status, timing of ART initiation, CD4 count at initiation [aOR (95% CI) = 2.5 (1.6, 3.9), p < 0.001].

Retention-in-care was lower in women initiating ART at breastfeeding than those initiating ART during ANC but this difference was not statistically significant [HR (95% CI) = 2.1 (0.9,4.6), p = 0.063]. This can be seen on the Kaplan Meier curves for women initiating ART at breastfeeding which remained below that for women initiating ART at ANC (Figure 4.6).

**4.3 Reasons for treatment discontinuation**

Of the 65 women who discontinued treatment, 29 (44.6%) were LTFU and the 36 (55.8%) who had intentionally stopped treatment and were successfully reachable were asked for reasons why treatments were stopped. The main reasons advanced included: (i) denial of HIV status, stigma and discrimination 19 (52.8%), (ii) religious reasons 9 (25.0%), and (iii) lack of transport fare to come to the clinic 4 (11.1%). Four (11.1%) women declined to provide any reason. All women reached were counselled by PE on the importance of resuming treatment. All those who had stopped treatment for religious reasons did not see any reason for returning and simply declared that their faith was going to heal them. Ten (52.6%) women who had stopped because of status denial, stigma and discrimination accepted to return for their treatment.

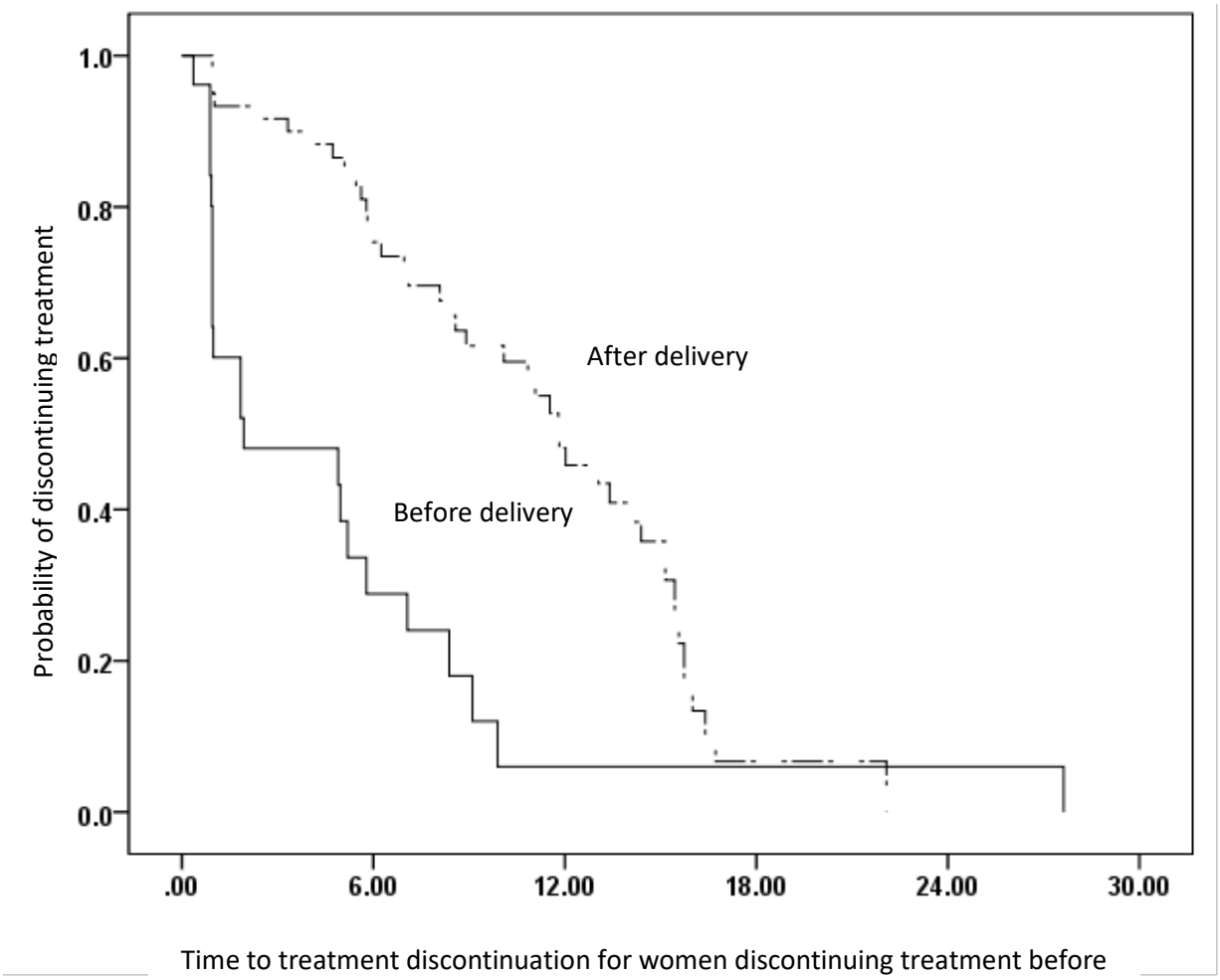


**Figure 4.3:** *Probability of women discontinuing treatment before and after delivery.*

**Table 4.2:** Treatment discontinuation (lost to follow-up & active treatment interruption) by sites and months after ART initiation following Option B+ procedures

| Health Facility | | Transferred to another ART clinic or died | Women analysed | Months to treatment discontinuation | | | |
|---|---|---|---|---|---|---|---|
| | | | | By month 6 | Between 6 and 12 months | Cumulative by month 12 | Between 12 and 27 months |
| Larger facilities with moderate staff turnover | CMA K | 6 | 75 | 4 (5.3) | 5 (6.7) | 9 (12.0) | 3 (4.0) |
| | PHC K | 6 | 66 | 6 (9.1) | 6 (9.1) | 12 (18.2) | 4 (6.1) |
| | DHK | 3 | 63 | 14 (22.2) | 2 (3.2) | 16 (25.4) | 2 (3.2) |
| Smaller facilities with high staff turnover | CMA N | 3 | 21 | 4 (19.0) | 3 (14.3) | 7 (33.3) | 1 (4.8) |
| | CHC F | 3 | 22 | 4 (18.2) | 4 (18.2) | 8 (36.4) | 3 (13.6) |
| **Total** | | **21** | **247** | **32 (13.0)** | **20 (8.1)** | **52 (21.1)** | **13 (5.3)** |

*Data are in numbers and percentages [n (%)]*

*CMA K: Urban integrated Health Center Kumba, PHC K: Presbyterian Hospital Kumba, DHK: District Hospital Kumba, CMA N: Integrated Health Center Ntam, CHC F: Catholic Health Center Fiango*.

**Table 4.3:** Risk factors associated with treatment discontinuation in women who were lost to follow- up or intentionally stopped their treatment after ART initiation following Option B+ procedures.

| Characteristics | Retained | Discontinued | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| **Age (years)** | | | | | | |
| 15-24 years | 47 (25.7) | 22 (33.8) | 1.5 (1.1-2.0) | **0.020** | 1.6 (0.9-2.8) | 0.091 |
| 25 years and above | 135 (74.2) | 43 (66.2) | 1 | | 1 | |
| **Educational Level** | | | | | | |
| None | 5 (2.7) | 0 (0.0) | - | | - | |
| Primary | 93 (51.1) | 41 (63.1) | 1.5 (0.8-3.1) | 0.223 | 1.6 (0.9-2.8) | 0.153 |
| Secondary and above | 84 (46.2) | 24 (36.9) | 1 | | 1 | |
| **Marital status** | | | | | | |
| Single | 43 (23.6) | 12 (18.5) | 1 | | 1 | |
| Married/cohabiting | 116 (63.7) | 43 (66.2) | 1.6 (0.9-2.8) | 0.131 | 1.7 (1.0—2.8) | 0.068 |
| Others (divorce or widow) | 23 (12.6) | 10 (15.4) | 1.2 (0.7-1.9) | 0.506 | 1.1 (0.6-2.0) | 0.897 |
| **Timing of ART initiation** | | | | | | |
| Antenatal Care (ANC or labour) | 174 (95.6) | 58 (89.8) | 1 | | 1 | |
| Breast feeding | 8 (4.4) | 7 (10.8) | 2.6 (0.6-11.5) | 0.201 | 2.8 (0.6-12.8) | 0.197 |
| **CD4 at initiation** | | | | | | |
| >350 cells/µL | 78 (42.9) | 28 (43.1) | 1 | | 1 | |
| ≤350 cells/µL | 104 (57.1) | 37 (56.9) | 1.0 (0.6-1.6) | 0.971 | 1.1 (0.7-1.7) | 0.741 |
| **Health Facility Type** | | | | | | |
| Larger sites with moderate staff turnover | 158 (86.8) | 46 (70.8) | 1 | | 1 | |
| Small sites with high staff turnover | 24 (13.2) | 19 (29.2) | 2.7 (1.7-4.4) | **<0.001** | 2.5 (1.6-3.9) | **< 0.001** |

*Data are in numbers and percentages [n (%)]*

The statistics in the table were generated using the generalised estimating equation within the generalised linear model accounting for correlation within clusters within health facilities. The point estimates in the multivariate analysis were adjusted for baseline age, educational level, marital status, timing of ART initiation and CD4 count at initiation.

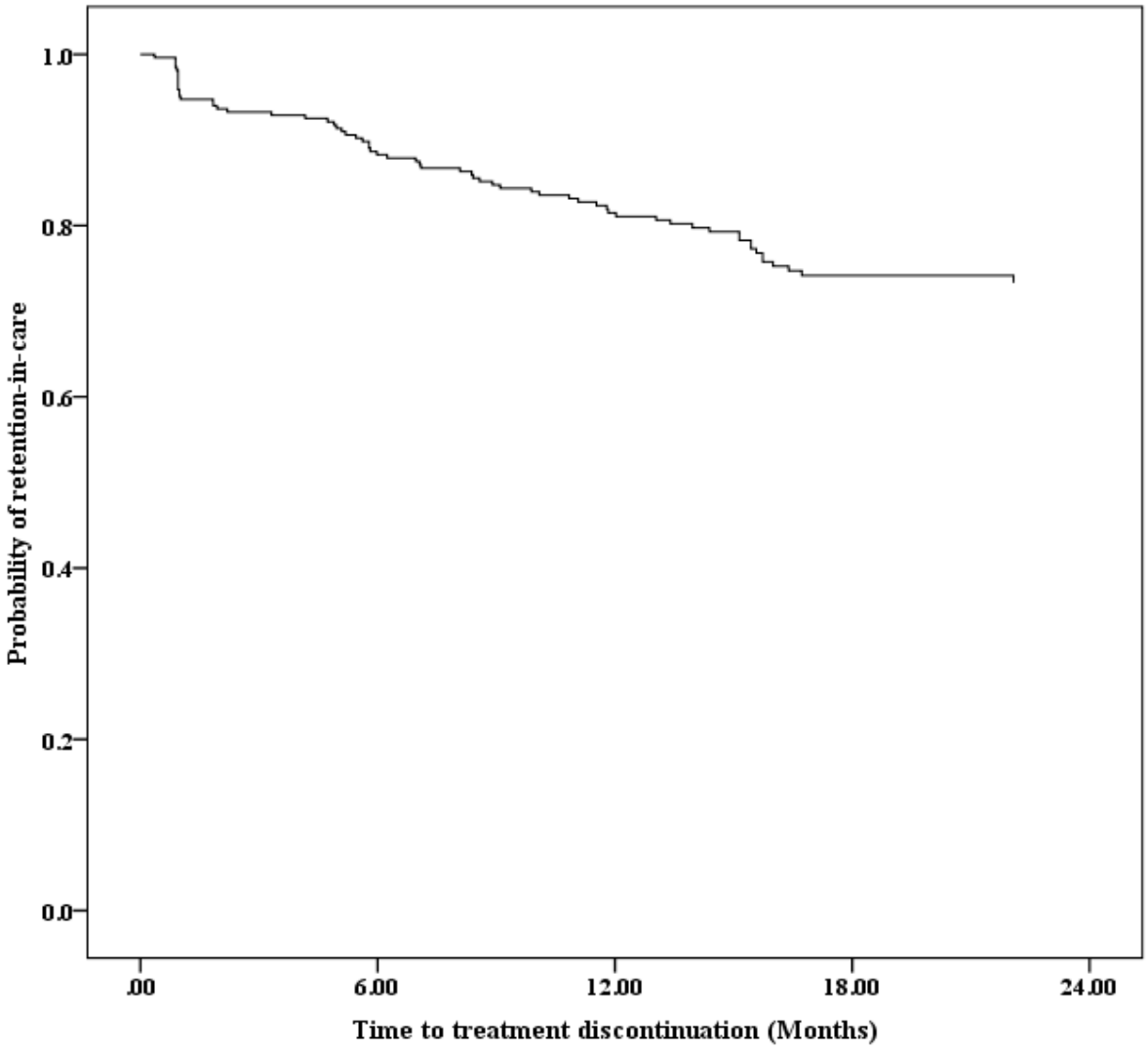


**Figure 4.4:** *Time to treatment discontinuation of the overall study participants*

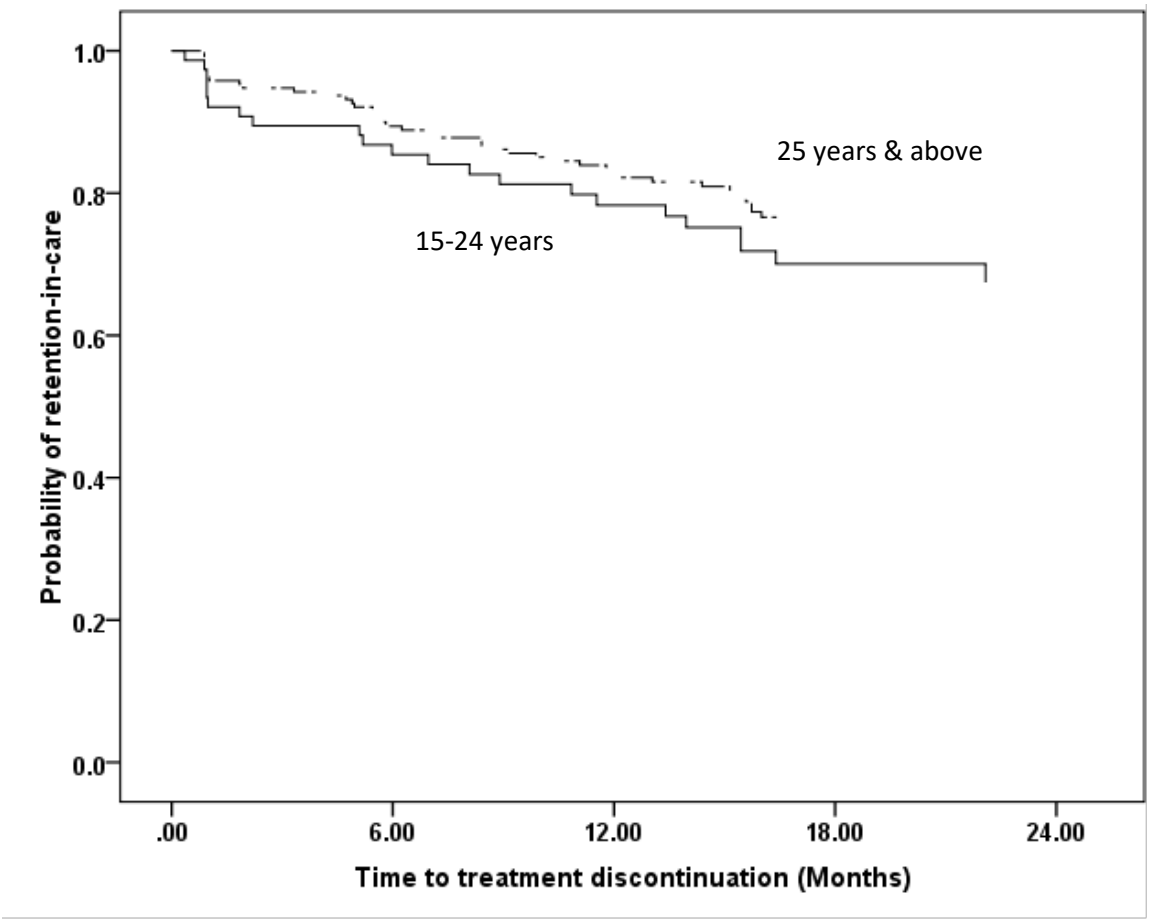


**Figure 4.5:** *Time to treatment discontinuation in women 15-24 years and those 25 years and above.*

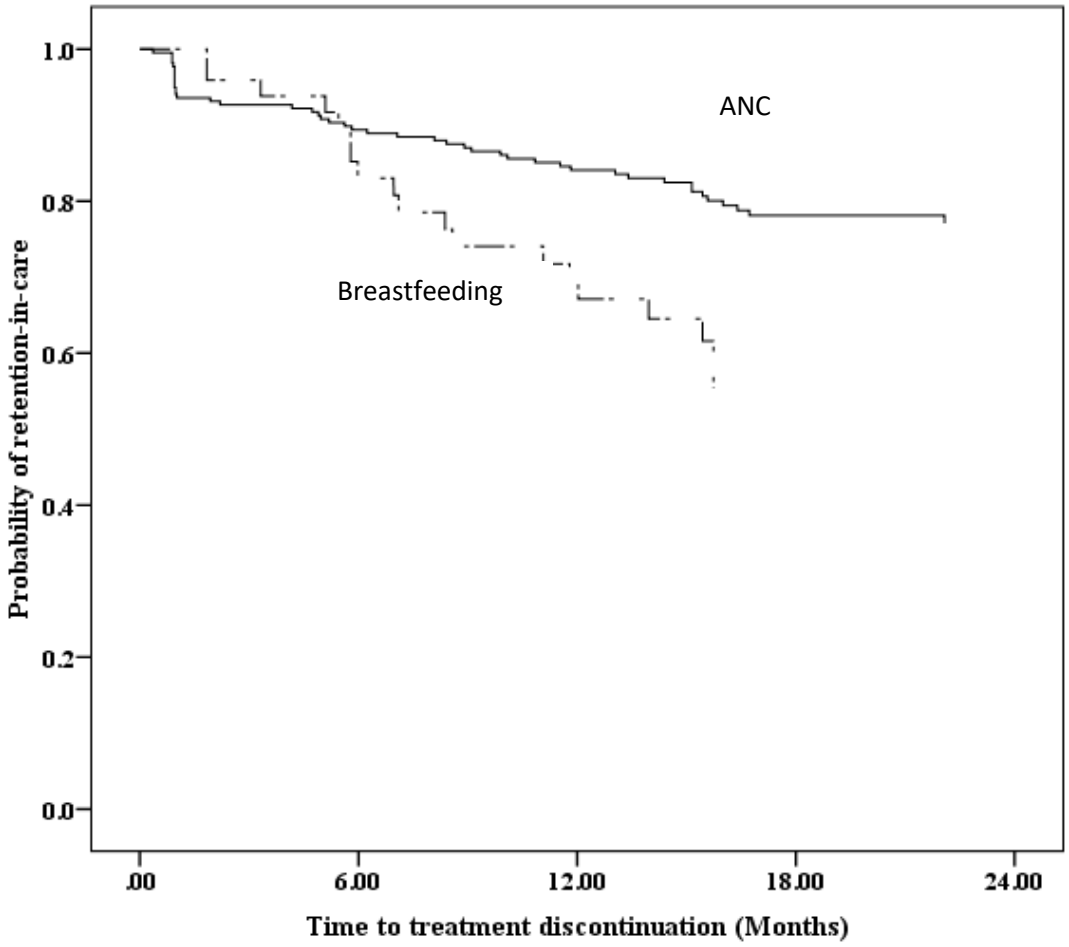


**Figure 4.6***: Time to treatment discontinuation in women initiating ART at antenatal care (ANC) and those initiating ART during the breastfeeding period.*

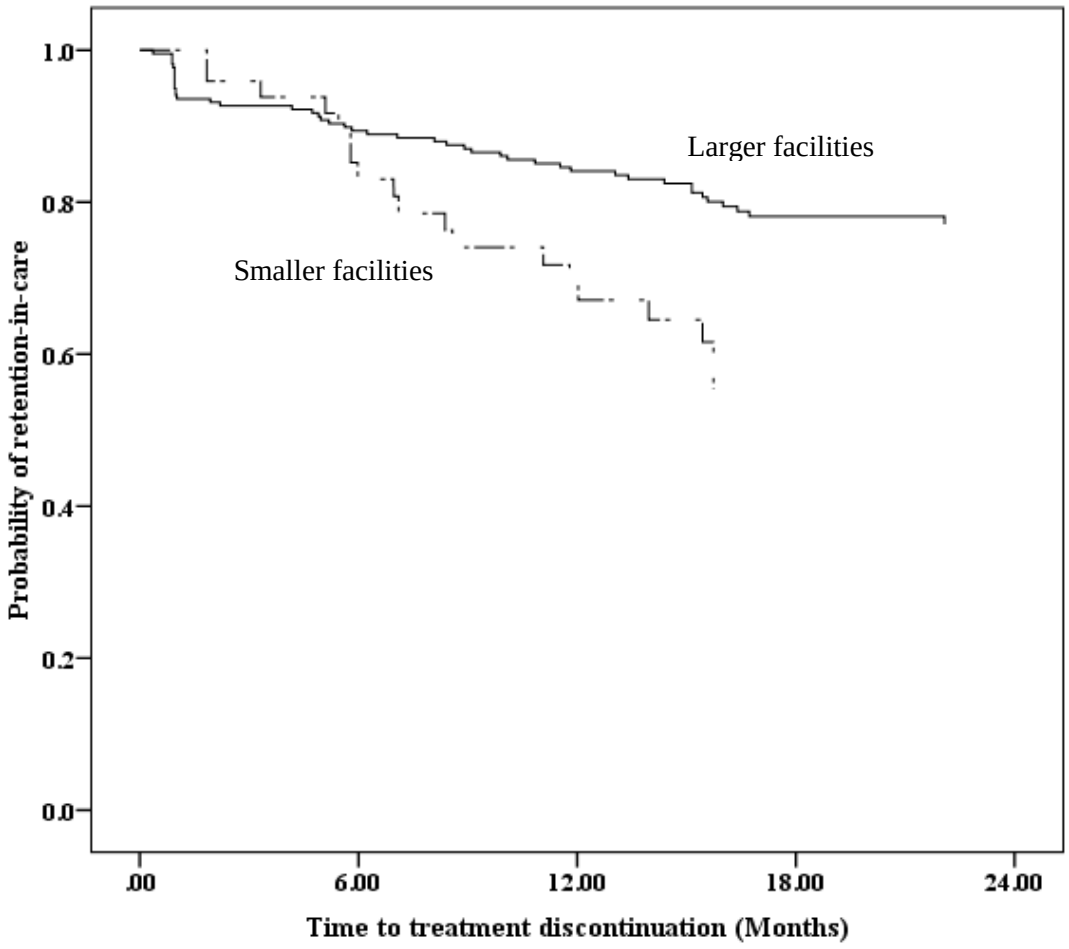


**Figure 4.7***: Time to treatment discontinuation in women attending small facilities with a high staff turnover and those attending larger facilities with moderate staff turnover.*

### 4.4 Service providers' turnover in Option B+ service provision

At the three large facilities only half of the trained staff were still providing PMTCT Option B+ services 6 months after training, and at the two small sites this was only a single staff member out of the four trained. It was only at one of the larger facilities that the staff trained and still providing services were exclusively managing women on Option B+. At all the four other sites the few staffs that remained were additionally tasked with multiple other functions, including on call duties resulting in absence or very few staff to provide PMTCT services at the following day. At some of these sites the peer educators who were assigned to follow-up on missed clinic appointments were found dispensing ARVs to women.

### 4.5 Adherence to ART

Adherence to lifelong ART was assessed for study participants who were available and responded to the adherence questionnaire and interpreted the visual analogue scale at 6 month and 12 months using a composite adherence score (CAS). The adherence at 6 months was the result of the CAS at 6 months and that at 12 months was the results of the CAS at 12 months. Women LTFU, died, transferred out to other ART facilities or had stopped treatment were excluded from the analysis. At 6 months 217 participants were assessed for adherence. Overall 128 (59.0%) women had a high adherence, 69 (31.8%) had a moderate adherence and 20 (9.2%) reported low adherence. Comparing all the adherence measures pharmacy refills tended to over estimate adherence followed by self report and the the visual analogue scale. At 12 months only 185 women were assessed for adherence. In all 116 (62.7%) had a high adherence, 48 (25.9%) had a moderate adherence and 21 (11.4%) had low adherence indicating a slight increase towards high adherence at month 12. Twelve months adherence was further dichotomized into good and poor adherence after validation with virologic outcome at 12 months. In all 164 (88.6%) women were assessed with good adherence and 21 (11.4%) had poor adherence. Younger women [OR (95%CI); 2.8 (0.9, 8.7)] and women attending Pentecostal churches [OR (95% CI); 6.1 (2.1, 17.6)] were more likely not to adhere to their ART treatment when

compared to older women and women who attended traditional christian churches. Also women who had just a primary level of education [OR (95%CI); 3.6 (2.2, 6.1)] and women employed in the informal sector [OR(95%CI); 2.1 (1.6-2.8)] were more likely to be non-adherent on treatment when compared with women with a secondary or higher level of education and those not employed (Table 4.5). After adjusting for demographics and other confounders, younger age, attending a Pentecostal church, low level of education and employment in the informal sector remained significantly associated with poor treatment adherence (table 4.6).

Assessing adherence both at two and three levels, adherence was not significantly associated with CD4+ T-cell count at treatment initiation (Tables 4.4 and 4.5). We thus failed to reject our null hypothesis.

**Table 4.4:** Adherence with different measures in three levels categorised by CD4- T cell count at treatment initiation

| **Adherence** | **N** | **CD4 count > 350 cells/μL N (%)** | **CD4 count ≤ 350cell/μL N (%)** |
|---|---|---|---|
| **Six Months** | **217** | **127 (58.5)** | **90 (41.5)** |
| **Pharmacy refill** | | | |
| Low | 17 (7.8) | 9 (7.1) | 8 (8.9) |
| Moderate | 17 (7.8) | 8 (6.3) | 9 (10.0) |
| High | 183 (84.3) | 110 (86.6) | 73 (81.1) |
| **Self-report** | | | |
| Low | 15 (6.9) | 7 (5.5) | 8 (8.9) |
| Moderate | 43 (19.8) | 30 (23.6) | 13 (14.4) |
| High | 159 (73.3) | 90 (70.9) | 69 (76.7) |
| **VAS** | | | |
| Low | 12 (5.5) | 6 (4.7) | 6 (6.7) |
| Moderate | 55 (25.3) | 32 (25.2) | 23 (25.6) |

| | | | |
|---|---|---|---|
| High | 150 (69.1) | 89 (70.1) | 61 (67.8) |
| **CAS** | | | |
| Low | 20 (9.2) | 10 (7.9) | 10 (11.1) |
| Moderate | 69 (31.8) | 41 (32.3) | 28 (31.1) |
| High | 128 (59.0) | 76 (59.8) | 52 (57.8) |
| **Twelve Month** | **185** | **109** | **76** |
| **Pharmacy refill** | | | |
| Low | 23 (12.4) | 14 (12.8) | 9 (11.8) |
| Moderate | 12 (6.5) | 7 (6.4) | 5 (6.6) |
| High | 150 (81.1) | 88 (80.8) | 62 (81.6) |
| **Self-report** | | | |
| Low | 11 (5.9) | 7 (6.4) | 4 (5.3) |
| Moderate | 31 (16.8) | 19 (17.4) | 12 (15.8) |
| High | 143 (77.3) | 83 (76.2) | 60 (78.9) |
| **VAS** | | | |
| Low | 14 (7.6) | 5 (4.5) | 9 (11.8) |
| Moderate | 36 (19.5) | 26 (23.9) | 10 (13.2) |
| High | 135 (73.0) | 78 (71.6) | 57 (75.0) |
| **CAS** | | | |
| Low | 21 (11.4) | 11 (10.1) | 10 (13.2) |
| Moderate | 48 (25.9) | 31 (28.4) | 17 (22.4) |
| High | 116 (62.7) | 67 (61.5) | 49 (64.5) |

*Data are in numbers and percentages [n (%)]*

**Table 4.5:** Risk factors of poor adherence to treatment at 12 months after initiating Option B+ in Kumba health district.

| Characteristics | N | Poor adherence | Good adherence | OR (95%CI) | P-value |
|---|---|---|---|---|---|
| **Number of patients** | **185** | **21 (11.4)** | **164 (88.6)** | | |
| **Age at ART initiation** | | | | | |
| 15-24 years | 50 (27.0) | 10 (47.6) | 40 (24.4) | 2.8 (0.9-8.7) | 0.072 |
| 25 years and above | 135 (73.0) | 11 (52.4) | 124 (75.6) | 1 | |
| **Educational Level** | | | | | |
| None | 4 (2.2) | 0 (0.0) | 4 (2.4) | - | |
| Primary | 91 (49.2) | 16 (76.2) | 75 (45.7) | 3.6 (2.2-6.1) | **<0.001** |
| Secondary and above | 90 (48.6) | 5 (23.8) | 85 (51.8) | 1 | |
| **Marital Status** | | | | | |
| Single | 43 (23.2) | 5 (23.8) | 38 (23.2) | 1 | |
| Married/cohabiting | 140 (75.7) | 16 (76.2) | 124 (75.6) | 1.0 (0.4-2.9) | 0.971 |
| Others (divorced, widow) | 2 (1.1) | 0 (0.0) | 2 (1.2) | - | |
| **Occupation** | | | | | |
| Unemployed | 78 (42.2) | 5 (23.8) | 73 (44.5) | 1 | |
| Employed formal sector | 9 (4.9) | 0 (0.0) | 9 (5.5) | - | |
| Employed informal sector | 98 (53.0) | 16 (76.2) | 82 (50.0) | 2.1 (1.6-2.8) | **<0.001** |
| **Number of children** | | | | | |
| None | 46 (24.9) | 4 (19.0) | 42 (25.6) | 1.2 (0.3-4.8) | 0.759 |
| 1 – 2 | 97 (52.4) | 14 (66.7) | 83 (50.6) | 2.2 (0.6-8.2) | 0.242 |
| 3+ | 42 (22.7) | 3 (14.3) | 39 (23.8) | 1 | |
| **Cell phone possession** | | | | | |
| No | 14 (7.6) | 1 (4.8) | 13 (7.9) | 0.6 (0.1-4.6) | 0.606 |
| Yes | 171 (92.4) | 20 (95.2) | 151 (92.1) | 1 | |
| **Religious affiliation** | | | | | |
| Traditional Christian churches (Catholic, Presbyterian and Baptist) | 108 (58.4) | 5 (23.8) | 103 (62.8) | 1 | |
| Pentecostals | 70 (37.8) | 16 (76.2) | 54 (32.9) | 6.1 (2.1-17.6) | **< 0.001** |

| | | | | | |
|---|---|---|---|---|---|
| Muslim | 5 (2.7) | 0 (0.0) | 5 (3.0) | | |
| **Timing of ART initiation** | | | | | |
| Breast feeding | 7 (3.8) | 0 (0.0) | 7 (4.3) | - | - |
| Antenatal Care (ANC or labour) | 178 (96.2) | 21 (100) | 157 (95.7) | | |
| **CD4 cell count on initiation,** | | | | | |
| ≤350 cells/µL | 76 (41.1) | 10 (47.6) | 66 (40.2) | 1.4 (0.5-3.8) | 0.575 |
| >350 cells/µL | 109 (58.9) | 11 (52.4) | 98 (59.8) | 1 | |
| **WHO stage** | | | | | |
| WHO stage 1 | 160 (86.5) | 18 (85.7) | 142 (86.6) | 1 | |
| WHO stage 2 | 21 (11.4) | 3 (14.3) | 18 (11.0) | 0.8 (0.2-2.8) | 0.683 |
| WHO stage 3 & 4 | 4 (2.2) | 0 (0.0) | 4 (2.4) | - | |
| **Health Facility Type** | | | | | |
| Small sites with high staff turnover | 26 (14.1) | 4 (19.0) | 22 (13.4) | 1.5 (0.3-7.1) | 0.597 |
| Larger sites with moderate staff turnover | 159 (85.9) | 17 (81.0) | 142 (86.6) | 1 | |

*Data are in numbers and percentages [n (%)]*

**Table 4.6:** Risk factors of poor adherence to treatment at 12 months following Option B+ initiation with adjusted OR in Kumba health district.

| Characteristics | Poor adherence | Good adherence | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| **Age (years)** | | | | | | |
| 15-24 years | 10 (47.6) | 40 (24.4) | 2.8 (0.9-8.7) | 0.072 | 4.3 (1.2-15.3) | **0.022** |
| 25 years and above | 11 (52.4) | 124 (75.6) | 1 | | 1 | |
| **Educational Level** | | | | | | |
| None | 0 (0.0) | 4 (2.4) | - | | - | |
| Primary | 16 (76.2) | 75 (45.7) | 3.6 (2.2-6.1) | **< 0.001** | 2.7 (1.9-3.9) | **< 0.001** |
| Secondary and above | 5 (23.8) | 85 (51.8) | 1 | | 1 | |
| **Occupation** | | | | | | |
| Unemployed | 5 (23.8) | 73 (44.5) | 1 | | 1 | |
| Employed formal sector | 0 (0.0) | 9 (5.5) | - | | - | |
| Employed informal sector | 16 (76.2) | 82 (50.0) | 2.1 (1.6-2.8) | **< 0.001** | 3.5 (2.7-4.7) | **< 0.001** |
| **Religious affiliation** | | | | | | |
| Traditional Christian churches (Catholic/Presbyterian and Baptist) | 5 (23.8) | 103 (62.8) | 1 | | 1 | |
| Pentecostals | 16 (76.2) | 54 (32.9) | 6.1 (2.1-17.6) | **< 0.001** | 5.8 (3.5-16.2) | **<0.001** |
| Muslim | 0 (0.0) | 5 (3.0) | - | | - | |
| **CD4 at initiation** | | | | | | |
| >350 cells/µL | 10 (47.6) | 66 (40.2) | 1.4 (0.5-3.8) | 0.575 | 2.3 (0.9-5.7) | 0.078 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≤350 cells/µL | 11 (52.4) | 98 (59.8) | 1 | | 1 | |
| **Health Facility Type** | | | | | | |
| Larger sites with moderate staff turnover | 4 (19.0) | 22 (13.4) | 1.5 (0.3-7.1) | 0.597 | 1.4 (0.4-4.9) | 0.583 |
| Small sites with high staff turnover | 17 (81.0) | 142 (86.6) | 1 | | 1 | |

*Data are in numbers and percentages [n (%)], OR (odd ratio), aOR (adjusted odd ratio)].*

The statistics in the table were generated using the generalised estimating equation within the generalised linear model accounting for correlation within clusters within heath facilities. The point estimates in the multivariate analysis were adjusted for baseline age, educational level, occupation, religious affiliation, timing of ART initiation, CD4 count at initiation and facility type.

### 4.6 Correlation between different adherence measures

The different adherence maesures were all correlated with each other and all were significantly correlated to the composite adherence score with a Spearman correlation ranging from 0.36 to 0.83 ($p < 0.001$ for all comparisms). However, the highest linear correlation was observed between the CAS and VAS which remained consistent both at 6 and 12 months with a Spearman correlation of $r = 0.83$ (Tables 4.7 and 4.8).

**Table 4.7:** Correlation coefficient between different adherence measures at 6 months

| | **Phamacy refill** | **Self-report** | **VAS** | **CAS** |
|---|---|---|---|---|
| Pharmacy refill | 1.00 | 0.42 | 0.52 | 0.62 |
| Self-report | 0.42 | 1.00 | 0.52 | 0.76 |
| VAS | 0.52 | 0.52 | 1.00 | 0.83 |
| CAS | 0.62 | 0.76 | 0.83 | 1.00 |

**Table 4.8:** Correlation coeffivient between the different adherence measures at 12 months

| | **Pharmacy refill** | **Self-report** | **VAS** | **CAS** |
|---|---|---|---|---|
| Pharmacy refill | 1.00 | 0.36 | 0.65 | 0.72 |
| Self-report | 0.36 | 1.00 | 0.49 | 0.71 |
| VAS | 0.65 | 0.49 | 1.00 | 0.83 |
| CAS | 0.72 | 0.71 | 0.83 | 1.00 |

### 4.7 Potential causes of missing treatment and reminders of drug taking

Among the women who were available at 12 months and responded to the adherence evaluation questionnaire they were also asked what could potentially cause them to miss taking medications and what were some of those things that also reminded them to take their medication. This is one of the useful aspects of the self-report assessment which is not feasible with the other assessment measures. Concerning the first question what could potentially cause them to miss taking medicines 121 (65.4%) women provided explanations. Some women gave more than one reason for missing to take their medications. Frequently cited reasons were forgetfulness 43 (35.5%), travel away from home 29 (24.0%) and lack of transport to the clinic 28 (23.1%). Stigmatisation, being distracted by the baby, being away for work and being involved in church or other social activites were also advanced ( Table 4.9 ).

**Table 4.9:** Reasons for potentially missing to take ART amongst women on Option B+ in Kumba health district.

| **Reasons for potentially not taking medications** | **N** | **% Respondents** |
|---|---|---|
| **Total women** | **185** | |
| **Non respondents** | **64** | **34.6** |
| **Respondents** | **121** | **65.4** |
| – Away for work | 5 | 4.1 |
| – Forgetfulness | 43 | 35.5 |
| – Lack of transport to come to pick up ARV | 28 | 23.1 |
| – Travel away from home | 29 | 24.0 |
| – Baby distraction | 5 | 4.1 |
| – Side effects mainly dizziness | 6 | 5.0 |
| – Stigmatisation | 5 | 3.3 |
| – Involved in church or social activities | 4 | 4.1 |
| – Lack of food | 2 | 1.7 |
| – Child Vaccination is over | 1 | 0.8 |

*NB* Percentatges are out of those who responded to each question. Some women gave more than one reason so total may add up to over 100.*

On the other hand women were more ready to share some of the things that reminded them to better take their medications. To the question what helps remind you to take your medications 172 (94.0%) women provided responses. The most frequently cited was the use of cell phone alarms 64 (37.2%), secondly most women said drug taking has become a routine in their lifes so it occurs more like an instinct 63 (36.6%) and the use of alarm clocks 22 (18.8%). Among the less frequently cited, interestingly 13 (7.6%) women declared that they were being reminded by their husbands, 4 (3.3%) relied on a TV series why another 4 (3.3%) had their drugs by their bedside (Table 4.10).

**Table 4.10:** Means of reminding women to take ART amongst women on Option B+ in Kumba Health district.

| **Treatment reminder** | **N** | **% Respondents** |
|---|---|---|
| **Total women** | **185** | |
| **Non respondents** | **13** | **7.0** |
| **Respondents** | **172** | **93.0** |
| – Phone alarm | 64 | 37.2 |
| – Clock alarm | 22 | 18.8 |
| – Become a daily routine | 63 | 36.6 |
| – Husband | 13 | 7.6 |
| – TV series | 4 | 2.3 |
| – Drugs by my bedside | 4 | 2.3 |
| – Sister/Mother | 1 | 0.6 |
| – Church bell/Prayer time | 1 | 0.6 |

*NB* Percentatges are out of those who responded to each question and many women gave multiple responses so may add up to over 100*

### 4.8 Viral Load

All clients who were retained-in-care at 12 months were eligible for viral laod collection. Overall, 165 (90.7%) women had their viral loads samples collected at 12 months. Those whose viral loads samples were not collected were either missed out because they did not attend clinic on the day the team collecting the viral load samples was around or they had collected their medications earlier on because they were either traveling or came from far off distances. Of the 165 women who had their VL done, 139 (84.2%) were undetectable i.e. <40 copies/µL, 14 (8.5%) had VL between 40-999 copies/µL and 12 (7.3%) had VL above 1,000 copies/µL. We used the WHO definition (Viral suppression < 1,000 copies/µL) to classify clients as either virologically suppressed or not and 153 (92.7%) women were virologically suppressed. Women with VL between 40-999 copies/µL were considered to be having a blip and were counselled accordingly. For those who had VL above 1,000 copies/µL they were counselled and adequately supported for adherence and a second sample was recollected after 4 weeks. Samples were successfully recollected for 8 out of the 12 women who were virologically unsupressed. Treatment failure was confirmed in five women whose second VL came back unsuppressed and they were immediately referred to the mian HIV treatment centre of the health district for consideration of switching them to second line therapy. Three women were resuppressed after counselling and adherence reinforcement. There was no clear association between women's socio-demographic or HIV characteristics and virologic suppression (Table 4.11).

**Table 4.11:** Virologic outcome for pregnant and breastfeeding women retained in care at 12 months after initiating Option B+ in Kumba health district.

| **Characteristics** | **N** | **Unsuppressed VL ≥ 1,000copies/μL N (%)** | **Suppressed VL < 1,000 copies/μL N (%)** | **P-value** |
|---|---|---|---|---|
| **Number of patients** | **165** | **12 (7.3)** | **153 (92.7%)** | |
| **Age at ART initiation** | | | | |
| 15-24 years | 44 (26.7) | 5 (41.7) | 39 (25.5) | 0.306 |
| 25 years and above | 121 (73.3) | 7 (58.3) | 114 (74.5) | Ref. |
| **Educational Level** | | | | |
| None | 4 (2.4) | 0 (0.0) | 4 (2.6) | - |
| Primary | 80 (48.5) | 6 (50.0) | 74 (48.4) | 0.851 |
| Secondary and above | 81 (49.1) | 6 (50.0) | 75 (49.0) | Ref. |
| **Marital Status** | | | | |
| Single | 38 (23.0) | 2 (16.7) | 36 (23.5) | Ref. |
| Married/cohabiting | 125 (75.8) | 10 (83.3) | 115 (75.2) | 0.782 |
| Others (divorced, widow) | 2 (1.2) | 0 (0.0) | 2 (1.3) | - |
| **Number of children** | | | | |
| None | 40 (24.2) | 3 (25.0) | 37 (24.2) | Ref. |
| 1 – 2 | 85 (51.6) | 9 (75.0) | 76 (49.7) | 0.104 |
| 3+ | 40 (24.2) | 0 (0.0) | 40 (26.1) | - |
| **Cell phone possession** | | | | |
| No | 14 (8.5) | 1 (8.3) | 13 (8.5) | 1.00 |
| Yes | 151 (91.5) | 11 (91.7) | 140 (91.5) | Ref. |
| **Religious affiliation** | | | | |
| Traditional Christian churches (Catholic, Presbyterian and Baptist) | 99 (60.0) | 5 (41.7) | 94 (61.4) | Ref. |
| Pentecostals | 62 (37.6) | 7 (58.3) | 55 (35.9) | 0.277 |
| Muslim | 4 (2.4) | 0 (0.0) | 4 (2.6) | - |

| | | | | |
|---|---|---|---|---|
| **Timing of ART initiation** | | | | |
| Breast feeding | 6 (3.6) | 0 (0.0) | 6 (3.9) | - |
| Antenatal Care (ANC or labour) | 159 (96.4) | 12 (100) | 147 (96.1) | Ref. |
| **CD4 cell count on initiation,** | | | | |
| >350 cells/µL | 70 (42.4) | 5 (41.7) | 65 (42.5) | Ref. |
| ≤350 cells/µL | 95 (57.6) | 7 (58.3) | 88 (57.5) | 0.956 |
| **WHO stage** | | | | |
| WHO stage 1 | 142 (86.1) | 11 (91.7) | 131 (85.6) | Ref. |
| WHO stage 2 | 19 (11.5) | 0 (0.0) | 19 (12.4) | - |
| WHO stage 3 & 4 | 4 (2.4) | 1 (8.3) | 3 (2.0) | 0.183 |
| **Health Facility Type** | | | | |
| Small sites with high staff turnover | 21 (12.7) | 3 (25.0) | 18 (11.8) | 0.185 |
| Larger sites with moderate staff turnover | 144 (87.3) | 9 (75.0) | 135 (88.2) | Ref. |

*Data are in numbers and percentages [n (%)]*

### 4.9 Adherence and virologic outcome

Considering the fact that women who were classified as highly adherent and those who were considered moderately adherent both had similarly high virological suppression, adherence at 12 months was regrouped into two categories such that high and moderate were classified as good adherence while low was classified as poor adherence. There was a strong association between virologic suppression and adherence using all measures of adherence at 12 months. Women with poor adherence were 16 times more likely not to have viral suppression at 12 months compared with those who were adherent when adherence was assessed with CAS [OR (95% CI) = 16.0 (4.3, 59.7), $p < 0.001$]. Poor adherence is thus a strong predictor of virologic failure (Table 4.12).

**Table 4.12:** Association between adherence and virologic suppression in pregnant and breastfeeding women at 12 months after ART initiation.

| **Adherence** | **N(165)** | **Unsuppressed VL (≥ 1000 copies/μL) 12 (7.3)** | **Suppressed VL (< 1000 copies/μL) 153 (92.7)** | **OR (95%CI)** | **P-value** |
|---|---|---|---|---|---|
| **Pharmacy refill** | | | | | |
| Poor adherence | 17 (10.3) | 6 (50.0) | 11 (7.2) | 12.9 (3.5-46.7) | **< 0.001** |
| Good adherence | 148 (89.7) | 6 (50.0) | 142 (92.8) | 1 | |
| **Self-report** | | | | | |
| Poor adherence | 7 (4.2) | 4 (33.3) | 3 (2.0) | 25.0 (4.7-131.1) | **< 0.001** |
| Good adherence | 158 (95.8) | 8 (66.7) | 150 (98.0) | 1 | |
| **VAS** | | | | | |
| Poor adherence | 10 (6.1) | 6 (50.0) | 4 (2.6) | 37.3 (8.3-167.5) | **< 0.001** |
| Good adherence | 155 (93.9) | 6 (50.0) | 149 (97.4) | 1 | |
| **CAS** | | | | | |
| Poor adherence | 15 (9.1) | 6 (50.0) | 9 (5.9) | 16.0 (4.3-59.7) | **< 0.001** |
| Good adherence | 150 (90.9) | 6 (50.0) | 144 (94.1) | 1 | |

*Data are in numbers and percentages [n (%)]*

### 4.10 Early infant diagnosis

A total of 253 (94.4%) life births occurred in the cohort. Two hundred and twenty infants had their PCR done giving an HIV-DNA PCR uptake of 86.9%. Of these, 184 (83.6%) were collected between 5 and 8 weeks of life and the rest 36 (16.4%) were collected after 8 weeks (Figure 4.8). The mean age at DNA-PCR collection was 8 (range: 5-59) weeks. The mean turn arround time for result was 6 (range: 2-34) weeks. Most PCR results (80.9%) were delivered to the collecting facility within 8 weeks of sample collection (Figure 4.9). Four (1.8%) children tested PCR-positive; two males and two females. Three of these children were exclusively breastfed and one was mixed fed. All four cases were delivered by the vaginal route. There was no difference between infection from babies of mothers initaiting ARV with a higher CD4+ T-cell count when compared to those with low a CD4+ T-cell count. There was also no association between socio-demographic and clinical characteristics and HIV infection in children.

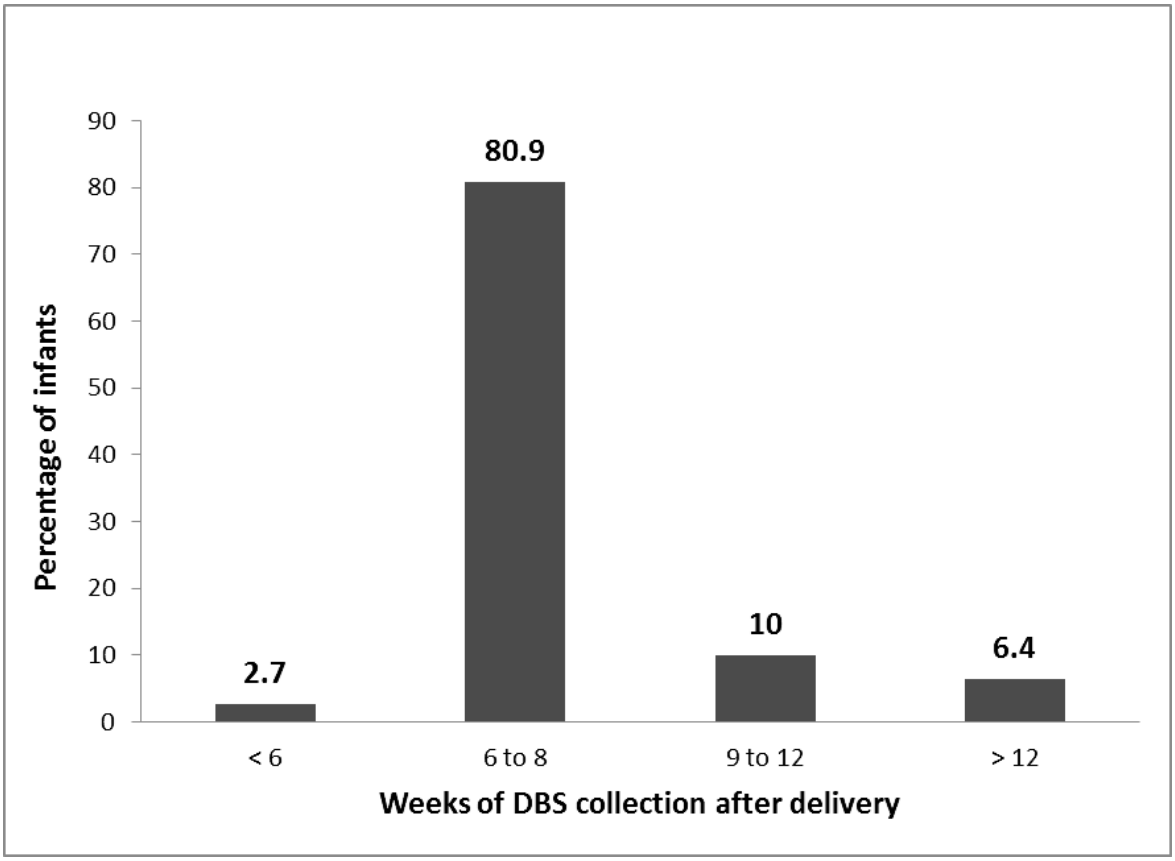


**Figure 4.8***: Timing of DBS collection in HEI delivered in the cohort of HIV-positive women initiating Option B+ in Kumba health district*

Most infants (83.7%) had their DBS samples collected before the second month of life with 80.9% collection done according to national guideline (6-8 week).

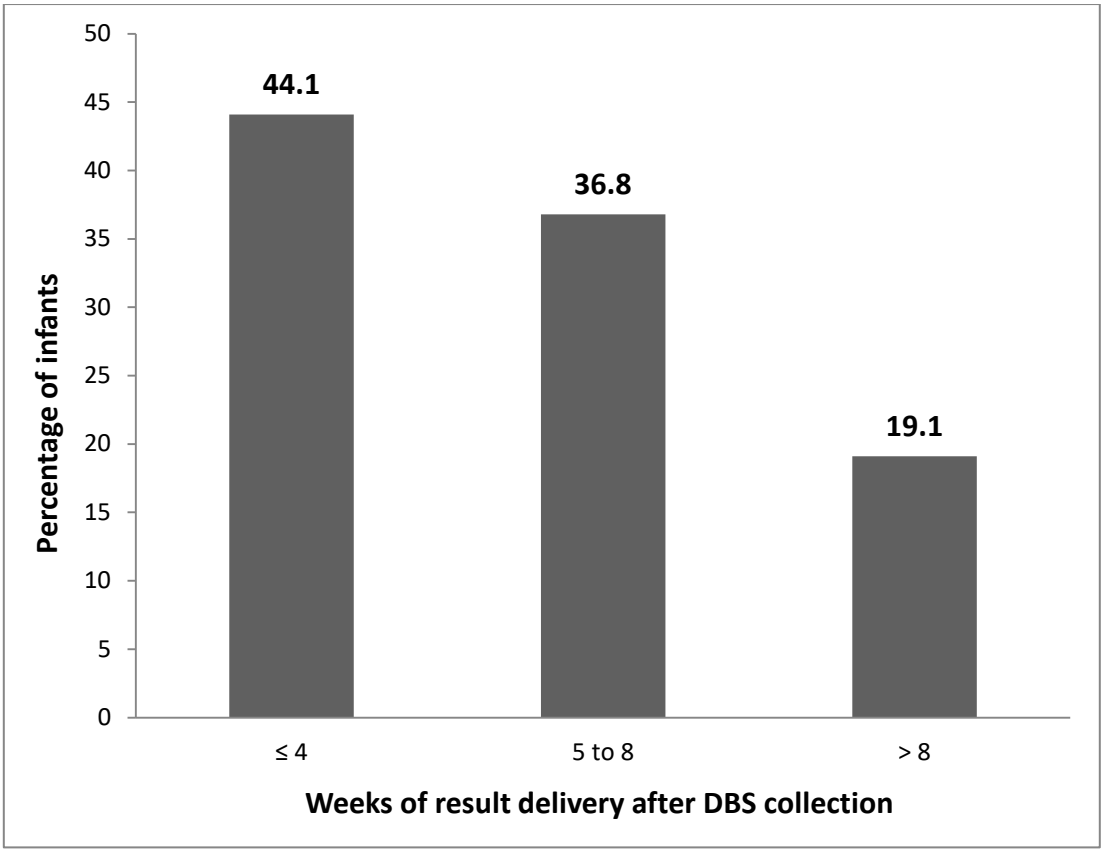


**Figure 4.9***: Time from DBS collection to delivery of PCR results to health facility (PCR Turnaround time) in HEI in the cohort.*

More than four fith (80.9%) of PCR results were processed and returned to the collecting facilities on or before two months of sample collection.

### 4.11 Pregnacy outcomes

Of the 268 women who were enrolled in the study, 15 (5.6%) were already in the postpartum period and breastfeeding while 231 (91.3%) life births occurred. The following pregnancy outcomes were recorded; 7 (2.8%) women had an abortion, 8 (3.2%) had stillbirths and two (0.7%) women died. Among the life births, the prevalence of low birth weight was 7.1% and that of premature births was 6.7%. There was no association between birth weight, gestational age at delivery and HIV infection in children.

### 4.12 Final HIV transmission

At database closure for HIV exposed infants born in this cohort, 122 (51.9%) children had a follow up of 18 months or more so had a HIV antibody rapid test done to confirm their final HIV status. Only one child of the 122 collected samples had a positive rapid test giving a 18 month HIV transmission rate of 0.8%. The cummulative overall MTCT rate in our study was 2.6%. However, this could not be conclusive since just about 50% of the children were followed up to 18 months and received a final rapid test. The lone child who was infected after an HIV antibody rapid test at 18 months, the mother's adherence at six and twelve months were perfect and she had an undetectable viral load at 12 months.

## 5. Discussion

### 5.1 HIV counselling and testing (HCT) and antiretroviral therapy (ART) uptake

With Option B+ being piloted in Cameroon, facility-level uptake of HTC, ART, retention-in-care and adherence to treatment needed to be determined and treatment discontinuation classified and evaluated. Facility-level HIV testing and counselling uptake (98.5%) was high, but ART uptake at 96.8% was even much higher than the 81.9% reported prior to the introduction of Option B+ from programmatic data (CNLS, 2014). With the introduction of Option B+ most countries have reported improvements in facility-level uptake of HTC and ART (Kieffer *et al*., 2014; Kim, Ahmed, Hosseinipour, *et al*., 2015). This high HTC and ART uptake needs to be consolidated into real programme benefit and success by having in place systems that will continually support women with the necessary psychosocial and physical support to maintain them in care and improve adherence. Starting treatment is very important but poor retention-in-care undermines programme and patient outcome including achieving sustained viral suppression which is one of the main and ultimate goals of the UNAIDS 90-90-90 agenda to be achieved by 2020 (UNAIDS, 2014a).

### 5.2 Retention-in-care

Retention-in-care was found to drop progressively within the first year after ART initiation with 88.0% and 81.1% of women still in care at 6 and 12 months, respectively. The 6 and 12 months retention rates obtained in this study were slightly higher than that previously reported in Malawi 82.6% and 76.9% respectively (CDC, 2013). This observed difference in the retention might not be significant but could be explained by the study methodology, as this study was conducted in parallel to a newly launched pilot activity in Cameroon which provided recently implemented resources and trained staff, while in Malawi the retention rates were calculated from programmatic data routinely collected by the sites. However, early implementation in Uganda also reported a 88.0% retention rate at 6 months (Kieffer *et al.*, 2014).

In general retention in ART care tends to drop overtime (Cornell *et al.*, 2010; Rosen, Fox, & Gill, 2007) and is especially challenging in women who are pregnant or breastfeeding (Clouse *et al*., 2014). However, in this study we observed a better retention rate at 12 months as compared to studies that suggest that women who initiate ART while pregnant have poorer retention in HIV care than men and non-pregnant women (Kaplan, Orrell, Zwane, Bekker, & Wood, 2008; Wang *et al*., 2011). These results, just like those from others settings, might point out the beneficial impact of focused adherence support and defaulter tracing for improved overall ART retention in pregnant or breastfeeding women. In this pilot project peer educators were hired and trained to follow-up pregnant women and mother-infant pairs during pregnancy and post-partum to reduce LTFU. Two to three weeks after missing an appointment the peer educators immediately embarked on tracing the woman either by phone calls or through home visits if she gave her consent to be traced. Such tracing programmes have proofed beneficial in bringing women back to care in many other sub-Saharan African settings (Ebuy *et al*., 2014; Tweya *et al.*, 2014).

Most of the women who did not complete the study procedures dropped out after delivery just like reported in other studies (Jean B Nachega et al., 2012). Treatment discontinuation was highest within the first 6 months after treatment initiation and 14 (43.8%) of women who discontinued their treatment during this period never returned to any refill visit. This was similar to reports from other African countries where most of the treatment discontinuations were early dropouts (Schnack *et al*., 2016; Tweya *et al.*, 2014). Some of these early dropouts might never had started treatment at all, hence supporting concerns of same day treatment initiation following HIV diagnosis as recommended within the Option B+ guidelines, implying that these women were not adequately prepared to start lifelong ART.

Treatment preparedness and readiness to start and commit to adhere to lifelong ART is critical for treatment success (Gebrekristos, Mlisana, & Karim, 2005), and loss to treatment retention was reported to be higher in women starting on Option B+ in Malawi as compared to those who were already on ART before pregnancy (Haas, Tenthani, *et al.*,

2016; Kim, Ahmed, & Abrams, 2015). In Malawi a 17% LTFU at 6 months after ART initiation was observed with a better retention-in-care in women who did not start ART on the same day of HIV diagnosis or who received focused counselling (Tenthani *et al.*, 2014). This further emphasizes the need to have the client adequately prepared that she understands the implications of lifelong ART. The decision to initiate ART might be too overwhelming and complex to take immediately after HIV diagnosis. In a commentary on women concerns about initiating Option B+, Matheson and colleagues argued, "if women are not adequately prepared they can experience various human right violations including lack of informed consent, involuntary or coercive HIV testing, limited treatment options, termination of pregnancy or coerced sterilization and pressure to start treatment" (Matheson *et al.*, 2015). World Health Organisation suggests that it is good practice to make a lot of efforts to reduce the time between HIV diagnosis and ART initiation based on the assessment of the person's readiness to start treatment. If the person decides not to start ART immediately, counselling should continue and the advantages of early initiation adequately exposed to the client and ART can be proposed at subsequent clinics (WHO, 2016).

With the very busy nature of our ANC and IWCs, and given the limited number of staff available for Option B+, service delivery, post-test counselling and adherence preparation could have been inadequate. This assumption was supported by our data indicating that high staff turnover and smaller facilities significantly affected retention-in-care and treatment leading to a greater likelihood of ART discontinuation. Health system factors like overburdened staff, long clinic waiting time and ability to capture and report data have been shown to affect retention-in-care at larger health facilities and ART programmes (Cornell *et al*., 2010). Fewer staff and multiple tasking was the main reason for lower retention at the smaller facilities. These facilities had only one Option B+ staff to provide services 6 months into the project. This same staff also had to perform all other duties. In one of the high volume site with the lowest discontinuation rate, Option B+ staff

was completely relieved from all other duties, such as on call duties thus avoiding absence or fewer staff to provide PMTCT services on the following day.

Socio-demographic and HIV related factors in this study were not significantly associated with treatment discontinuations. Other studies found higher discontinuation rates related to younger age (Tweya *et al.,* 2014) or lower maternal educational level (Gourlay, Birdthistle, Mburu, Iorpenda, & Wringe, 2013) which were associated in our analysis only with non-significant higher odds possibly due to a small sample size. We also observed an over 2.7 times higher, non-significant odd of treatment discontinuation in women who initiated ART during breastfeeding as compared to those starting during pregnancy. This could be associated with waning maternal concerns for infant HIV transmission postpartum and more attention tends towards the care of the baby, requiring focused counselling support (Clouse *et al*., 2014). In Malawi women starting ART at pregnancy were more likely to be LTFU than those who started ART while breastfeeding. However, the authors indicated that this improved retention could have been due to the additional motivation in terms of food supplements that were given to breastfeeding women for their children from 6 to 24 months which was not the case in the present study (Tweya *et al.*, 2014). There was however, no difference in retention-in-care between women initiating lifelong ART with a lower CD4+ T-cell count when compared to those initiating treatment with a higher CD4+ T-cell count. We thus failed to reject our null hypothesis. Other studies have produced conflicting results. In a study by Grimsrud and colleagues in South Africa (Grimsrud *et al*., 2016) they found a higher rate of LTFU for women initiating treatment with a higher CD4+ T-cell count. Yet in another study still from South Africa, Clouse and colleagues found a lower rate of LTFU among patients initiating treatment with a higher CD4+ T-cell count (Clouse *et al.*, 2013). These two studies had different cut off values defining higher CD4+ T-cell count (≥300 cells/µL and 201-350 cells/µL respectively) which were completely different from our cut off of CD4+ T-cell count was > 350 cells/µL. Our small sample size could have also been responsible for the lack of association as we

thought women with higher CD4+ T-cells because they are not sick may be more likely to drop out of care compared with those initiating treatment for their own health.

Of the women who discontinued treatment, 36 (55.4%) intentionally decided to stop ART leaving their infants at high risk of HIV infection. Status denial, stigma and discrimination (52.9%) were top among reasons for stopping ART followed by religious reasons (25.0%) and lack of transport fare (11.1%) to attend clinics. Lack of transport to facility has been frequently reported as a reason for discontinuing treatment. Our study was limited to the Kumba health district to reduce the difficulty of travelling by bad roads during the rainy season. Decentralisation of HIV services has been reported to be associated with improved retention by reducing transportation cost, travel time and clinic waiting time among other benefits. A study in Malawi reported a higher LTFU rate at hospital (9.9%) than at rural health centres (1.5%), such that the use of rural centres resulted in a 77% reduction in risk of attrition (Massaquoi *et al*., 2009). WHO now strongly advises national programmes to decentralise HIV and AIDS care and treatment programmes to improve retention-in-care (WHO, 2016).

Furthermore, women who were declared LTFU could often not be traced because of incorrect contacts or contact details that were changed without informing the facility staff. This as well might be attributed to stigma and discrimination, or poor staff treatment at the clinic as reported in a South African study (Clouse *et al.*, 2014). Stigma and fear of status disclosure to partners, family or community members are the most frequently reported barriers to ART or PMTCT procedures in sub-Saharan Africa (Gourlay *et al.*, 2013; Jacobi *et al.,* 2013) . Counselling messages to newly diagnosed HIV-positive women should include normalizing language to reduce stigma and social desirability bias (Simoni *et al*., 2006; Vinten, 1998), so that women could provide correct location details and phone numbers for subsequent tracing. Also staff should on a regular basis remember to update clients' contacts. This could be done annually to be sure they are still in possession of the right addresses and contacts of their clients.

Other tracing outcomes provided valuable information which could be used to further strengthen retention-in-care. Silent self-transfers to other health facilities were very common among women in this study that could have been as well related to stigma and discrimination. There is an inherent need to improve communication between ART clinics and Option B+ sites for better linkages and documentation of transferred-out cases, avoiding misclassification that could underestimate retention rates.

### 5.3 Adherence to ART treatment and virologic outcomes

Retention-in-care has for long in many circumstances been used as a surrogate measure of adherence, but retention as is often defined gives just a snapshot of the patient's attendance at the clinic which may not necessarily reflect adequate medication taking. More so retention measured at a given time point fails to register missed visits thus failing to capture patterns of attendance and care received by mothers and children (N. C. Rollins et al., 2014). Adherence to treatment and care is therefore very important if we must adequately evaluate the success of the PMTCT programme. Apart from factors preventing adherence in non-pregnant adults, the nausea and vomiting of pregnancy and possible side effects of the drugs on the foetus are additional factors that makes adherence in pregnancy a challenge. Post-delivery attention is turned towards the baby and in most circumstances the mother turns to pay less attention to her own health and medications thus compromising adherence postpartum (Clouse *et al.*, 2014).

The few studies in Cameroon that have assessed adherence to ART have mainly focussed on men and non-pregnant women and have used one or the other measures like self-reports, pill counts or pharmacy records with variable results (Mahy *et al.*, 2011; Mbopi-Kéou *et al*., 2012; Mbuagbaw *et al.*, 2012). Using just one or the other of these measures have been shown to be without limitations either under or overestimating adherence (Liu *et al.*, 2001; Steel *et al.,* 2007). We therefore, measured adherence for women initiated on Option B+ in Kumba health district and retained in care, Cameroon using a composite adherence score. To the best of our knowledge this is the first study in Cameroon to

measure adherence for pregnant and breastfeeding women using a composite adherence score. Understanding the implication of Option B+ which requires healthy women being started on lifelong ART we hypothesized that women with a lower CD4+ T-cell count at treatment initiation will better adhere to treatment since they are considered taking it for their own health than those who were initiated on treatment with a higher CD4+ T-cell count.

Among our study participants at 6 months 59.0% reported perfect adherence and 62.7 % at 12 months this is much lower than that reported by Hass and colleagues in Malawi (Haas, Msukwa, *et al.*, 2016). This difference is likely due to the approach used to measure adherence. The Malawian study used pharmacy records alone to measure adherence unlike in our study where adherence was measured with a composite score combing three different measures.

The different adherence measures employed were all correlated with each other and all were significantly correlated to the composite adherence score with a Spearman correlation ranging from 0.36 to 0.83 ($p < 0.001$ for all comparisms). VAS however, showed the strongest correlation with CAS. Some authors have argued that the use of CAS for measuring adherence may be cumbersome in clinical settings (Simoni *et al*., 2006). As shown by our results like that reported by Giordano and colleagues (Giordano *et al.,* 2004) a simple easy to use tool as the VAS could be conveniently used in clinical and research settings and will still produce results similar to the CAS. On the other hand, several studies have shown that with non-nucleoside reverse transcriptase inhibitors and boosted protease inhibitors (PIs) containing regimens you do not need perfect adherence for virologic suppression (Bangsberg, 2006; Maggiolo et al., 2005; Jean B Nachega et al., 2007).

After validating the adherence measured with virologic outcome, we went ahead and classified adherence into two categories as good or poor and overall, 88.6% of women reported good adherence to Option B+ treatment protocol at 12 months post ART initiation. This was comparable (87.0%) with that of the study of adherence with Option

B+ carried out in Ethiopia (Ebuy *et al.*, 2014) and from western Kenya (89.0%)(Ayuo e*t al*., 2013) but slightly higher than adherence reported for the same target group from Nnewi in Nigeria (78.3%) (Igwegbe, Ugboaja, & Nwajiaku, 2010). This difference could be explained by the PMTCT options used. The study from Nigeria was conducted in the era of Option A but this study and those from Ethiopia and Kenya were from women initiating Option B+.

The main predictors of poor adherence to lifelong ART for women included in this study were younger age at treatment initiation, lower level of education, employment in the informal sector and belonging to a Pentecostal church.

Younger age and lower education level have been reported as predictors of treatment discontinuation which could indirectly affect adherence to treatment (Tenthani *et al*., 2014; Tweya *et al.*, 2014). A study in Nigeria found the contrary with older rather than younger age being a predictor of non-adherence (Igwegbe *et al.*, 2010). This discrepancy in the results may well be due to the way the data was collected and presented. In this study and the studies from Malawi age was categorised into two while the Nigerian study had three age categories which differed greatly from ours.

Employees in the informal sector have to work extra hard to maintain their jobs or generate their own income thus leaving them with little time to concentrate on their health and treatment unlike employees in the formal sector who in this study were mainly public civil servants or those unemployed. Studies have shown that conflict with work commitment and the difficulty of disclosing ones status to an employer affected ARV adherence in women on Option B+ (Clouse *et al.*, 2014). Flexible clinics opening hours like in the evenings or on Saturdays when most workers are free and do not need to take time or a day off just to attend clinic could improve adherence on treatment for most of these women.

Pentecostal preaching with its emphasis on salvation and strong social cohesion helps to prevents their members from engaging in as much extra- and pre-marital sex as other Christian denominations, thus protecting against HIV transmission (Garner, 2000).

However, Zou *et al.,* in 2009 noted, "At community level, religious organisations are influential social networks that have the power to support or stigmatize PLHIV, promote or impede HIV education, and endorse or reject medical treatment of HIV" (Zou *et al.*, 2009). In this study belonging to a Pentecostal church was a strong predictor of poor adherence to treatment. This is supported by our findings that most of the women who stopped their treatment for religious reasons did not find any reason for returning to care and claimed they will be healed by their faith.

There was no difference in adherence between women initiating treatment with a lower CD4+ T-cell count compared to those with a higher CD4+ T-cell count; we thus failed to reject our null hypothesis.

Like many studies from sub-Saharan African countries many participants in this study cited forgetfulness, being away from home (J. B. Nachega et al., 2004) and lack of transport to the health facility and side effects of drugs as possible reasons for missing doses of their ARVs (Ayuo *et al*., 2013; Ekama *et al.*, 2012; Igwegbe *et al*., 2010; Tweya *et al.,* 2014). This information generated from the self-report interviews can be very useful during adherence counselling of HIV-positive pregnant and breastfeeding women. On the other hand our participants also indicated that reminder aids like cell phones, clock alarms and reminder from family members helped improve their adherence. However, others women claimed that medication taking have become a routine for them so they do not need reminders. The high frequency of routine may be because of the women best intention to continue taking their medication or methodological reasons such as social desirability concerns. Many studies have shown that the use of cell phones and other reminders gadgets can greatly improve adherence (Hardy *et al*., 2011; Mbuagbaw, 2014; Reynolds *et al*., 2007). The role of family members like husbands, sisters and mothers as treatment buddies emphasised the need to continuously counsel and support HIV-positive women to disclose their status to significant orders in order to get the maximum benefits of disclosure (Ebuy *et al*., 2014; Igwegbe *et al.*, 2010). HIV status disclosure should remain voluntary as this could be accompanied by partner violence (Colombini, James, & Ndwiga,

2016; Ezechi *et al.,* 2009). Instead women who decline to disclose should be counselled and encouraged until they feel safe to disclose.

Viral suppression in the study participants retained in care at 12 months was very good. A total of 92.7% (153/165) of women achieved virological suppression (<1,000copies/µL) as per WHO definition (WHO, 2013). Poor adherence to antiretroviral drugs has been reported to be the major challenge to achieving this main goal of antiretroviral therapy (Maggiolo *et al*., 2005). Adherence at 12 months after ART initiation significantly predicted virologic outcome with patients reporting poor adherence more likely not to achieve adequate virologic suppression. The virologic-suppression rates were similar or superior to those in cohorts of non-pregnant adults in Africa (El-Khatib *et al*., 2011; Haas, Msukwa, *et al.*, 2016), suggesting that virologic suppression is achievable both in pregnancy or breastfeeding. High virologic suppression was reflected by the low rate of mother-to-child transmission of 1.8% at 6–8 weeks in this study. Most of the women in this study started ART in the 1$^{st}$ and 2$^{nd}$ trimesters of pregnancy (73.3%). We believe that good adherence overall and initiation of ART early in pregnancy in most women accounted for the excellent suppression rates and low early MTCT rate. The initiation of ART before 30 weeks' gestation could improve virologic suppression at delivery and may have reduced the risk of in utero transmission.

**5.4 Infant and children HIV-free survival**

Option B+ was conceived with the vision of increasing ART coverage for pregnant and breastfeeding women and eliminating new cases of HIV infection among children. The rate of retention-in-care was good (81.1%) at 12 months and 83.6% of the infants' had their DBS samples for DNA-PCR collected between 5 and 8 weeks of delivery thus respecting the national protocol (CNLS, 2015). These results were superior to the 80% between 5 and 13 weeks obtained by Pérez and colleagues in Thyolo, Malawi (Martínez Pérez *et al*., 2014). This difference could be solely explained by the fact that we were in a pilot project with a lot more resources available for patient tracking why the result from Thyolo were from routine data collected by health facilities. The mean PCR turnaround time in this

study was 6 weeks showing a marked improvement from what has been previously reported in national reports in the pre-Option B+ era (CNLS, 2014). The early HIV transmission to infants of 1.8% in this study showed a significant dropped in value when compared to the national early transmission rate of 5.2% published by UNAIDS in its 2016 on the fast track report (UNAIDS, 2016a). It was also much lower (3.6%) than that reported in Malawi (Herce et al., 2015). The national rate of 5.2% early transmission included sites that were still practicing option A in the country by the end of 2015. We found a very low final MTCT rate (2.6%) when compared to the national rate of 12.6% reported by UNAIDS in its 2016 report (UNAIDS, 2016a). Though this rate was expected to be lower in this pilot study but due to the fact that administratively the database was closed when just about half of the children born in the cohort had a complete follow-up this could not be conclusive. A much longer follow up will be required to confirm this finding.

**5.5 Pregnancy outcomes**

Some pregnancy outcomes like abortions, stillbirths, low birth weights and premature deliveries were observed in our cohort. In a meta-analysis, HIV infected women were at higher risk of having a low birth weight infant or a preterm delivery infant compared with uninfected women (Xiao *et al.,* 2015). However, since we did not have any comparative group and the timing of these events were not carefully planned with treatment initiation, the association with the treatment protocol or HIV infection status of the women could not be established. More work is needed to confirm these findings and to explore specific aetiology pathways by which such effects may operate. A study in the United States rather confirms that the increasing use of ART during pregnancy has rather resulted in a decline in the rate of low birth weight and prematurity (Schulte, Dominguez, Sukalac, Bohannon, & Fowler, 2007). Another study showed that PI containing regimens were more associated with preterm birth but there were no differences in rates of low birth weight and stillbirth, regardless of therapy (Cotter, Garcia, Duthely, Luke, & O'Sullivan, 2006). Contrary to reports that preterm delivery and low birth weight increased the risk of MTCT of HIV

(Landesman *et al.,* 1996), we did not find any association between birth weight, gestational age at delivery and HIV infection in children. This lack of association could also be explained by our small sample size.

### 5.6 Study limitations

Limitations for the generalizability of our results are mainly study procedure related. This includes prospective data collection within a newly launched pilot activity, available tracing information and optimized tracing procedures for all study participants, and treatment counselling possibly beyond the usual routine procedures. However, though our results reflect what has been reported in many other studies the following cautions are necessary in the implementation of these findings. As we considered LTFU as missed retentions there is a possibility of misclassification which could have affected our retention rates. Also our adherence to Option B+ by women in this cohort might have been overestimated as early dropouts were excluded from the analysis. The viral suppression rate was very high and could have been overestimated as only women retained in care had viral load testing. The small sample size could explain the lack of significant association between many socio-demographic and clinical characteristics with treatment discontinuation and adherence to ART treatment. Since our participants were recruited while at clinic visits the good retention-in-care and high adherence to treatment for women retained in care may not be extrapolated to the entire population of women expected at ANC and IWC. However, our results are consistent with other studies of HIV-positive women receiving PMTCT Option B+ services in other sub-Saharan African settings. Despite these limitations, we believe that the study findings are useful to inform implementation of PMTCT Option B+ in Cameroon and other comparable settings.

## 6. Conclusions and implications

In conclusion we observed promising 12 months retention-in-care and adherence to Option B+ in pregnant or breastfeeding women initiating Option B+ in Kumba health district comparable to other African reports. Retention rates were lowest at small health facilities with a high staff turnover and multiple task assignments, while adherence was poor for younger women, women with low level of education, those employed in the informal sector and those attending Pentecostal churches. Our findings suggest an urgent need to expand the Option B+ related human resources and also to reinforce counselling messages for younger and less educated women initiating Option B+. Adequate task shifting, reduction of staff mobility, improved staff working conditions and motivation, implying improved quality of post-test counselling may improve retention and adherence to therapy. Furthermore, enhancing community interventions, decentralization of service delivery, HIV workplace policies, defaulters tracking and reducing stigma and religious beliefs are measures that may improve retention-in-care and adherence to lifelong therapy. More studies are needed with larger cohorts and a longer follow up time in Cameroon to better assess treatment outcomes like final HIV transmission rates for a comprehensive evaluation of the impact of Option B+ in Cameroon.

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## 8. Annexes

### Annex 1: Questionnaire

**Data Collection Form (Version 2.0, 1st Feb .2014)**

**Centre Code |___|** **Patient Identification N°**

**|___|___|___|___|___|___|**

**Study: ARV Adherence and retention cohort: HIV-positive pregnant women on option B+**

This study seeks to find out how well HIV-positive pregnant women on antiretroviral medicines (ARV) take their drugs. Please you are therefore, invited to answer these questions as honestly as you can to express your own experiences.

You do not have to answer if you do not want to but completing as much of the questionnaire as you can would help us to better manage any problems that you may be facing with taking your medication.

**Date of enrolment:** [__|__] - [__|__] - [__|__|__|__] (dd/mm/yyyy)

**VISIT I**

**I. a). Socio-demographic information of participant**

| No | Question | Response (Enter the number corresponding to the correct response in the check box) | Skip to |
|---|---|---|---|
| Q101 | Physical Address | Quarter.....<br>Telephone Number.....<br>Telephone number of contact Person..... | |
| Q102 | Date of Birth | [__|__] - [__|__] - [__|__|__|__] (dd/mm/yyyy) | |
| Q103 | Age (years) | [__|__] | |
| Q104 | Marital Status | [__]<br>1= Single, 2= Married, 3= Widow, 4=Divorced, 5=Concubine ("come we stay") | If 1,3,4, 5 go to Q106 |
| Q105 | Form of marriage | [__]<br>1=Monogamy, 2=Polygamy, | |
| Q106 | Highest Level of education | [__]<br>0=None, 1= Completed primary, 2=Completed Secondary, 3= Completed high school, 4=University and higher | |

| | | | |
|---|---|---|---|
| Q107 | Division of origin | ..... | |
| Q108 | Religious affiliation | [__]<br>1=Catholic, 2=Presbyterian, 3= Baptist, 4=Pentecostal, 5= Moslem,<br>6=Others(Specify)..... | |
| Q109 | Occupation | [__]<br>1=Unemployed, 2=Housewife; 3= Farmer,<br>4=Business, 5= Pupil/Student; 6= Staff employed in the civil sector, 7= Staff employed in the private sector, 8= others (Specify)..... | |
| Q110 | Do you have children? | [__]<br>0=No 1=Yes | If 0 go to Q113 |
| Q111 | Number of children | [__\|__] | |
| Q112 | Age of last child (years) | [__\|__] | |

**I. b). Information on current pregnancy**

| | | | |
|---|---|---|---|
| Q113 | Date of ANC visit | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q114 | LMP | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q115 | Gestational Age | [__\|__]Weeks | |
| Q116 | Gravida | [__\|__] | |
| Q117 | Parity | [__\|__] | |

**I. c). Current HIV status (With present pregnancy)**

| | | | |
|---|---|---|---|
| Q118 | Date of HIV diagnosis | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q119 | HIV test result (type) | [__]<br>1=HIV type I, 2=HIV type 2, 3= HIV type 1 & 2, 9= Unknown | |
| Q120 | WHO clinical stage at diagnosis | [__]<br>0=WHO stage I, 1=WHO stage II, 2=WHO stage III,<br>3= WHO stage IV, 9= Unknown/Not sure | |
| Q121 | Date of last CD4 Count | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |
| Q122 | Last CD4 count | [__\|__\|__\|__]cells per mL, [__] Not available | |
| Q123 | Creatinine level | [__\|__\|__\|__]mg/dL, [__] Not available | |
| Q124 | Hb level | [__\|__ ]. [__] g/dl | |
| Q125 | Weight | [__\|__\|_ ]. [__] kg | |
| Q126 | Height | [__\|__ ]. [__] m | |
| Q127 | Ever used ARV before | [__] | |

| | | | |
|---|---|---|---|
| | | 0=No 1=Yes | |
| Q128 | Present ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= AZT/3TC/EFV<br>3= TDF/3TC/NVP<br>4= TDF/3TC/EFV<br>5= Others (specify)..... | |
| Q129 | Date of initiation on this treatment | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q130 | Place of ARV initiation | [__]<br>1= ANC, 2= Labour room, 3=Postpartum, 4=IWC,<br>5=HIV treatment centre | |
| Q131 | On Cotrimoxazole prophylaxis | [__]<br>0=No 1= Yes | |
| Q132 | Partner tested for HIV | [__]<br>0=No 1=Yes | |
| Q133 | Partner HIV status | [__]<br>0=Negative, 1=Positive, 2=Indeterminate,<br>9= Unknown | |
| Q134 | Partner's HIV results (type) | [__]<br>1=HIV type I, 2=HIV type 2, 3= HIV type 1 & 2,<br>9= Unknown | |
| Q135 | Partner's on ARV | [__]<br>0=No , 1=Yes, 3=Don't know | |

**Visit done by:** _____

**Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**VISIT II.**

**LABOUR AND DELIVERY**

| No | Question | Response ( Enter the number corresponding to the correct response in the check box ) | Skip to |
|---|---|---|---|
| Q201 | Date of delivery | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q202 | Place of delivery | [__]<br>1=Health facility, 2=Home,<br>3= Others (specify)..... | If 2,3 go to Q204 |
| Q203 | Delivery conducted by | [__]<br>1= Doctor, 2=Nurse, 3=Midwife ,<br>4= Others (specify).....<br>9= Unknown | |
| Q204 | Home delivery conducted by | [__]<br>1.= Relative, 2.= Friend, 3=Neighbour,<br>4= Nurse/midwife 5=Traditional Birth Attendant | |
| Q205 | Mode of delivery | [__]<br>1=Vaginal, 2= Caesarean Section , 3= Forceps,<br>4= Ventouse | |
| Q206 | Gestational age at delivery | [__\|__] Weeks | |
| Q207 | Birth weight of baby | [__\|__\|__\|__] g | |
| Q208 | APGAR Score (5min) | [__\|__ ] | |
| Q209 | Sex | [__]<br>1= Male, 2= Female | |
| Q210 | Premature rupture of membranes | [__]<br>0=No 1= Yes | |
| Q211 | Episiotomy | [__]<br>0=No 1= Yes | |
| Q212 | Multiple delivery | [__]<br>0=No 1= Yes | |
| Q213 | Baby resuscitation after delivery | [__]<br>0=No 1= Yes | |
| Q214 | Other birth outcomes | [__]<br>1=Still birth, 2=Infant death after delivery, 3= birth defect, 4=Others (Specify)..... | |
| Q215 | Mother's viral load | [__\|__\|__\|__\|__\|__\|__] copies<br>[__] Not available | |

**Visit done by:** _____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**VISIT III.**

**III. a. 6-8 WEEK POSTPARTUM FOLLW-UP / EID**

| No | Question | Response (Enter the number corresponding to the correct response in the check box ) | Skip to |
|---|---|---|---|
| Q301 | Date of postpartum visit | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q302 | Baby Feeding option | [__]<br>1= Exclusive breast feeding, 2= Exclusive artificial feeding, 3=Mixed feeding,<br>4= Others (specify)..... | |
| Q303 | Is baby on Nevirapine | [__]<br>0= No 1= Yes | |
| Q304 | Date of initiation on Nevirapine | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q305 | Baby initiated on Cotrimoxazole prophylaxis | [__]<br>0= No 1= Yes | |
| Q306 | PCR1collected | [__]<br>0= No 1= Yes | |
| Q307 | Date of collection of baby PCR1 | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy)<br>[__] Not available | |
| Q308 | Date of delivery of results PCR1 | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy)<br>[__] Not available | |
| Q309 | Baby PCR1 results | [__]<br>0= Negative, 1= Positive, 2=Indeterminate | If 0,2 go to Q313 |
| Q310 | Baby started on ARV | [__]<br>0= No 1= Yes | |
| Q311 | ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= Triomune Baby/Junior<br>3= AZT/3TC/LPV/r<br>4= Others (specify)..... | |
| Q312 | Date of initiation on ARV | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q313 | PCR2 collected | [__]<br>0= No 1= Yes | |
| Q314 | Date of collection PCR2 | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy)<br>[__] Not available | |
| Q315 | PCR2 results | [__]<br>0=Negative, 1=Positive, 2= Indeterminate | |
| Q316 | Date of result PCR 2 | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy)<br>[__] Not available | |

**III. b. MOTHER'S TRACING INFORMATION**

| | | | |
|---|---|---|---|
| Q317 | Attended visit | [__]<br>0= No 1= Yes | |
| Q318 | Traced to attend clinic visit | [__]<br>1=Traced by phone call and came to clinic, 2=Traced through home visit and came to clinic, 3= Not traceable, 4= Others (specific)..... | |
| Q319 | Date of clinic attendance after tracing | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy)<br><br>[__] Not available | |
| Q320 | Reasons for not attending post-delivery visits | [__]<br>1 = Lack of money, 2= Sick/disease, 3 = Afraid of stigmatization, 4= Do not like the PMTCT service/interventions, 5= Fear of family, relatives and community, 6 = Religious believes. | |
| Q321 | If did not return for clinic what is mother status | [__]<br>1=Transfer out, 2=Lost to follow-up, 3= Death, 9= Unknown | |

**Visit done by:** _____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**VISIT IV.**

**SIX MONTH AFTER ARV INITIATION**

**IV. a) Follow-up information**

| No | Question | Response (Enter the number corresponding to the correct response in the check box ) | Skip to |
|---|---|---|---|
| Q401 | Date of visit | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q402 | CD4 count | [__\|__\|__\|__]cells per mL<br>[__] Not available | |
| Q403 | Viral load | [__\|__\|__\|__\|__\|__\|__] copies<br>[__] Not available | |
| Q404 | Current ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= AZT/3TC/EFV<br>3= TDF/3TC/NVP<br>4= TDF/3TC/EFV<br>5= Others (specify)..... | |
| Q405 | Side effects of ARV | [__]<br>0=None, 1=Skin rash, 2=Jaundice, 3= Dizziness<br>4= Night mares<br>5= Others (specify)..... | |
| Q406 | Has ARV been switched or substituted during last 6months | [__]<br>0= No, 1=Yes | |
| Q407 | Date of ARV regimen change | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |
| Q408 | Reasons for switching or substitution | [__]<br>1= Severe side effects, 2= Stock out of drugs,<br>3= Treatment failure, 9= Unknown | If 3 go to Q410 |
| Q409 | In case of substitution what is the new ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= AZT/3TC/EFV<br>3= TDF/3TC/NVP<br>4= TDF/3TC/EFV<br>5= Others (specify)..... | |
| Q410 | In case of treatment failure what is the 2nd Line regimen | [__]<br>1= AZT/3TC/LPV/r<br>2= AZT/3TC/ATV/r<br>3= TDF/3TC/LPV/r<br>4= TDF/3TC/ATV/r<br>5= Others (specify)..... | |

**IV. b) Child's Information**

| | | | |
|---|---|---|---|
| Q411 | Baby status | [__]<br>1= Alive, 2=Death, 9 = Unknown | If 2 go to Q417 |
| Q412 | Baby still on NVP syrup | [__]<br>0=No, 1=Yes | |
| Q413 | Baby on ARV | [__]<br>0=No, 1=Yes | |
| Q414 | Baby on Cotrimoxazole | [__]<br>0=No, 1=Yes | |
| Q415 | Baby still breastfeeding | [__]<br>0=No, 1=Yes | |
| Q416 | If not breastfeeding date of weaning | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |
| Q417 | If death, date of death | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |

**IV. c) Adherence information**

"I understand that most people taking antiretroviral medication (anti-HIV drugs) find it very difficult to take their medication regularly and may miss some doses. So I will not be surprised if you have had this happen to you. It is important for me to understand how you are really doing with your medicine. Don't worry about telling me if you don't always take all your doses. I need to know what is really happening, not what you think I want to hear".

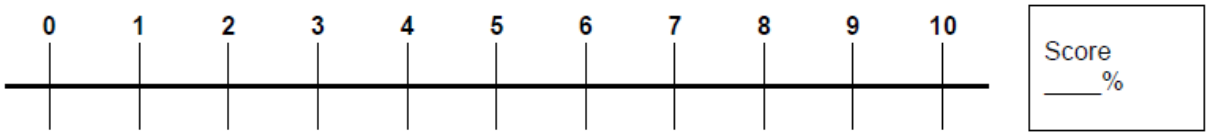
| **1) Pharmacy refills** | | | |
|---|---|---|---|
| Q417 | Number of ARV refill appointments respected in the last 6 months | [__]<br>1= 1refill, 2=2 refills, 3= 3 refills, 4=4 refills, 5=5 refills, 6=6 refills | |

| **2) Self-Reported Adherence** | | | |
|---|---|---|---|
| Q418 | Do you sometimes find it difficult to remember to take your medicine? | [__]<br>0=No, 1=Yes | |
| Q419 | When you feel better, do you sometimes stop taking your medicine? | [__]<br>0=No, 1=Yes | |
| Q420 | Thinking back over the past 4 days, have you missed any of your doses? | [__]<br>0=No, 1=Yes | |

| | | | |
|---|---|---|---|
| Q421 | Sometimes if you feel worse when you take the medicine, do you stop talking it? | [__]<br>0=No, 1=Yes | |
| Q422 | What causes you to miss some doses of your drug? | .....<br>..... | |
| Q423 | What helps you remember to take your drugs? | .....<br>..... | |

**4) Q424: Visual Analogue Scale (VAS)**

"Now I would like to ask you to estimate how much of your prescribed ARV you took in the last month. A mark at the left end where there is a number zero means you have taken no medications. A mark in the middle means you have taken about half of your medications. A mark on the right end where you can see the number ten means you have taken every single dose of your medications. Please put a mark on this line somewhere between zero and 10 to describe your best guess about how much of your prescribed medication you took in the last month".




**Composite Adherence Assessment (***To be determined by supervisor***)**

| **Adherence measure** | **SCORE** | | |
|---|---|---|---|
| **Pharmacy Refill** | Had 6 refills (3) | Missed 1 refill (2) | Missed 2 or more refills (1) |
| **Self-Report** | No to all Questions (3) | Yes to 1 question (2) | Yes to 2 or more questions (1) |
| **VAS** | 90% or more (3) | 70 & 80% (2) | Less than 70% (1) |
| **Overall Adherence** | **High** | **Moderate** | **Low** |

| **Adherence tool** | **Score** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Medication refill** | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 2 | 2 | 1 |
| **Self-Report** | 3 | 3 | 3 | 2 | 2 | 2 | 1 | 2 | 1 | 1 |
| **VAS** | 3 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 |
| **Total score** | 9 | 8 | 7 | 7 | 6 | 6 | 5 | 5 | 4 | 3 |
| **CAS** | **High** | **Moderate** | | | | | **low** | | | |

**Visit done by:** _____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

**VISIT V.**

**TWELVE MONTH AFTER ARV INITIATION**

**V. a) Follow-up information**

| No | Question | Response (Enter the number corresponding to the correct response in the check box ) | Skip to |
|---|---|---|---|
| Q501 | Date of visit | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy) | |
| Q502 | CD4 count | [__\|__\|__\|__]cells per mL<br>[__] Not available | |
| Q503 | Viral load | [__\|__\|__\|__\|__\|__\|__] copies<br>[__] Not available | |
| Q504 | Current ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= AZT/3TC/EFV<br>3= TDF/3TC/NVP<br>4= TDF/3TC/EFV<br>5= Others (specify)..... | |
| Q505 | Side effects of ARV | [__]<br>0=None, 1=Skin rash, 2=Jaundice, 3= Dizziness<br>4= Night mares<br>5= Others (specify)..... | |
| Q506 | Has ARV been switched or substituted during last 6months | [__]<br>0= No, 1=Yes | |
| Q507 | Date of ARV regimen change | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |
| Q508 | Reasons for switching or substitution | [__]<br>1= Severe side effects, 2= Stock out of drugs,<br>3= Treatment failure, 9= Unknown | If 3 go to Q510 |
| Q509 | In case of substitution what is the new ARV regimen | [__]<br>1= AZT/3TC/NVP<br>2= AZT/3TC/EFV<br>3= TDF/3TC/NVP<br>4= TDF/3TC/EFV<br>5= Others (specify)..... | |
| Q510 | In case of treatment failure what is the 2nd Line regimen | [__]<br>1= AZT/3TC/LPV/r<br>2= AZT/3TC/ATV/r<br>3= TDF/3TC/LPV/r<br>4= TDF/3TC/ATV/r<br>5= Others (specify)..... | |

**IV. b) Child's Information**

| | | | |
|---|---|---|---|
| Q511 | Baby status | [__]<br>1= Alive, 2=Death, 9 = Unknown | If 2 go to Q517 |
| Q512 | Baby still on NVP syrup | [__]<br>0=No, 1=Yes | |
| Q513 | Baby on ARV | [__]<br>0=No, 1=Yes | |
| Q514 | Baby on Cotrimoxazole | [__]<br>0=No, 1=Yes | |
| Q515 | Baby still breastfeeding | [__]<br>0=No, 1=Yes | |
| Q516 | If not breastfeeding date of weaning | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |
| Q517 | If death, date of death | [__\|__] - [__\|__] - [__\|__\|__\|__] (dd/mm/yyyy),<br>[__] Not available | |

**V. c) Adherence information**

"I understand that most people taking antiretroviral medication (anti-HIV drugs) find it very difficult to take their medication regularly and may miss some doses. So I will not be surprised if you have had this happen to you. It is important for me to understand how you are really doing with your medicine. Don't worry about telling me if you don't always take all your doses. I need to know what is really happening, not what you think I want to hear".

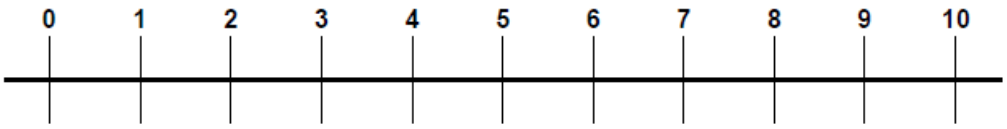
| **1) Pharmacy refills** | | | |
|---|---|---|---|
| Q517 | Number of ARV refill appointments respected in the last 6 months | [__]<br>1= 1refill, 2=2 refills, 3= 3 refills, 4=4 refills, 5=5 refills, 6=6 refills | |

| **2) Self-Reported Adherence** | | | |
|---|---|---|---|
| Q518 | Do you sometimes find it difficult to remember to take your medicine? | [__]<br>0=No, 1=Yes | |
| Q519 | When you feel better, do you sometimes stop taking your medicine? | [__]<br>0=No, 1=Yes | |
| Q520 | Thinking back over the past 4 days, have you missed any of your doses? | [__]<br>0=No, 1=Yes | |

| | | | |
|---|---|---|---|
| Q521 | Sometimes if you feel worse when you take the medicine, do you stop talking it? | [__]<br>0=No, 1=Yes | |
| Q522 | What causes you to miss some doses of your drug? | .....<br>..... | |
| Q523 | What helps you remember to take your drugs? | .....<br>..... | |

**4) Q524: Visual Analogue Scale (VAS)**

"Now I would like to ask you to estimate how much of your prescribed ART you took in the last month. A mark at the left end where there is a number zero means you have taken no medications. A mark in the middle means you have taken about half of your medications. A mark on the right end where you can see the number ten means you have taken every single dose of your medications. Please put a mark on this line somewhere between zero and 10 to describe your best guess about how much of your prescribed you took in the last month".




**Composite Adherence Assessment (***To be determined by supervisor***)**

| **Adherence measure** | **SCORE** | | |
|---|---|---|---|
| **Pharmacy Refill** | Had 6 refills (3) | Missed 1 refill (2) | Missed 2 or more refills (1) |
| **Self-Report** | No to all Questions (3) | Yes to 1 question (2) | Yes to 2 or more questions (1) |
| **VAS** | 90% or more (3) | 70 & 80% (2) | Less than 70% (1) |
| **Overall Adherence** | **High** | **Moderate** | **Low** |

| **Adherence measure** | **SCORE** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Pharmacy Refill** | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 1 |
| **Self-Report** | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 1 | 1 |
| **VAS** | 3 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 1 |
| **Total score** | 9 | 8 | 7 | 7 | 6 | 6 | 5 | 4 | 3 |
| **Overall Adherence (CAS)** | **High** | **Moderate** | | | | | **low** | | |

**Visit done by:** _____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__

**VISIT VI.**

**FINAL HIV STATUS OF INFANT**

| | | | |
|---|---|---|---|
| Q701 | Date of infant's HIV rapid test | [__|__] - [__|__] - [__|__|__|__] (dd/mm/yyyy)<br><br>[__] Not Available | |
| Q702 | Result of infant's HIV rapid test | [__]<br>0=Negative, 1=Positive, 2= Indeterminate, 9=Unknown | |

**Checked by:**_____ **Signature:** _____ **Date:** |__|__|/|__|__|__|/|__|__|__|__|

Visit done by: _____ **Signature: _____** **Date: |__|__|/|__|__|__|/|__|__|__|__|**

**PI' s Final verification**

Name_____

Signature_____

Date: |__|__|/|__|__|__|/|__|__|__|__|

**Study Case Report Form (Version 1.0, 1st Feb. 2014)**

**Patient Status At Exit From Study**

**Centre Code |___|** **Patient Identification N°**

|___|___|___|___|

*This form is filled out at the last visit or when a patient is not more coming for her appointments and efforts to trace her have failed.*

Date of exit (completion or termination) : [__|__] - [__|__] - [__|__|__|__] (dd/mm/yyyy)

What is the Mother's Status?

[__] Patient completed follow-up

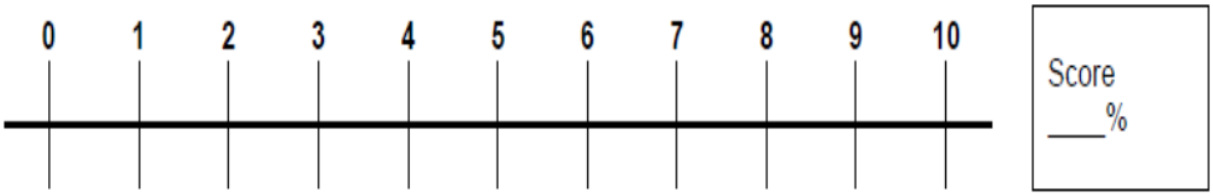
[__] Early termination

Reasons for early termination.

| | | |
|---|---|---|
| 01 | Withdrawn informed consent | [__] |
| 02 | Moved out of study area (Transferred out) | [__] |
| 03 | Lost to follow-up | [__] |
| 04 | Death, Date. [__|__] - [__|__] - [__|__|__|__] (dd/mm/yyyy) | [__] |
| 05 | Stopped treatment | [__] |
| 06 | Reasons for stopping: Religion [_1_], S & D[_2_], Status denial [_3_],Transport [_4_], | [__] |
| 07 | Others (specify): | |

**Annex 2: Visual Analogue Scale (VAS)**

"Now I would like to ask you to estimate how much of your prescribed ARV you took in the last month. A mark at the left end where there is a number **ZERO (0)** means you have taken no medications. A mark in the **MIDDLE (5)** means you have taken about half of your medications. A mark on the right end where you can see the number **TEN (10)** means you have taken every single dose of your medications. Please put a mark on this line somewhere between **ZERO and TEN** to describe your best guess about how much of your prescribed medication you took in the last month".



**Annex 3: Curriculum vitae**


**Name:** Pascal Nji Atanga
**Date / Place of birth:** 13th October 1969, Mankon
**Sex:** Male
**Family situation:** Married with four children
**Nationality:** Cameroonian
**Address:** Cameroon Baptist Convention Health Services
**E-mail:** nji_atanga@yahoo.com/abonkwechinje@gmail.com
**Telephone:** 237 677 608 073


**EDUCATION**

| Period | Institution | Field of study | Degree/certificate obtained |
|---|---|---|---|
| 2013-date | Ludwig-Maximillians-Universität München, Germany | PhD-International Health | |
| 2003-2004 | Free University of Brussels, Belgium | Public Health | Master of Public Health Methodology (great distinction) |
| 1992-1999 | University of Yaoundé I, Cameroon | General Medicine | Medical Doctor (Honours) |

**PROFESSIONAL EXPERIENCE**

| Period | Institution | Position/Responsibility |
|---|---|---|
| 2014-date | Cameroon Baptist Convention Health Services | Pediatric HIV/AIDS and PMTCT advisor |
| 2009-date | Faculty of health science, Department of public health, University of Buea, Cameroon | Assistant lecturer of Public Health |
| 2007-2013 | Ministry of Public Health | Chief of unit supervision, monitoring and evaluation (cumulatively focal point for PBF and Research). |
| 2006-2013 | Ministry of Public Health | Regional coordinator (previously, Regional PMTCT focal point) |

**OTHERS**

| | |
|---|---|
| **Membership of professional organizations** | Member of the Cameroon Medical Council since 1999<br>Member of the Cameroon Association of Public Health since 2007<br>Member of the Society for AIDS in Africa (SAA) since 2011 |
| **Other skills and interests** | I use English proficiently and French independently. Can work with computer programs like Microsoft word, excel, PowerPoint, Publisher and the statistic program SPSS. I have travelled widely in Africa, Europe and the US for studies, international conferences and consultancies. Hobbies are travelling, jogging, watching movies and listening to music. |
| **Awards** | Presidential price (overall best graduating student of the 24th batch of medical doctors from the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, 1999). Many scholarship awards (MPH, PhD, International conferences) |

**Annex 4: List of publications**


Angwafo, F. F., **Atanga, P. N.**, Minkoulou, E., Fouda, P., Kim, K. S., Adams-Campbell, L., & Zoung-Kanyi, J. (2003). Factors Influencing Patient Survival in a Group of Men with Prostate Cancer in Yaoundé, Cameroon. *UroOncology, 3*(1), 7-11.

**Atanga, P. N**., Jacobi, C. A., Bin, L. K., Mbome, V. N., Akam, W., Bogner, J. R., . . . Malfertheiner, P. (2013). HIV/AIDS-related stigma felt by people living with HIV from Buea, Cameroon. *AIDS care, 25*(2), 173-180.

Meriki, H. D., Tufon, K. A., Afegenwi, M. H., Nyindem, B. A., **Atanga, P. N.,** Anong, D. N., . . . Nkuo-Akenji, T. (2014). Immuno-haematologic and virologic responses and predictors of virologic failure in HIV-1 infected adults on first-line antiretroviral therapy in Cameroon. *Infectious diseases of poverty, 3*(1), 1.

Meriki, H. D., Tufon, K. A., **Atanga, P. N.**, Ane-Anyangwe, I. N., Anong, D. N., Cho-Ngwa, F., & Nkuo-Akenji, T. (2013). Drug resistance profiles of Mycobacterium tuberculosis complex and factors associated with drug resistance in the Northwest and Southwest Regions of Cameroon. *PLOS ONE, 8*(10), e77410.

**Atanga, P. N.**, Ndetan, H. T., Achidi, E. A., Meriki, H. D., Hoelscher, M., & Kroidl, A. (2016). Retention in care and reasons for discontinuation of lifelong antiretroviral therapy in a cohort of Cameroonian pregnant and breastfeeding HIV-positive women initiating 'Option B+'in the South West Region. *Tropical Medicine & International Health, 22*(2), 161-170.

**Annex 5: Statement on Pre-release and contribution**

The currently presented thesis entitled “Retention-in-Care, Adherence and Treatment outcomes in a cohort of HIV-positive pregnant and breastfeeding women enrolled in a pilot project implementing “Option B+” in Cameroon” is my original research conceived for the purpose of the PhD programme. Part of this work is currently under review for publication by the journal of Tropical Medicine and International Health (TMIH). The manuscript entitled “Retention-in-care and reasons for discontinuation of lifelong antiretroviral therapy in a cohort of Cameroonian pregnant and breastfeeding HIV-positive women initiating "Option B+" in the South West Region” has passed the first review and the reviewer’s comments have been addressed and the manuscript resubmitted for consideration for publication.

Two abstracts from this work have been presented in international conferences and thus published in the conference abstract books. Firstly, at the 6$^{th}$ International Workshop on Women and HIV in Boston, USA in February, 2016 as an oral abstract presentation and secondly at the 21$^{st}$ International AIDS Conference in July, 2016 in Durban, South Africa as a poster presentation.

I conceived this study, wrote the proposal, planned and supervised the data and sample collection and personally built the database into which I entered and cleaned the data before analysis. I also drafted the manuscript which is currently under review and wrote the entire thesis with close supervision from my direct and local supervisors. However, other co-authors and scientific collaborators proof-read and edited the manuscript and the thesis.

The samples in this study were analysed at the Chantal Biya International Reference Centre for HIV/AIDS research in Yaoundé, Cameroon. The statistics were analysed by an associate Professor of Public Health and Biostatistics of the Research Institute, Parker University, Dallas, TX, USA.

**Annex 6: Acknowledgements**

Special gratitude go to my habilitated supervisor, Professor Dr. Michael Hoelscher, my direct supervisor, Dr. Arne Kroidl and my local supervisor, Professor Eric Achidi Akuma for their availability, invaluable ideas and and close mentorship they provided towards the realisation of this work.

Very special thanks go to the CIH administration for the constant guidance and the research periods subsistence scholarships which immensely supported my family throughout this two and a half year of this research.

I am also very grateful to all the study participants, the study staff and the staff of the participating units and most especially to the management of all the health facilities in which the study was conducted.

I am particularly grateful to the administration and the staff of the Emerging Disease Reference Laboratory of the Faculty of Science of the University of Buea for providing me with their expertise and the laboratory space for the storage of the research samples.

I deeply appreciate the scientific contributions and support from Dr. Henry Dilonga, Dr. Ndetan Harrison, Dr. Ndefon Peter, Dr. Cho-Ngwa Fidelis, Dr. Chuo Victor, Dr. Aguh Valentine and Mr. Ajime Tom Tanjeko. I equally thank my classmates for their constant encouragement during the course of my studies.

I am equally very grateful to the Cameroon Baptist Convention Health Services who secured the funds from PEPFAR for the pilot project within which this study was conducted.

I am forever indebted to my family especially, my wife (Martha), my kids (Faith, Princely, Promise and Chrisimmaculate), my beloved mum (Christina Atanga) and dad (Pa Moses Atanga), Loveline, Eveline, Christabel, Jean Claude and wife, Martin and wife and all other beloved family members for their love and immense financial and moral support.