# Alternative methodological approaches to assess long-term HIV virological and clinical outcomes in resource-limited settings

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# Alternative methodological approaches to assess long-term HIV virological and clinical outcomes in resource-limited settings

Thesis submitted for the degree of Doctor of Medical Sciences at the University of Antwerp to be defended by **Anita MESIC**

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# Alternative methodological approaches to assess long-term HIV virological and clinical outcomes in resource-limited settings

Alternatieve methodologische benaderingen om lange-termijn virologische en klinische HIV- behandelingsresultaten te evalueren in een setting met beperkte middelen

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# Summary

The public health approach to the HIV epidemic stands behind successful global scale up of access to HIV care and reduced morbidity and mortality among people living with HIV (PLHIV) over the last two decades. However, with increasing size and lifespan of the HIV cohorts, programs are facing challenging tasks to maintain virological suppression among PLHIV on antiretroviral treatment (ART) and their retention in care over time. Achievement of the virological suppression is key to the success of ART in an individual and for public health. Viral load (VL) monitoring is considered as the main tool to assess if the desired response is achieved. Most frequently, programs report virological outcomes as proportion of PLHIV on ART who achieved virological suppression at a given point of time. This cross-sectional approach does not reflect that, while on treatment, PLHIV might transition between suppressed and unsuppressed VL, causing over- or underestimation of the viremic state of the cohort. Furthermore, with the increasing longevity of HIV cohorts, retention in HIV-care follows a more cyclical pattern: PLHIV disengage from care for a short or long period, followed by re-engagement. HIV care for these populations can be challenging due to pre-existing ART exposure and HIV drug resistance, and frequent re-engagement with advanced HIV disease. Studies examining retention in HIV care often capture a cross-sectional status. There is limited evidence on the effect of cyclical patterns of retention on health outcomes. The research presented in this thesis studied virological outcomes, disengagement/re-engagement in care and advanced HIV disease and evaluated their relationship with unfavorable outcomes, based on the Médecins Sans Frontières (MSF) HIV program in Myanmar. The studies were conducted between 2001 and 2019 over a focused timeline. To achieve set objectives, four studies were conducted. Three studies used an observational, retrospective cohort design and one study was a systematic review of existing literature. The observational studies of this thesis were set up in the MSF HIV programs in Yangon Region, Kachin and Shan States in Myanmar. PLHIV receiving ART in the MSF HIV program in Myanmar were enrolled in the observational studies.

The thesis shows that the implementation of the VL cascade continues to be a major challenge. With the VL cascade, we refer to all the steps needed to achieve viral suppression: do a VL test, if not suppressed ensure better pill intake or a stronger regimen is used, so that viral suppression is again achieved. Instead of reporting general country-level VL coverage, the VL cascade analysis should be routinely performed as stratified by regions and populations, including all the steps of the cascade. This will support the national programs to develop strategies which maximize the potential effect of VL monitoring on outcomes among all population groups. Based on the findings presented in this thesis, cross-sectional VL should remain the main indicator for clinical decision-making and programmatic monitoring. Cumulative viremia (CV) indicators, which show how many people with HIV had

a detectable VL over a certain period, can estimate total burden of viremia over time and as such could better reflect quality of HIV care or act as predictor of health outcomes and local HIV epidemic control. However, methods to estimate CV indicators need to be improved, standardized and adapted for use in programmatic and clinical settings.

Our findings confirm that disengagement from care and reengagement were frequent and were associated with a high burden of advanced HIV disease, virological failure and subsequent disengagement. Therefore, we highlight the need for improved monitoring of retention and monitoring of access to a package of care for advanced HIV disease in each program. Three population groups were identified as being at risk for unfavorable health outcomes in our studies, namely PLHIV with advanced HIV disease, those re-engaging with HIV care or key population (people who inject drugs and sex workers). Differentiated service delivery, thus adapted to the needs of subgroups, is necessary. Additional research questions were identified, addressing knowledge gaps, that the studies included in this thesis were not able to address.

# Samenvatting

Een strategie gericht op volksgezondheid staat aan de basis van de succesvolle wereldwijde opschaling van de toegang tot HIV-zorg en de verminderde morbiditeit en mortaliteit onder mensen met HIV in de afgelopen twee decennia. Echter, met de toenemende omvang en levensduur van de HIV-cohorten, staan de programma's voor de uitdagende taak om virale onderdrukking bij mensen met HIV op antiretrovirale behandeling te handhaven en de continuïteit van zorg te verzekeren. Het bereiken van virale onderdrukking is de sleutel tot het succes van antiretrovirale behandeling bij een individu en HIV-controle in de gemeenschap. Virale onderdrukking wordt beschouwd als het belangrijkste hulpmiddel om te beoordelen of de gewenste behandelingsrespons wordt bereikt. Meestal rapporteren programma's virale resultaten als percentage van mensen met HIV op antiretrovirale behandeling die op een bepaald moment virale onderdrukking bereikten. Deze cross-sectionele benadering weerspiegelt niet dat mensen met HIV tijdens de behandeling kunnen overgaan van een onderdrukte naar een niet-onderdrukte virale lading, waardoor de viremische toestand van de cohort wordt over- of onderschat. Bovendien, met de toenemende levensduur van HIV-cohorten, komt een cyclisch patroon van retentie vaker voor: mensen met HIV stoppen behandeling voor een korte of lange periode, gevolgd door hernieuwde betrokkenheid en heropstarten van behandeling. HIV zorg voor deze populaties kan een uitdaging zijn vanwege reeds bestaande blootstelling aan antiretrovirale behandeling en resistentie tegen HIV-geneesmiddelen, en gevorderde HIV-ziektestatus na een onderbreking. Studies die retentie in de HIV zorg onderzoeken, geven vaak een transversale status weer en er is beperkt bewijs over het effect van het cyclische patroon van retentie op gezondheidsresultaten. Het onderzoek gepresenteerd in dit proefschrift bestudeerde virale resultaten, onderbreken/heropstarten van behandeling, en de HIV-ziektestatus na een onderbreking en evalueerde hun relatie met ongunstige uitkomsten. Data werden verzameld met behulp van het HIV-programma van Artsen zonder Grenzen (AZG) in Myanmar van 2001 tot 2019. Er zijn vier onderzoeken uitgevoerd om de gestelde doelen te bereiken. Drie studies gebruikten een observationeel, retrospectief cohortontwerp en één studie was een systematisch literatuuronderzoek. De observationele studies van dit proefschrift zijn opgezet in het HIV-programma van AZG, operationeel in de regio Yangon en de staten Kachin en Shan in Myanmar. Mensen met HIV die antiretrovirale behandeling ontvingen in het HIV-programma van AZG in Myanmar namen deel aan de observationele studies.

De bevindingen van het proefschrift weerspiegelen dat de implementatie van de virale lading (VL)-cascade een grote uitdaging blijft. Met de virale lading cascade verwijzen we naar alle stappen die nodig zijn om virale onderdrukking te bekomen: een VL test doen, indien niet onderdrukt ervoor zorgen m.b.v. een betere pilinname of een sterker regime dat virale onderdrukking opnieuw bereikt wordt. In plaats van het niveau van

virale onderdrukking per land te rapporteren, zou de VL-cascadeanalyse gestratificeerd per regio en voor verschillende subpopulaties moeten gedaan worden. Dit zal nationale programma's ondersteunen bij het ontwikkelen van strategieën die kunnen helpen bij het maximaliseren van het potentieel effect van VL-monitoring op behandingsresultaten bij alle bevolkingsgroepen. Op basis van de bevindingen gepresenteerd in het proefschrift zou een cross-sectionele analyse van virale onderdrukking de belangrijkste indicator moeten blijven voor klinische besluitvorming en programmatische monitoring. Cumulatieve viremie-indicatoren, die tonen in welke mate mensen met HIV in een bepaalde periode een detecteerbare virale lading hadden, kunnen de virale onderdrukking op langere termijn schatten en zouden als zodanig de kwaliteit van de HIV-zorg beter kunnen weerspiegelen of kunnen fungeren als een teken van HIV-controle en het effect van lokale bestrijding van de HIV-epidemie. Methoden om cumulatieve viremie-indicatoren te schatten moeten echter worden verbeterd, gestandaardiseerd en aangepast voor gebruik in programmatische en klinische omgevingen.

Onze bevindingen bevestigen dat het onderbreken van behandeling en zorg en het zich opnieuw engageren na een onderbreking frequent voorkwamen en geassocieerd waren met gevorderde HIV-ziekte, viraal falen, en het opnieuw onderbreken van de behandeling. Daarom benadrukken wij de noodzaak voor verbeterde monitoring van retentie en monitoring van de toegang tot een zorgpakket voor gevorderde HIV-ziekte in elk programma. Drie risicogroepen werden geïdentificeerd: namelijk PLHIV met een gevorderde HIV-ziekte, zij die na een onderbreking opnieuw hun hiv-behandeling starten, en "sleutelgroepen", zoals mensen die drugs injecteren en sekswerkers. Een gedifferentieerde dienstverlening, dus aangepast aan de noden van subgroepen, is noodzakelijk. Er werden aanvullende onderzoeksvragen geïdentificeerd voor het aanpakken van kennislacunes die de studies in dit proefschrift niet verhielpen.

# Chapter 1 |

## General introduction

# 1.1 Background

## 1.1.1 Global burden of HIV

Since the beginning of the Human Immunodeficiency Virus (HIV) pandemic, 84.2 million (95% CI 64.0–113.0 million) people have been infected with HIV and 40.1 million (33.6–48.6 million) have died from Acquired Immune Deficiency Syndrome (AIDS)-related illnesses [1].

In 2021, there were an estimated 38.4 million (33.9–43.8 million) people living with HIV (PLHIV) globally; however, the HIV pandemic disproportionately affects regions of the world. Sub-Saharan Africa has been carrying the highest burden of HIV: two-thirds of PLHIV live in this region, followed by Asia and the Pacific with an estimated 6.0 million (4.9–7.2 million) PLHIV in 2021 (Figure 1-1) [1].

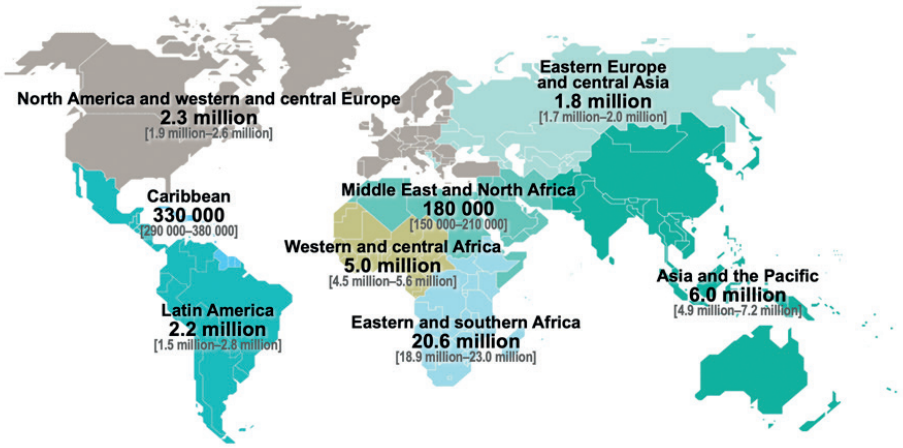


**Figure 1-1|** People estimated to be living with HIV in 2021[1]

## 1.1.2 Global HIV response: achievements and remaining gaps

The world has committed to end the AIDS epidemic by 2030. To accelerate achieving this ambitious goal, the Joint United Nations Programme (UNAIDS) 95-95-95 targets are expected to be reached by 2025. The targets refer to: "95% of the people who are living with HIV know their HIV status, 95% of people who know that they are living with HIV are on lifesaving antiretroviral treatment, and 95% of people who are on treatment are virally suppressed". [2].

1 *Source: Adapted from the Joint United Nations Programme on HIV/AIDS (UNAIDS). IN DANGER: UNAIDS Global AIDS Update 2022. Geneva: UNAIDS; 2022 [15 May 2023]; Available from: https://www.unaids.org/sites/default/files/media_asset/2022-global-aids-update_en.pdf.*

Major gains were made across the 95-95-95 targets: 85% (75–97%) of PLHIV were aware of their HIV status, 28.7 million people were on ART (75% (66–85%)) and 68% (60–78%) were virologically suppressed (Figure 1-2) in 2021 [3]. In the same year, approximately 1.5 million new HIV infections occurred, which is a 32% decline in comparison with 2010. Since the peak in 2004, when 2.0 million (1.6–2.7 million) PLHIV died of AIDS-related illnesses, mortality reduced by 68% because of expanded access to HIV testing and massive scale up of early initiation of ART (Figure 1-3) [4]. However, trends in new HIV infections and HIV-related mortality depend on access to HIV care. In 2021, we could observe signs of reduced expansion of HIV services, when the number of new people on ART in 2021 increased only by 1.47 million compared to 2.0 million in previous years [5].

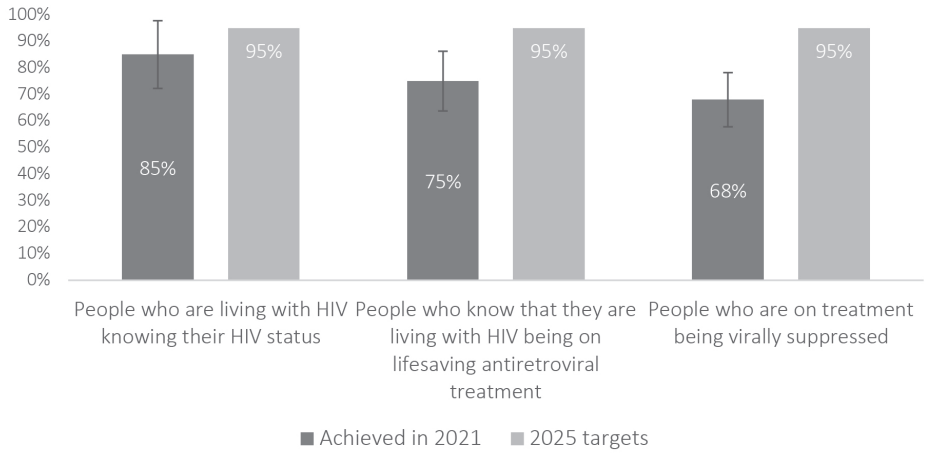


**Figure 1-2|** Testing and treatment cascade among people living with HIV in 2021[2]

In the last three years, due to the COVID-19 pandemic, economic and humanitarian crises had an impact on global HIV response. The UNAIDS reported concerning trends of slowing down progress, reduction in funding and widening inequalities [6]. The use of a public health approach enabled a massive scale up of access to HIV care in the settings with the highest burden and limited resources. The key principles of such an approach are based on simplification and standardization of ART, task sharing, decentralization and integration of HIV care and treatment wherever is possible [4]. However, with growing numbers of PLHIV engaged in HIV care, as well as longer lifespans of HIV cohorts, the public health approach needs to be refined to successfully respond to the remaining challenges: effective engagement with care for those who are still left behind, improved linkage to care for those disengaged, increased retention in care and improved viral suppression.

2 *Source: Adapted from Joint United Nations Programme on HIV/AIDS (UNAIDS) epidemiological estimates 2022. Available at: https://aidsinfo.unaids.org/*

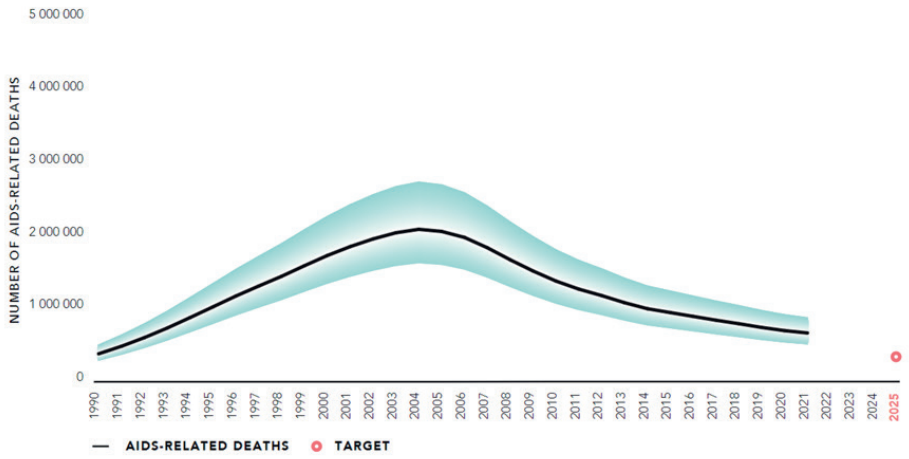


**Figure 1-3|** Global number (with 95%CI) of AIDS-related deaths 1990–2021[3]

## 1.1.3 The most affected populations

People with less social power and marginalized populations were being hit the hardest by the HIV epidemic. In multiple settings, households with the least economic power had the lowest uptake of HIV testing and treatment services and were reported to achieve the lowest rates of HIV virological suppression, when on ART [7]. Adolescent girls and young women (age 15–24 years) were three times more likely to acquire HIV than men of the same age group in sub-Saharan Africa in 2021. Key populations (sex workers, people who inject drugs, gay men and other men having sex with men, transgender women and incarcerated populations) and their sexual partners accounted for 70% of the global HIV infection burden (Figure 1-4). Relative risk of HIV acquisition among these populations is estimated to be 14–35 times higher in comparison with the general population. Punitive and discriminatory laws and policies are responsible for undermined HIV response among key populations. These practices discourage people from accessing and remaining in care and diminish efforts to reach those most at risk of infection, severe disease and death [5]. Despite a shift toward initiating ART in all children, the inequality in HIV treatment coverage between children and adults has been increasing, as only half of the children living with HIV accessed treatment in 2021. A high proportion of children living with HIV access care with advanced HIV disease, and there is high mortality within the first 6 months of initiating ART in all settings [7]. In 2021, children comprised 4% of PLHIV in 2021 but 15% of all AIDS-related deaths [8].

3 *Source: Joint United Nations Programme on HIV/AIDS (UNAIDS) epidemiological estimates 2022. Available at: https://aidsinfo.unaids.org/*

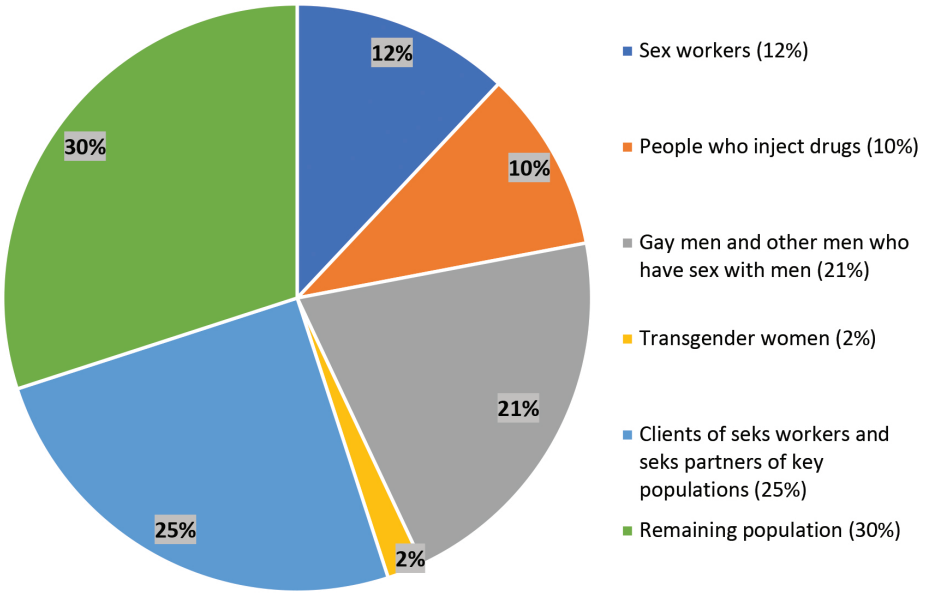


**Figure 1-4|** Global distribution of acquisition of new HIV infections by population [4]

## 1.1.4 Remaining burden of advanced HIV disease

In 2021, an estimated 650,000 (510,000–860,000) people died of AIDS-related illnesses worldwide, which is mostly because of the persistent challenge of Advanced HIV Disease (AHD) [8]. AHD is defined as having a CD4 cell count <200 cells/mm$^3$ or clinical stage III or IV disease. In addition, all children <5 years of age with HIV are considered to have AHD. PLHIV with AHD are at the highest risk of opportunistic infections and death. Leading causes of mortality among PLHIV remain tuberculosis and cryptococcal meningitis [9, 10]. Since 2017, the World Health Organization (WHO) has recommended a package of care for the management of AHD [11].

In the early stage of the global HIV response, those who presented with AHD were PLHIV who had not yet received ART ("late presenters"). Nowadays, we are observing a trend of an increasing proportion of ART-experienced PLHIV with AHD [11–13]. This group is represented by those who disengage from and then re-engage with HIV care. Studies report that 11–77% of PLHIV on ART temporarily disengage from care during the decades of their observational periods [11, 14–17] due to individual and health system related reasons. Unfortunately,

4 *Source: Adapted from Joint United Nations Programme on HIV/AIDS (UNAIDS). IN DANGER: UNAIDS Global AIDS Update 2022. Geneva: UNAIDS; 2022 [15 May 2023]; Available from: https://www.unaids.org/sites/default/files/media_asset/2022-global-aids-update_en.pdf*

standardized indicators to monitor the burden of AHD and the frequency of temporary disengagement from HIV care are not included in the routine HIV program monitoring. Therefore, HIV programs often lack specific information on these major challenges in the HIV epidemic control.

### 1.1.5 Virological suppression among PLHIV on ART

Another group of PLHIV frequently presenting with AHD are those who experience virological treatment failure. The WHO defines virological failure as two consecutive HIV viral load (VL) test results ≥1,000 copies/mL after at least three months of ART, with enhanced adherence support following the first VL result ≥1,000 copies/mL. Virological failure is an indication for treatment regimen change with an aim to achieve suppression of the VL, immune reconstitution and prevention of morbidity, mortality and transmission. Regular access to VL testing for PLHIV on ART, timely review of the test results by clinicians, followed by appropriate actions taken, are necessary to achieve full potential of the VL cascade.

From a recent systematic review, which synthesized evidence on VL cascade in low- and middle-income countries, we could learn about substantial gaps. The review reports VL coverage between 25% and 95% among adults, 2–94% among children, adolescents, and young people and 32–84% among pregnant women. Furthermore, the findings indicate 66% (38–77%) uptake of follow-up VL tests among PLHIV with initially elevated results; 62% (50–75%) of confirmed treatment failure among those with a follow-up test and only 45% (36–71%) switching rate among those with confirmed treatment failure [18].

While the number of PLHIV who know their HIV status and who receive ART increased over time, the proportion of those with viral suppression has remained stable with substantial variations across regions and sub-populations [19]. In 2021, the UNAIDS estimated that 68% (60–78%) of all PLHIV and 92% (81–98%) of PLHIV on ART were virologically suppressed [20]. However, such reporting does not indicate any of the gaps in the VL cascade. Additionally, this is a cross-sectional indicator that does not account for the fact that virological suppression might not be stable and PLHIV might transition between suppressed and unsuppressed viremia. By overlooking these transitions, a cross-sectional approach in studying virological outcomes might under- or overestimate virological state of an individual or an HIV cohort [21, 22]. Underestimated viremia may result in missed opportunities to improve individual health, and in ongoing HIV transmission.

# 1.2. HIV epidemic in Myanmar

## 1.2.1 General information about the country

Myanmar is a lower-middle-income country in Southeast Asia with estimated population of 53.8 million [23]. Administratively, the country is composed of the capital Nay Pyi Taw and 14 states and regions (Figure 1-5). Myanmar has been suffering from decades of internal conflict, military rule, and sanctions from the international governments, which escalated in the last two years with severe consequences for the country's economic growth and development, as well as the state of the health care system. The total health expenditure in 2019 was 4.68% of the Myanmar gross domestic product (GDP) and the country has the highest out-of-pocket expenditure among the Association of Southeast Asian Nations [24].



## 1.2.2 HIV burden in Myanmar

There were an estimated 270,000 (260,000–290,000) PLHIV in Myanmar and 6,600 (4,800–9,100) died of AIDS-related illnesses in 2021. In the same year the HIV incidence declined by 35% compared to 2010. An estimated 11,000 people were newly infected in Myanmar in 2021 [20].

The HIV epidemic in Myanmar is concentrated among specific populations (people who inject drugs, sex workers, men having sex with men, transgender population) and consequently in the regions of the country where concentration of these populations is higher (Figure 1-6). While the country-wide HIV prevalence in the general population in 2021 was estimated at 0.57%, it was much higher among people who inject drugs (PWID), female sex workers (FSW) and gay men and other men who have sex with men (MSM) at 19%, 8.3% and 8.6%, respectively. These key populations carried more than 70% of the new HIV infections in Myanmar [24, 25], though are not evenly distributed across the country. Almost one third (26%) of the PWID lives in Kachin, followed by Shan (19%) and Yangon (3%). The population of sex workers is the highest in Yangon (23% of total country's sex worker population), Shan (6%) and Kachin (5%). Similarly, 23% of MSM were reported in Yangon, while 5% and 2% of the MSM population resided in Kachin and Shan, respectively. As a consequence, Kachin, Yangon and Shan were reported to be states with the highest general HIV prevalence in the country in 2021 with 2.76%, 0.96% and 0.95%, respectively (unpublished national programmatic data).


**Figure 1-5|** Map of Myanmar[5]

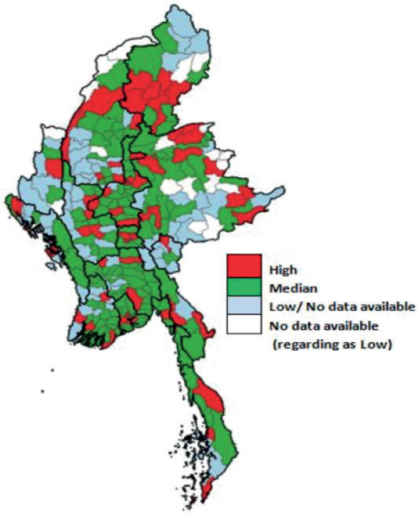


**Figure 1-6|** HIV burden in Myanmar townships[6]

5 *Source: https://www.worldmap1.com/map/myanmar/map_of_Myanmar.gif*

6 Source: https://www.globalhep.org/sites/default/files/content/resource/files/2022-11/NACP%20Progress%20Report%202019.pdf

## 1.2.3 HIV response: achievements and remaining gaps

External funding for HIV response in Myanmar has been challenged by its complex political background. Until 2014, the HIV testing and treatment services were provided mostly in the private sector, including Non-Governmental Organizations (NGOs). However, funding from the Global Fund was granted in 2014, which enabled scaling up of the public health response and improved access to HIV care across the country [26]. The country adopted the WHO guidelines for the management of PLHIV and achieved 71% ART coverage in 2021 [27]. Due to scale up of early ART initiation, Myanmar reduced AIDS-related mortality by 40% since 2010 [28]. Despite these successes, progress towards 95-95-95 targets remains slow (Figure 1-7). Furthermore, since 2019, there is a strong commitment from the Myanmar National AIDS Programme (NAP) to gradually transfer all PLHIV cared for in the private sector to the public health care services. This is an important step towards long-term national ownership and sustainability of the HIV response in Myanmar. Therefore, there is an urgent need to generate evidence on how to support growing HIV cohorts in the public health system in Myanmar.



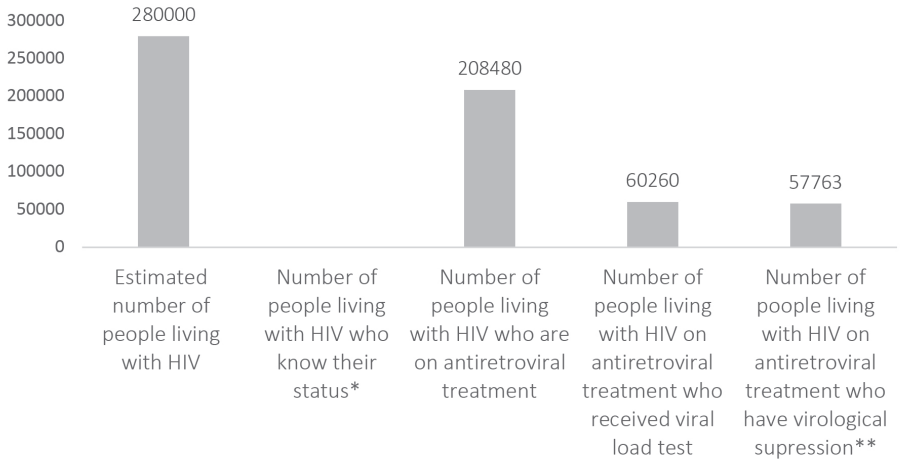


**Figure 1-7|** Cumulative cross-sectional cascade for HIV treatment and care, Myanmar, 2022[7]

*Data not available

** Number of patients on antiretroviral treatment who received a viral load test in the past 12 months and have VL of <1000 copies/ml; ART: antiretroviral treatment; PLHIV: people living with HIV

## 1.2.4 The most affected populations

Key populations in Myanmar are considered as the main drivers of the HIV epidemic and they experience high burden of stigma, discrimination, and structural barriers when accessing HIV prevention and care in the country [24, 25]. Awareness about HIV status among key populations has been low: 27.9% among PWID, and 41% and 31% among FSW

7 *Source:Adapted from HIV and AIDS data hub for Asia and Pacific. Available*

and MSM, respectively. Access to prevention services remains limited and ART coverage in these groups remains suboptimal. In 2020, 21.9%, 44.1% and 59.1% of PWID, MSM and FSW, respectively, were receiving HIV treatment [29]. The last national strategic plan increases focus on these priority populations and geographical areas with high burden of HIV [30], but the implementation of the ambitious plans so far has been driven by the NGOs, who experience very limited operational space due to political climate in the country. In addition, multiple social barriers and punitive laws and policies, such as criminalization of sex work, same sex activities and drug use, as well as the presence of compulsory detention centers for PWID do not provide an enabling environment for HIV response [27].

### 1.2.5 Remaining burden of advanced HIV disease

In the country, which experienced a delayed national response to HIV, it is expected to observe a remaining high burden of AHD. Data published in 2018 indicate 58% PLHIV diagnosed with AHD upon enrolment to HIV care and high rates of early mortality and loss to follow-up [31]. The report identified AHD as one of the risk factors for unfavorable treatment outcomes in the large Myanmar cohort. The NAP fully adopted the WHO recommendations for the management of HIV in their national guidelines [32]. However, implementation of the full package of care for AHD in the public system is suboptimal at each level of health care: there is limited access to CD4 count testing, screening for opportunistic infections is reserved for symptomatic patients only and treatment of the most common opportunistic infections is suboptimal, even in the hospital setting [24]. This major gap in provision of high quality HIV care for the most-severely sick PLHIV is further compromised by the collapse of the health care system in the last two years, driven by the COVID-19 pandemic and political situation.

### 1.2.6 Virological monitoring in Myanmar

Decentralization of HIV testing and treatment and increase in ART coverage has not been followed by improved access to virological treatment monitoring. Reported VL monitoring coverage varies from 34–72% and access remains centralised and limited to the private sector [33–35]. Even though studies from Myanmar reported good long-term immunological and virological treatment outcomes among PLHIV on treatment in the private sector (NGO), there is further evidence on the gaps of the VL cascade in the public system [35]. A study from Myanmar that reported high rates of virological failure, but low rates of switching to second-line treatment, highlighted the importance of adequate utilization of the VL cascade, as one-third of those who did not switch their treatment died or were lost to follow-up (LFU) from care [36].

## 1.3 Thesis Aim and Objectives

### 1.3.1 Aim

Research questions explored in this thesis were generated while I worked as an HIV clinician and program implementer in Myanmar from 2009 until 2014. The thesis aims to document the VL cascade, explore viremic status of a long-term HIV cohort and investigate factors associated with unfavorable virological outcomes—to provide evidence about possible refinement of our approach to virological monitoring. By assessing how frequently PLHIV disengage from HIV care and documenting what the risk factors for advanced HIV disease are, treatment failure and attrition, after their re-engagement with HIV care, the thesis highlights new challenges that occur in long-lasting HIV cohorts. Moreover, the thesis aims to provide evidence on how to adapt clinical and program monitoring to address the needs of these specific populations.



### 1.3.2 General objective

To investigate alternative methodological approaches for clinical and programmatic monitoring of the HIV cohorts in resource-limited settings.

### 1.3.3 Specific objectives

1. To assess whether a history of disengagement and re-engagement from HIV care predicts virological failure among PLHIV on first line ART.
2. To apply alternative methods for the analysis of virological suppression in long-term ART cohorts on second-line ART.
3. To synthesize evidence about the use of cumulative viremia in the monitoring of HIV cohorts.
4. To describe the burden of AHD among PLHIV who re-engage with HIV care and to investigate risk factors for attrition after reengagement.

## 1.4 Thesis structure

The research presented in this thesis studied virological outcomes, disengagement/ re-engagement in care and advanced HIV disease and evaluated their relationship with unfavorable outcomes using Médecins Sans Frontières (MSF) HIV program in Myanmar from 2001 until 2019 as a case study.

In the first part, I investigated virological outcomes in a long-term HIV cohort, by using standard and alternative methodologies. The results are presented in the following thesis Chapters:

**Chapter 3** describes **viral load cascade**, **incidence of treatment failure** and associated **risk factors**.

**Chapter 4** presents an alternative longitudinal approach to measure HIV viremia, risk factors for **cumulative HIV viremia** and how this indicator is associated with mortality.

**Chapter 5** synthetizes existing evidence on the use of cumulative HIV viremia and its association with different health outcomes.

Secondly, I investigated **disengagement** from and **re-engagement** with HIV care and its association with treatment failure and AHD. The results are presented in the following thesis Chapters:

**Chapter 3** explored the burden of **cumulative appointment delay** in our cohort and how it predicts treatment failure.

**Chapter 6** describes the burden of **advanced HIV disease** in a cohort of PLHIV who re-engaged with HIV care, after being LFU, and assessed how is **re-engagement** related with the future attrition from care.

Finally, **Chapter 2** summarizes research methods used in the PhD research. **Chapter 7 and 8** summarize the findings of all the studies, draw broad conclusions referring to the findings from the presented studies and provide ideas for future research in these areas.

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# Chapter 2 |

## Methodology

## 2.1 Study design

To achieve specific objectives, we have conducted four studies. Three studies used an observational, retrospective cohort design (Objective 1, 2 and 4) and one study was a systematic review of existing literature. Details of study designs, periods, populations and statistical analyses are presented in Table 2-1.

## 2.2 Study population

PLHIV receiving ART in the MSF HIV program in Myanmar in the period from 2001 until 2019 were enrolled in the observational studies. Sample size in specific studies varied from 1,352 to 25,260. Details about the study populations are presented in Table 2-1.

## 2.3 Study setting

The observational studies used within the thesis were set up in the MSF HIV programs in Yangon Region, Kachin and Shan States in Myanmar (Figure 2-1). MSF is as an NGO that focuses on delivering medical humanitarian assistance to victims of conflict, natural diseases, epidemics or healthcare exclusion [1].

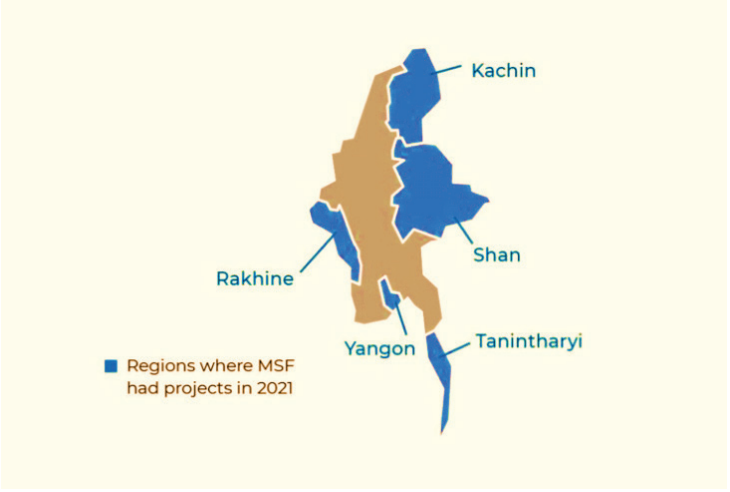



**Figure 2-1|** Regions of Myanmar where Médecins Sans Frontières implemented their medical programs[1]

1 *Source: Adapted from https://www.msf.org/myanmar*

In Myanmar, MSF has been providing free-of-charge comprehensive HIV care since 2001. During the period 2001–2019 the organization enrolled more than 58,000 PLHIV into HIV care. The major milestones in implementation of the HIV programs are illustrated in Figure 2-2.

**Model of care:** Being the main provider of HIV care in Myanmar until 2014, MSF reached the limits of its capacity in terms of human resources and space. Therefore, they have piloted the first differentiated model for ART delivery among stable PLHIV on ART. In differentiated model of care patients are categorized by clinical condition and based on this the frequency, level of medical staff, intensity and location of services is tailored to their needs. This approach reduced the number of visits for stable PLHIV and allowed physicians to spend more time on more sick patients [2].



**HIV testing:** Between 2003 and 2019 MSF enrolled anyone who tested HIV positive, either by a test done in the MSF clinic or referred from other partners involved in HIV care, in the country into the HIV program.

**HIV treatment:** Before 2014, based on the internal MSF resources and guidelines at the time, ART was initiated only to PLHIV with severe immunosuppression (CD4 cell count <200 cells/$mm^3$). From 2014 onwards, the ART enrolment criteria became more inclusive. The threshold to start ART increased stepwise, from CD4 cell count <200 cells/$mm^3$ to "Test and Treat" in 2016, with ART initiation regardless of the CD4 cell count [3]. Participants enrolled in our studies received ART regimens recommended by the WHO and the national guidelines at the time. This included: first-line treatment as combination of two nucleoside/nucleotide reverse transcriptase inhibitors (zidovudine, tenofovir, lamivudine, abacavir) with a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) and second-line regimen, which was composed of two nucleoside/nucleotide reverse transcriptase inhibitors and one protease inhibitor (atazanavir/ritonavir or lopinavir/ritonavir).

**Management of AHD:** Since 2009, MSF implemented a package of care for the management of AHD. This included: routine CD4 monitoring; intensified screening and treatment for tuberculosis, cryptococcal disease, talaromycosis (skin smear microscopy) and other common opportunistic infections; treatment for these infections and access to targeted, and later routine, VL monitoring with rapid HIV treatment for failure cases. MSF adapted their package to the WHO guidelines in 2017 [4]

**Table 2-1|** Overview of the methodology of the studies included in the thesis

| Objective | Title of the publication | Design | Period | Population: type and size | Main endpoints | Statistical methods |
|---|---|---|---|---|---|---|
| 1 | Predictors of virological failure among people living with HIV receiving first-line antiretroviral treatment in Myanmar [5] | Cohort analysis | 2001–2017 | PLHIV enrolled on ART who had at least one HIV VL test available after receiving at least 6 months of standard first-line ART.<br>Sample size: N=25,260 | Descriptions of VL cascade<br>Incidence rate of virological failure<br>Hazard ratio for virological failure | Descriptive statistics<br>Multivariable Cox regression |
| 2 | Viraemic-time predicts mortality among people living with HIV on second-line antiretroviral treatment in Myanmar [6] | Cohort analysis | 2014–2018 | PLHIV aged above 5 years who had received second-line ART for over 6 months and had at least two HIV VL test results.<br>Sample size: N=1,352 | Calculation of viremic time<br>Odds ratio for higher viremic time<br>Hazard ratio for mortality | Descriptive statistics<br>Multivariable fractional logistic regression<br>Multivariable Cox regression |
| 3 | Systematic review on cumulative HIV viremia among people living with HIV receiving antiretroviral treatment and its association with mortality and morbidity | Systematic review | 2008–2022 | Quantitative studies reporting on HIV CV and its association with health outcomes among PLHIV on ART.<br>Studies included: N=26 | Summary of CV burden and methodologies<br>Association between CV and morbidity and mortality | Descriptive statistics |
| 4 | Advanced HIV disease and associated attrition after re-engagement in HIV care in Myanmar from 2003 to 2019 [7] | Cohort analysis | 2003–2019 | PLHIV aged above 5 years who received ART and who re-engaged in care after being declared lost to follow-up<br>Sample size: N=7,608 | Prevalence of advanced HIV disease at re-engagement with HIV care<br>Incidence rate of attrition after re-engagement based on presence/absence of advance HIV disease<br>Hazard ratio for attrition after re-engagement among PLHIV with advanced HIV disease | Descriptive statistics<br>Multivariable Cox regression |

CV: Cumulative Viremia; VL: Viral load

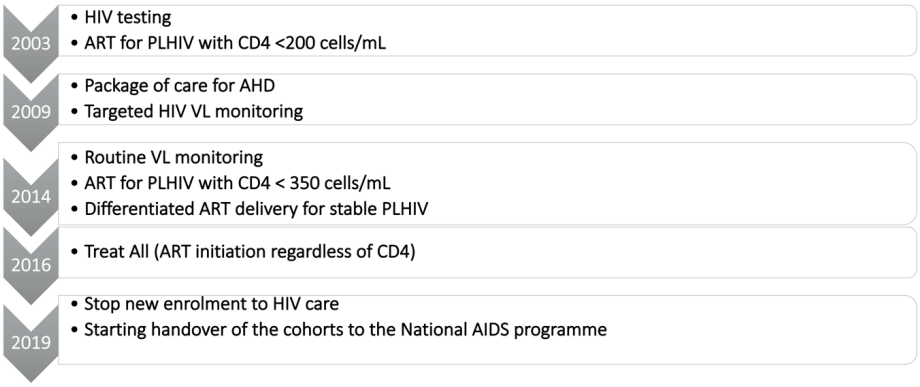



**Figure 2-2|** Milestones in implementation of HIV care in MSF HIV programs in Myanmar 2003–2019[2]



**Virological monitoring:** In 2009, MSF introduced targeted virological monitoring for those with immunological and/or clinical failure. From 2014 onwards, yearly routine VL monitoring targeted all children and patients on second-line ART. Since 2016, yearly routine VL testing was introduced for all patients on ART.

**Management of treatment failure:** Management of virological failure was based on a public health approach. Patients with viremia (VL >200 copies/mL defined as the limit of detection) received 3–6 counseling sessions over a period of 3 months and were then prescribed a follow-up VL test. Those with two consecutive VL test results above the threshold for failure (≥5,000 copies/mL until 2012, ≥1,000 copies/mL after 2012) were switched to a new ART regimen. If the follow-up VL did not show failure, enhanced adherence support continued together with three-monthly monitoring until undetectable viremia was observed. Access to HIV drug-resistance testing has been very limited and reserved for patients who are failing second-line ART.

## 2.4 Data management and analyses

### 2.4.1 Observational cohort studies

Observational studies performed in the thesis (Chapter 3, 4 and 6) used routine program data collected from standardized patient forms. During every visit by the patient, the health care worker recorded clinical, laboratory and other follow-up information into the forms, which were further encoded in the MSF HIV program database, FUCHIA (Follow-up and Care of HIV Infection and AIDS) by the trained data encoders. Anonymized individual data

2 *Source: Figure was created by using unpublished programmatic data and for the purpose of illustrating programmatic milestones in the PhD thesis only.*

were extracted from FUCHIA and imported into STATA statistical software version 14.0 (STATACorp, Texas, USA) or RStudio (versions 3.5.1 and 3.6.0 (RStudio, Boston, MA, USA).

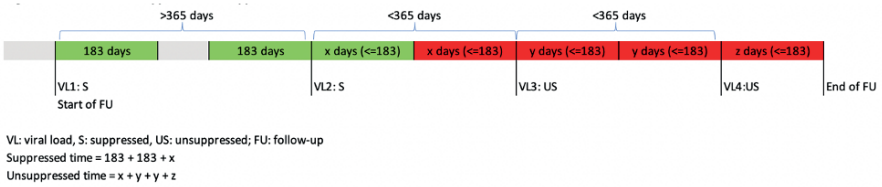
Analyses of the programmatic data used in the studies reported in the Chapters 3, 4 and 6 were performed with an input from the program managers and clinicians and with a support of different statisticians. Details about the performed analyses are described separately in Chapters 3, 4, and 6. A short summary of the most frequently used statistical approaches listed in Table 2-1.

Baseline characteristics were described using frequencies and percentages for categorical variables. The normal distribution of continuous variables was assessed by skewness/kurtosis test for normality and plotting histograms for each of the continuous variables. When the distribution was not normal, we calculated medians and interquartile ranges (IQR), otherwise mean with standard deviation (SD) would be reported. In Chapter 6, to calculate the odds ratios (OR) and respective 95% confidence intervals (CI) for having viremic-time we performed a fractional logistic regression analysis. In Chapters 3, 4 and 6 we used Cox proportional hazard regressions to compute hazard ratios (HR) and respective 95% CI. The proportional hazards assumption was tested using scaled Schoenfeld residuals. To build multivariable regression models, variables were selected based on results from the bivariable and stratified analyses, where associations with the outcomes and primary exposure variables were assessed, as well as presence of interaction. Where effect modification (interaction) was identified in stratified analysis, we tested whether the addition of interaction terms significantly improved the model fit. Only complete cases, thus without missing information for any of the variables selected in the analysis, were considered for multivariable analysis. Forward stepwise selection was used to construct the final multivariable models. All analyses were two-tailed, with a significance level of 0.05.

### 2.4.2 Systematic review

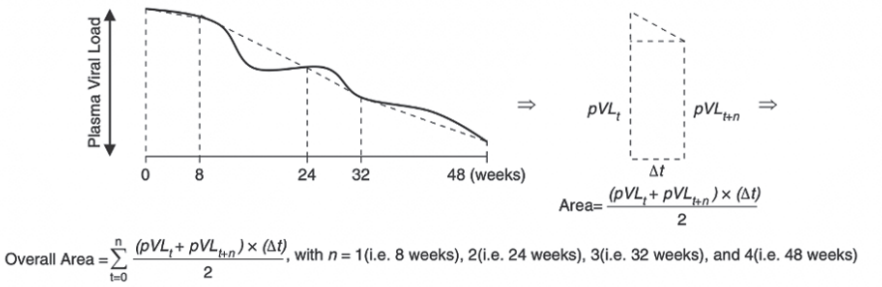
Detailed description of the methodology applied to perform the systematic review is available in the chapter 5. In summary, we searched MEDLINE via PubMed, Embase, Scopus, and Web of Science from January 1, 2008 to August 1, 2022 using a predefined search strategy (Supplement 5-1). We included quantitative studies reporting HIV CV and its association with health outcomes among PLHIV on ART. CV was defined as a proportion of follow-up time on ART under or above a certain VL threshold (Figure 2-3) or as viremia copy-years or a variation of this definition (Figure 2-4), which estimates the area under a patient's VL curve. Studies reporting HIV CV among ART-naïve PLHIV or those that did not clearly specify the ART history of study participants were excluded from the review. Two reviewers extracted data independently in accordance with a predefined data extraction

sheet. Outcomes of interest were CV and any health outcomes related to PLHIV on ART. All results were tabulated.




To calculate the viraemic-time, cumulative unsuppressed time was divided by follow-up time (both in days). Cumulative unsuppressed or suppressed time was the time during which we assumed that a patient had HIV VL above or below the limit of detection, respectively. Follow-up time was defined as a sum of cumulative unsuppressed and suppressed time.

**Figure 2-3** | An example of cumulative viremia calculated as viremic-time[3]




Trapezoidal rule to obtain the area under the plasma viral load of each patient enrolled in the randomized clinical trial, with plasma viral load measured at baseline and at weeks 8, 24, 32 and 48.

**Figure 2-4** | An example of cumulative viremia calculated as an area under viral load curve and reported as copy-years/mL or $\log_{10}$ copy-years/mL[4]

3 *Source: Adapted from Mesic A, et al. Viremic-time predicts mortality among people living with HIV on second-line antiretroviral treatment in Myanmar: A retrospective cohort study. PLoS One. 2022;17(7):e0271910. Epub 20220729. DOI: 10.1371/journal.pone.0271910*

4 *Source: Adapted from: Lima VD, et al. Comparing the efficacy of efavirenz and boosted lopinavir using viremia copy-years. J Int AIDS Soc. 2014;17:18617. DOI: http://dx.doi.org/10.7448/IAS.17.1.18617*

## 2.5 Ethics

All observational studies received ethical approval from the Department of Medical Research Ethical Review Board, Myanmar (DMR 2019/125, DMR 2019/153 and DMR 2021/128) and fulfilled the exemption criteria set by MSF independent Ethical Review Board for a posteriori analysis of routinely collected clinical data. The systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database CRD42021283891).

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# Chapter 3 |

## Predictors of virological failure among people living with HIV receiving first line antiretroviral treatment in Myanmar

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†Lutgarde Lynen and Htun Nyunt Oo contributed equally to this work

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# 3.1 Abstract

**Background:** Progress toward the global target for 95% virological suppression among those on antiretroviral treatment (ART) is still suboptimal. We describe the viral load (VL) cascade, the incidence of virological failure and associated risk factors among people living with HIV receiving first-line ART in an HIV cohort in Myanmar treated by the Médecins Sans Frontières in collaboration with the Ministry of Health and Sports Myanmar.

**Methods:** We conducted a retrospective cohort study, including patients with at least one HIV VL test result and having received at least 6 months' standard first-line ART. The incidence rate of virological failure (HIV VL ≥1,000 copies/mL) was calculated. Multivariable Cox's regression was performed to identify risk factors for virological failure.

**Results:** We included 25,260 patients with a median age of 33.1 years (interquartile range, IQR 28.0–39.1) and a median observation time of 5.4 years (IQR 3.7–7.9). Virological failure was documented in 3,579 (14.2%) participants, resulting in an overall incidence rate for failure of 2.5 per 100 person-years of follow-up. Among those who had a follow-up VL result, 1,258 (57.1%) had confirmed virological failure, of which 836 (66.5%) were switched to second-line treatment. An increased hazard for failure was associated with age ≤19 years (adjusted hazard ratio, aHR 1.51; 95% confidence intervals, CI 1.20–1.89; p<0.001), baseline tuberculosis (aHR 1.39; 95% CI 1.14–1.49; p<0.001), a history of low-level viremia (aHR 1.60; 95% CI 1.42–1.81; p<0.001), or a history of loss-to-follow-up (aHR 1.24; 95% CI 1.41–1.52; p=0.041) and being on the same regimen (aHR 1.37; 95% CI 1.07–1.76; p<0.001). Cumulative appointment delay was not significantly associated with failure after controlling for covariates.

**Conclusions:** VL monitoring is an important tool to improve program outcomes; however, limited coverage of VL testing and acting on test results hampers its full potential. In our cohort children and adolescents, PLHIV with history of loss-to-follow-up or those with low-viremia are at the highest risk of virological failure and might require more frequent virological monitoring than is currently recommended.

**Keywords:** First-line antiretroviral treatment; HIV; Lost-to-follow up; Low viremia; Myanmar; Virological failure

## 3.2 Background

There is a global commitment to end the AIDS epidemic by 2030 [1] and the global HIV response has improved access to care and survival among people living with HIV (PLHIV) [2]. However, by the end of 2018, virological suppression for PLHIV on antiretroviral treatment (ART) was 85%, which is still below the UNAIDS target of 95%. Scale-up of routine HIV viral load (VL) testing in resource-limited settings has been suboptimal due to the cost and complexity of VL testing, but also due to the lack of awareness about the benefits of regular VL monitoring among health care providers and patients [3]. In 2018, UNAIDS reported an estimate of 49% (95% CI 38–63%) proportion of virological suppression among all PLHIV in the Asia and Pacific region [2]. In 2017, less than 5% of those globally receiving ART were thought to be receiving second-line ART [4]. A study from sub-Saharan Africa identified poor access to HIV VL monitoring as the main reason for a delayed switch to second-line treatment. VL monitoring was poorly used even when available in this cohort: 40% of patients with virological failure were not switched to second-line ART, whereas 30% had been switched without proof of failure [4]. A study from Myanmar reported high rates of virological failure, but low rates of switching to second-line treatment [5]. Lack of switching was attributed to clinical or programmatic factors, such as delayed reporting of the VL results, concerns about adherence or pill burden, or centralized decision-making [6]. The cost of second-line treatment, was also prohibitive, being 2.5 times more expensive than the first-line therapy at the time [7]. Improper management of patients with treatment failure leads to poor treatment outcomes, accumulation and transmission of HIV drug resistance and increases cost of HIV care delivery [8, 9]. Myanmar has the second highest HIV prevalence in Southeast Asia with an estimated 0.57% of the general population being HIV-positive [2]. In 2018 there were an estimated 240,000 PLHIV in the country with the highest HIV burden among sex workers, men having sex with men and people who inject drugs [10]. The National AIDS Programme achieved 77% ART coverage by the end of 2019 [11]. Despite significant improvements in access to HIV care and national guidelines recommending routine HIV VL testing [12], only 72% of PLHIV on ART had access to VL monitoring in 2019 in the country [11]. Virological suppression among those who had access to HIV VL testing was 95%, thus it is on track to the 95% UNAIDS target [13].

Previous studies identified poor adherence [14–16], advanced HIV disease (AHD) [15–18], tuberculosis co-infection [14], and longer time on first-line ART as predictors of ART failure [16]. Recent studies reported an association between having low-level viremia and virological failure [19, 20]. With the increasing life span of the HIV cohorts, it is increasingly common for people to interrupt treatment for a short period of time or to be lost-to-follow up (LFU) and then re-engage in care. Studies report that 11–77% of patients enrolled in HIV care temporarily disengage [21–25]. In most HIV programs the frequency of treatment

interruptions is very likely underestimated. HIV care is more complex for patients previously exposed to ART and at risk of HIV drug resistance, especially if presenting back into care with AHD [26, 27]. To our knowledge association between cumulative appointment delay and treatment failure has not been explored in any of the previous studies.

Since 2003 Médecins Sans Frontières (MSF) has been providing HIV care in Yangon, Kachin and Shan States. VL monitoring was introduced in 2009, initially as a targeted approach for those most at risk of failure. Since 2016 all patients were eligible for routine HIV VL monitoring once per year. In this study we describe the VL cascade, the incidence of virological failure and associated risk factors, including the cumulative appointment delay, among PLHIV receiving first-line ART in the HIV cohort treated by MSF in Myanmar.

## 3.3 Methods

### 3.3.1 Design and study population

We conducted a retrospective cohort study of patients enrolled on ART in the MSF HIV program in Myanmar between 01 January 2001 and 31 October 2017. The study included patients who had at least one HIV VL test available after receiving at least 6 months of standard first-line ART (Figure 3-1).

### 3.3.2 Study setting

The study was conducted in the MSF HIV programs in Yangon, Kachin and Shan States in Myanmar. The study sites provided a comprehensive package of HIV care free of charge. Clinical care was provided by medical doctors and nurses, while trained counselors and outreach adherence supporters provided counseling and adherence support [28]. Since 2009 HIV VL testing targeted those with immunological and/or clinical failure, and those switching their first-line regimen because of modified guidelines. From 2014 onwards, yearly routine VL monitoring targeted all children and patients on second-line ART. Since 2016, yearly routine VL testing was introduced for all patients on ART. Patients with viremia (VL>200 copies/mL defined as a limit of detection) received 3–6 counseling sessions over a period of 3 months and were then prescribed a follow-up VL test. Those with two consecutive VL results above the threshold for failure (≥5,000 copies/mL until 2012, ≥1,000 copies/mL after 2012) were started on a second-line ART regimen. If the follow-up VL did not show failure, enhanced adherence support continued together with three-monthly VL monitoring until undetectable viremia was observed. For the first-line treatment a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (zidovudine, tenofovir, lamivudine, abacavir) with a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) was used. Second-line regimen was composed of two nucleoside/

nucleotide reverse transcriptase inhibitors, ideally not used in the first-line regimen and one protease inhibitor (atazanavir/ritonavir or lopinavir/ritonavir).

### 3.3.3 Study variables

The study used routine program data collected from standardized patient forms and encoded in the MSF HIV program database, FUCHIA (Follow-up and Care of HIV Infection and AIDS). Values recorded during the ART initiation visit were considered baseline for: age, marital status, gender, World Health Organization (WHO) stage, body mass index (BMI), risk group, and tuberculosis co-infection. We defined CD4 at ART initiation as the measurement taken closest to the date of ART initiation, within 92 days before or after initiation. BMI was used as a binary variable (<18.5kg/m², ≥18kg/m²) and values > 40kg/$m^2$ were considered errors and defined as missing. Yearly coverage of VL was defined as the proportion of patients active and in care at the end of the year, who had at least one VL measurement in that year. Virological failure was defined as a patient with a VL≥1,000 copies at a visit ≥183 days after ART initiation. Those with a follow-up VL≥1,000 copies/ml, within 183 days of a previous VL showing virological failure, had confirmed virological failure. Low-level viremia was defined as a VL between 200 and 999 copies, occurring ≥183 days after ART initiation, and prior to a first episode of virological failure. Starting dates were defined for each patient based on the earliest visit date at which ART was prescribed. If this date was before 2009, then the start date was set to 1st January 2009 for regression analyses. The reason for this is that VL testing only started to become widely available after 2009; thus, the need to avoid overweighting those who started treatment before 2009 but had no chance of having VL tests. For calculation of operational indicators in the cascade analysis, the original ART start date was used, regardless of whether this was before 2009 or not. End dates were defined based on the earliest occurring visit date at which there was either a virological failure, death, switch to second line ART or reached the maximum visit for that patient without event. For the definition of LFU, each visit had an expected next visit date. We calculated the difference between expected and actual next visit date in days. If this difference was greater than 60 days then the earlier visit was marked as LFU. Using this, the following variables were created: number of times a patient was LFU, total days patient was LFU (including the initial 60 days). Cumulative appointment delay was calculated as the number of days of delay between the dates of appointment and the actual dates visits took place. Time under observation was calculated as the time between starting and ending dates in years. Time on ART was calculated as time under observation minus time LFU.

### 3.3.4 Data analysis

Baseline characteristics were described using frequencies and percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. We compared proportions for categorical variables using a chi-squared test (with Holm

correction). The purpose of this was to both describe the cohort and to roughly estimate selection bias. The incidence rate for virological failure was calculated as the number of patients with a first VL≥1,000 copies over the total observation time. Using Cox proportional hazard models, we computed hazard ratios (HR) and respective 95% confidence intervals (CI). Significant variables from the bivariable analyses were investigated for confounding and effect modification using Mantel-Haenszel statistics and Woolf's tests, as well as testing for co-linearity. Only dichotomized versions of variables were included in multivariable analyses. Variables were selected for multivariable analysis based on results from bivariable and stratified analyses. Where effect modification was identified in stratified analysis, we tested whether the addition of interaction terms significantly improved the model fit based on Akaike Information Criterion (AIC) and analysis of variance. Only complete cases, thus without missing information for any of the variables selected in the analysis, were considered for multivariable analysis. The final multivariable model was selected based on step-wise forward Cox proportional hazards regression using the AIC and likelihood ratio tests. The model proportional hazards assumption was tested using scaled Schoenfeld residuals. Assumptions of non-linearity were assessed visually. All analyses were two-tailed, with a significance level of 0.05, and carried out using R statistical software version 3.6.0 (Foundation for Statistical Computing, Vienna, Austria).

## 3.4 Results

### 3.4.1 Inclusion

As illustrated in the Figure 3-1, during the period 2001–2017 there were 51,010 patients enrolled in MSF programs. 5,873 (11.5%) patients in the cohort were LFU or died before ART was initiated. Among patients who started on ART, 35,356 (78.3%) received >6 months standard first line treatment. Among the 35,356, there were 7,858 (22.2%) who initiated treatment before 2009, before VL monitoring was implemented; and 27,498 (77.8%) initiating treatment during or after 2009. Among the 35,356, we recorded 140,779 person-years of follow-up time. During this time, 25,260 (71.4%) patients had at least one HIV VL test result available. HIV VL test coverage increased over time, with below 10% of individuals having a visit in 2013 and a VL test during the same year, to 57% in 2017 (Figure 3-2). Patients may have had multiple visits and multiple tests in one year however only the first result in a specific year was considered. A patient is included in the total count of each year they were receiving ART for at least part of the year.

### 3.4.2 Baseline characteristics

Baseline characteristics of the first-line cohort, stratified by having received an HIV VL test, are presented in Table 3-1. Among 25,260 patients included in the analysis of virological outcomes, the median age was 33.1 years (IQR 28.0–39.1) and 54.7% were male. The median

observation time was 5.4 years (IQR 3.7–7.9). The median CD4 count was 143 cells/mm$^3$ (IQR 55–264) in 10,236 patients tested. Nearly half (45.6%) presented with WHO stage III or IV disease. Approximately one in four of this cohort (n=6,656; 26.4%) were diagnosed with tuberculosis at baseline. Overall, 9,861 (39.0%) patients had one episode of low-level viremia and in 2,438 (24.7%) patients this occurred more than once. There were 2,440 (9.7%) patients LFU at least once, and 419 (1.66%) more than once. Most patients (86.7%, n=21,918) were late at least once for a scheduled appointment. When considering delays to all scheduled appointments in total, about one in four (n=6,005, 23.8%) had a cumulative appointment delay greater than 60 days.

Comparison between patients who did or did not have at least one HIV VL test showed that those who had HIV VL test results tended to be younger (median 33.1 years vs. 34.1 years; p<0.001), had been on ART after 2009 for a longer time (median 5.4 years vs. 2.8 years, p<0.001), and tended to have lower CD4 counts at ART initiation (median 143 cells/mm$^3$ vs. 189 cells/mm$^3$; p<0.001). Baseline tuberculosis was diagnosed more frequently among those who received HIV VL testing (24.8% vs. 20.7%; p<0.001) and a lower proportion of them had a history of LFU (10.9% vs. 14.0%; p<0.001). History of injecting drug use was less frequently reported among those with access to VL testing (5.8% vs. 7.9%; p<0.001). Those who had access to HIV VL testing had more episodes of late appointments, but a lower cumulative number of days being late, and only 25% of them accumulated ≥60 days late for appointments, in comparison with 28.2% of those who had never received a HIV VL test (p<0.001).

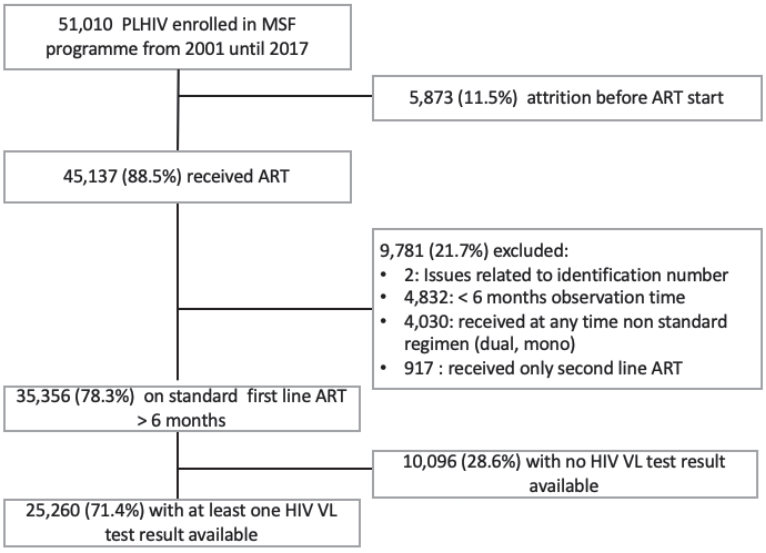
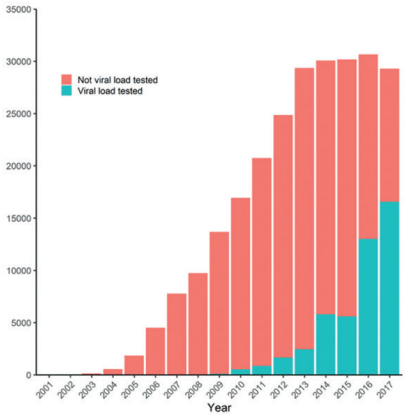



**Figure 3-1|** Flowchart of inclusion pathway in the study




| Year | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Individuals (N) | 4 | 6 | 137 | 559 | 1851 | 4506 | 7770 | 9744 | 13672 | 16940 | 20742 | 24860 | 29364 | 30076 | 30168 | 30655 | 29290 |
| Tested individuals (n) | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 91 | 546 | 866 | 1658 | 2458 | 5804 | 5597 | 13017 | 16557 |
| Tested individuals (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 4 | 7 | 8 | 19 | | 42 | 57 |

**Figure 3-2|** Number of people with at least one visit per year, categorized by receipt of at least one viral load test result in the same year

**Table 3-1|** Baseline characteristics of the first-line cohort by receipt of HIV VL testing

| Variable | Value | Total n=35356 | (%) | HIV VL test result not available n=10096 | (%) | HIV VL test result available n=25260 | (%) | P-value* |
|---|---|---|---|---|---|---|---|---|
| Age at ART initiation >19 years | | 32387 | 91.6 | 9774 | 96.8 | 22613 | 89.5 | <0.001 |
| Gender (Female) | | 15749 | 44.5 | 4294 | 42.5 | 11455 | 45.3 | 0.02 |
| Divorced | | 10 | 0.0 | 8 | 0.1 | 2 | 0.0 | 0.108 |
| Married | | 20165 | 57.0 | 6190 | 61.3 | 13975 | 55.3 | <0.001 |
| Separated | | 2178 | 6.2 | 673 | 6.7 | 1505 | 6.0 | 0.363 |
| Single | | 8163 | 23.1 | 2010 | 19.9 | 6153 | 24.4 | <0.001 |
| Widow | | 3927 | 11.1 | 1058 | 10.5 | 2869 | 11.4 | 0.409 |
| Man who has sex with men | | 250 | 0.7 | 55 | 0.5 | 195 | 0.8 | 0.437 |
| History of injection drug use | | 2785 | 7.9 | 1331 | 13.2 | 1454 | 5.8 | <0.001 |
| History of sex work | | 508 | 1.4 | 120 | 1.2 | 388 | 1.5 | 0.37 |
| History of blood transfusion | | 584 | 1.7 | 143 | 1.4 | 441 | 1.7 | 0.482 |
| Economic migrant | | 675 | 1.9 | 241 | 2.4 | 434 | 1.7 | 0.053 |
| History of imprisonment | | 515 | 1.5 | 169 | 1.7 | 346 | 1.4 | 0.498 |

| Variable | Value | Total n=35356 | (%) | HIV VL test result not available n=10096 | (%) | HIV VL test result available n=25260 | (%) | P-value* |
|---|---|---|---|---|---|---|---|---|
| Displaced person | | 106 | 0.3 | 41 | 0.4 | 65 | 0.3 | 0.434 |
| Having HIV+ partner | | 1902 | 5.4 | 760 | 7.5 | 1142 | 4.5 | <0.001 |
| Body mass index <18.5kg/m$^2$ | | 6829 | 19.3 | 1592 | 15.8 | 5237 | 20.7 | <0.001 |
| | Missing | 21289 | 60.2 | 6091 | 60.3 | 15198 | 60.2 | |
| Baseline WHO stage | 1 | 11501 | 32.5 | 3426 | 33.9 | 8075 | 32.0 | <0.001 |
| | 2 | 1108 | 3.1 | 261 | 2.6 | 847 | 3.4 | |
| | 3 | 9710 | 27.5 | 2406 | 23.8 | 7304 | 28.9 | |
| | 4 | 5516 | 15.6 | 1336 | 13.2 | 4180 | 16.5 | |
| | Missing | 7521 | 21.3 | 2667 | 26.4 | 4854 | 19.2 | |
| Baseline Tuberculosis | | 8754 | 24.8 | 2088 | 20.7 | 6666 | 26.4 | <0.001 |
| Baseline CD4 (cells/mm$^3$) | <200 | 8434 | 23.9 | 2013 | 19.9 | 6421 | 25.4 | <0.001 |
| | 200–500 | 4,668 | 13.2 | 1,483 | 14.7 | 3185 | 12.6 | |
| | >500 | 928 | 2.6 | 298 | 3.0 | 630 | 2.5 | |
| | Missing | 21326 | 60.3 | 6302 | 62.4 | 15024 | 59.5 | |
| Time on ART (years) | <2 | 6773 | 19.2 | 4174 | 41.3 | 2599 | 10.3 | <0.001 |
| | 2–5 | 11984 | 33.9 | 3500 | 34.7 | 8484 | 33.6 | |
| | >5 | 16599 | 46.9 | 2422 | 24.0 | 14177 | 56.1 | |
| No treatment change | | 11355 | 32.1 | 5411 | 53.6 | 5944 | 23.5 | <0.001 |
| | Missing | 204 | 0.6 | 117 | 1.2 | 87 | 0.3 | |
| History of low viremia | | 9861 | 27.9 | NA | NA | 9861 | 39.0 | |
| Frequency of low viremia | 1 | 7423 | 21.0 | NA | NA | 7423 | 29.4 | |
| | ≥2 | 2438 | 6.9 | NA | NA | 2438 | 9.7 | |
| History of lost-to-follow-up | | 3850 | 10.9 | 1410 | 14.0 | 2440 | 9.7 | <0.001 |
| Number of times lost-to-follow-up | 1 | 3176 | 9.0 | 1155 | 11.4 | 2021 | 8.0 | <0.001 |
| | 2 | 512 | 1.4 | 194 | 1.9 | 318 | 1.3 | |
| | ≥3 | 162 | 0.5 | 61 | 0.6 | 101 | 0.4 | |
| Cumulative appointment delay ≥60 days | | 8852 | 25.0 | 2847 | 28.2 | 6005 | 23.8 | <0.001 |
| Cumulative appointment delay (days) | 1–59 | 21507 | 60.8 | 5594 | 55.4 | 15913 | 63.0 | <0.001 |
| | 60–181 | 4492 | 12.7 | 1286 | 12.7 | 3206 | 12.7 | |
| | 182–364 | 1709 | 4.8 | 586 | 5.8 | 1123 | 4.4 | |
| | ≥365 | 2651 | 7.5 | 975 | 9.7 | 1676 | 6.6 | |

*Chi$^2$ test with Holm correction; VL: viral load

## 3.4.3 HIV VL cascade

Of 25,260 patients with at least one VL test result available, 3,579 (14.2%) had documented virological failure, with a calculated incidence of failure of 2.5 per 100 person-years (3,579 patients with failure during 143,160 years of follow-up). Among those with virological failure, 2,202 (61.5%) had a consecutive VL test within six months of the first test that showed virological failure (Figure 3-3). Of those with a consecutive VL test 1,258 (57.1%) individuals had confirmed virological failure. Among those with confirmed virological failure, 836 (66.5%) switched to second-line ART within six months since confirmed virological failure. Among those with confirmed virological failure, the median time between the virological failure and confirmed virological failure was 3.6 months (IQR 2.4–4.8) and the median time between second-line ART initiation and confirmed virological failure was 3.7 months (IQR 2.3–5.7).

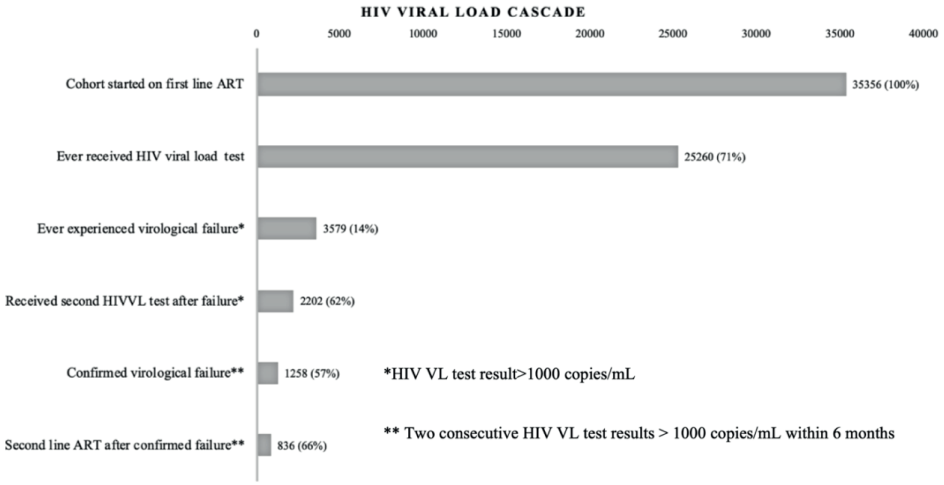



**Figure 3-3|** Viral load testing cascade among the first-line cohort (n = 35,356)
**Note: The** % against each bar are calculated using the total cohort number in the above bar as the denominator.

## 3.4.4 Predictors of virological failure

Using univariable regression, patients whose marital status was single (HR 1.66; 95% CI 1.54–1.78 p<0.001), who were economic migrants (HR 1.63; 95% CI 1.30–2.05; p<0.001), those with baseline BMI <18.5 kg/m2 (HR 1.38; 95% CI 1.25–1.53; p<0.001), CD4>500 cells/mm$^3$ (HR 1.64; 95% CI 1.34–2.00; p<0.001), or WHO stage two (vs. WHO stage one; HR 1.26; 95% CI 1.06–1.49; p<0.001) were more likely to have virological failure (Table 3-2). Also PLHIV who experienced low-level viremia (HR 1.59; 95% CI 1.49–1.79; p<0.001), were LFU at least once (HR 1.80; 95% CI 1.65–1.96; p<0.001), or had a cumulative appointment delay over 60 days (vs. those who were never late; HR 1.69, 95% CI 1.58–1.81, p<0.001) were

more likely to experience virological failure. Females (HR 0.86; 95% CI 0.81–0.92; p<0.001) or those with age >19 years at ART initiation (0.36; 95% CI 0.35–0.42; p<0.001) had lower hazards of virological failure.

The multivariable analysis was conducted on 8,308 patients (32.9%) with complete information for all the variables required (Table 3-3), those presenting with baseline tuberculosis (adjusted hazard ratio (aHR) 1.39; 95% CI 1.14–1.49; p<0.001), with a history of low-level viremia (aHR 1.60; 95% CI 1.42–1.81; p<0.001), a history of LFU (aHR 1.24; 95% CI 1.41–1.52; p=0.041), or being on the same treatment regimen since the start of treatment (aHR 1.37; 95% CI 1.07–1.76; p<0.001) were associated with an increased hazard of failure, while controlling for other covariates. Starting ART at the age >19 years was associated with 34% lower hazard of failure (95% CI 0.53–0.83; p<0.001). Cumulative appointment delay was not significantly associated with failure after controlling for other covariates. We observed an interaction between sex work and gender (aHR 2.30; 95% CI 0.54–9.66; p=0.26) and between gender and being single (aHR 1.43; 95% CI 1.08–1.89; p=0.013). The differences between the characteristics of the population included in the final regression model and the entire population on first-line ART in this cohort, are presented in the Supplement 3-1.



**Table 3-2|** Crude hazard ratios (HR) for virological failure among PLHIV with more than 6 months of first-line ART and at least one VL test (n = 25,260)

| Variable | No virological failure (n=21681) | | Virological failure (n=3579) | | HR (CI 95%) | P value* |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| Age at ART initiation >19 years | 19752 | 87.3 | 2861 | 12.7 | 0.36 (0.35–0.42) | <0.001 |
| Female | 9954 | 86.7 | 1501 | 13.3 | 0.86 (0.81–0.92) | <0.001 |
| Divorced | NA | NA | 0 | | NA | |
| Married | 12295 | 88.0 | 1680 | 12.0 | 0.71(0.66–0.75) | <0.001 |
| Separated | 1271 | 84.5 | 234 | 15.5 | 1.90 (0.95–1.23) | 0.228 |
| Single | 4948 | 80.4 | 1205 | 19.6 | 1.66 (1.54–1.78) | <0.001 |
| Widow | 2533 | 88.2 | 336 | 11.8 | 0.73 (0.65–0.81) | <0.001 |
| MSM | 163 | 83.6 | 32 | 16.4 | 1.81 (0.77–1.54) | 0.646 |
| History of IDU | 1260 | 86.7 | 194 | 13.3 | 1.13 (0.98–1.31) | 0.099 |
| History of sex work | 319 | 82.2 | 69 | 17.8 | 1.24 (0.98–1.58) | 0.074 |
| History of transfusion | 391 | 88.7 | 50 | 11.3 | 0.77 (0.58–1.02) | 0.063 |
| Economic migrant | 357 | 82.3 | 77 | 17.7 | 1.63 (1.30–2.05) | <0.001 |
| History of imprisonment | 304 | 87.9 | 42 | 12.1 | 1.02 (0.75–1.39) | 0.889 |
| History of displacement | 56 | 86.2 | 9 | 13.8 | 1.27 (0.66–2.45) | 0.472 |

| Variable | No virological failure (n=21681) | | Virological failure (n=3579) | | HR (CI 95%) | P value* |
|---|---|---|---|---|---|---|
| Having HIV + partner | 994 | 87.0 | 148 | 13.0 | 0.92 (0.78–1.08) | 0.297 |
| BMI <18.5 kg/m3 | 4339 | 82.9 | 898 | 17.1 | 1.38 (1.25–1.53) | <0.001 |
| Baseline WHO stage | | | | | | |
| 1 | 6979 | 86.4 | 1096 | 13.6 | Ref | |
| 2 | 696 | 82.2 | 151 | 17.8 | 1.26 (1.06–1.49) | 0.008 |
| 3 | 6263 | 85.7 | 1041 | 14.3 | 0.91 (0.84–0.99) | 0.033 |
| 4 | 3602 | 86.2 | 578 | 13.8 | 0.83 (0.75–0.91) | <0.001 |
| Baseline CD4>500 cells/mm$^3$ | 530 | 84.1 | 100 | 15.9 | 1.64 (1.34–2.00) | <0.001 |
| Baseline Tuberculosis | 5757 | 86.4 | 909 | 13.6 | 0.88 (0.81–0.95) | <0.001 |
| No ART regimen changes during observation time | 4330 | 72.8 | 1664 | 27.2 | 6.60 (6.16–7.06) | <0.001 |
| History of low-level viremia | 8032 | 81.5 | 1829 | 18.5 | 1.59 (1.49–1.70) | <0.001 |
| Frequency of low-level viremia | | | | | | |
| 0 | 13649 | 88.6 | 1750 | 11.4 | Ref | |
| 1 | 6395 | 86.2 | 1028 | 13.8 | 1.15 (1.07–1.24) | <0.001 |
| ≥2 | 1637 | 67.1 | 801 | 31.9 | 3.11 (2.86–3.38) | <0.001 |
| History of loss-to-follow-up | 1837 | 75.3 | 603 | 24.7 | 1.80 (1.65–1.96) | <0.001 |
| Frequency of loss-to-follow-up | | | | | | |
| 0 | 19844 | 87.0 | 2976 | 13.0 | Ref | |
| 1 | 1556 | 77.0 | 465 | 23.0 | 1.69 (1.53–1.86) | <0.001 |
| 2 | 214 | 67.3 | 104 | 32.7 | 2.28 (1.87–2.77) | <0.001 |
| ≥3 | 67 | 66.3 | 34 | 33.7 | 2.32 (1.66–3.26) | <0.001 |
| Cumulative appointment delay ≥60 days | 4809 | 80.0 | 1196 | 20.0 | 1.69 (1.58–1.81) | <0.001 |

***** Wald test for the hazard ratio estimate of each exposure variable - comparing counts of those exposed with virological failure to those without

**Table 3-3|** Adjusted hazard ratios for virological failure among complete cases with more than 6 months of first-line ART and at least one VL test and complete data on key variables (n = 8,308)

| Variable | aHR* | 95% CI | P-value |
|---|---|---|---|
| Female | 0.89 | 0.76–1.04 | 0.147 |
| Age at ART initiation >19 years | 0.66 | 0.53–0.83 | <0.001 |
| Baseline CD4 500 cells/mm$^3$ | 1.23 | 0.96–1.59 | 0.094 |
| Baseline tuberculosis | 1.30 | 1.14–1.49 | <0.001 |
| Married | 0.90 | 0.76–1.06 | 0.187 |
| Single | 0.83 | 0.66–1.03 | 0.089 |
| History of sex work | 0.71 | 0.18–2.86 | 0.633 |
| History of IDU | 1.05 | 0.77–1.43 | 0.764 |
| History of loss-to-follow-up | 1.24 | 1.01–1.52 | 0.041 |
| History of low viremia | 1.60 | 1.42–1.81 | <0.001 |
| Cumulative appointment delay >=60 days | 0.94 | 0.79–1.12 | 0.473 |
| No history of changing ART regimen | 1.37 | 1.07–1.76 | 0.012 |

* Adjusted Hazard Ratio adjusted for variables presented in the table and history of ever receiving following categories of regimens: zidovudine/lamivudine/emtricitabine+abacavir/tenofovir;stavudine/zidovudine+lamivudine/emtricitabine+efavirenz; stavudine/zidovudine+lamivudine/emtricitabine+nevirapine; tenofovir/abacavir+lamivudine/emtricitabine +efavirenz or tenofovir/abacavir+ lamivudine/emtricitabine +nevirapine; and time being on ART < or>= 2 years since access to viral load monitoring 1 January 2009); interaction between sex work and gender and gender and being single included in the model.



## 3.5 Discussion

Our study investigated virological outcomes in PLHIV receiving first-line ART in Myanmar. During the long observation period, a total of 25,260 (71.4%) PLHIV received at least one VL test and 14.2% experienced virological failure (2.5 per 100 person-years). Our results are comparable with previous reports from resource-limited settings, where virological failure occurred in 4.3–34.0% of PLHIV on first-line ART [14, 15, 29–32]. Previous studies from Myanmar reported good long-term immunological and virological treatment outcomes among PLHIV on treatment [33], with one cohort experiencing a virological failure rate of 3.2 per 100 person-years [5]. In general, higher virological suppression rates have been reported in Asia than in Africa [34], although any comparison of virological outcomes is challenging, as local VL monitoring guidelines differ, and study follow-up times vary between the cohorts.

We showed that the risk of virological failure was lower among those initiating ART if they were aged >19 years (90% of the study cohort) compared to those with or younger than 19 years. This finding is similar to that reported in other studies. The higher risk of failure among children and adolescents may be explained by suboptimal adherence, lack of pediatric drug formulations, and lack of care models responsive to the specific needs of these subgroups

[5, 17, 35–37]. Patients in our cohort study, with baseline tuberculosis were at higher risk of virological failure, consistent with findings from other studies, which identified advanced HIV disease as a strong predictor of treatment failure [5, 14, 17, 32, 38, 39]. Almost 10% of our participants were LFU at least once, and the vast majority (86.8%) had been late for at least one appointment. This is in concordance with other studies showing that temporary disengagement from care can be very common in these cohorts (11–77%) [21–25]. When LFU and appointment delay are not measured continuously, but only at a given moment in time, the frequency of treatment interruptions is very likely to be underestimated [21]. Our study relied on a rigorously updated program database with regards to visit dates, which allowed us to identify delay and treatment interruptions. The cumulative appointment delay was <60 days for 63% of the cohort. In the univariable analysis cumulative appointment delay ≥60 days was associated with higher risk of virological failure ($p<0.001$), but when controlling for other variables the association was not significant. However, having at least one single time point with treatment interruption of at least 60 days while being LFU was associated with increased risk of failure. This is similar to findings from other contexts [5, 38]. Adding cumulative appointment delay in the risk of virological failure analysis was not valuable in this cohort, but different cut-off values for cumulative appointment delay or delay per year on ART could be explored in future analyses.

A systematic review reported that history of treatment change was associated with an approximately 2.5-fold higher risk of virological failure in cohorts in Myanmar and Malawi [14]. In our cohort, PLHIV who remained on the same first-line ART regimen during the study period were at a higher risk of failure. It is possible that previous reports used a different definition of "treatment change". In our cohort, patients with treatment changes may have been followed up more closely, with better management of adverse events and possibly a lower risk of drug-drug interactions.

Increasing evidence shows that low-level viremia is associated with unfavorable treatment outcomes. A large multicenter cohort in South Africa detected low-level viremia in 23% of PLHIV, with risk of subsequent failure in this group observed as 2.6 times higher (95% CI 2.5–2.6; $p<0.0001$) than in PLHIV who did not experience low-level viremia (19). In our study, 39% of patients had at least one episode of low-level viremia, and a history of low viremia was associated with an increased risk of treatment failure. A study from Sweden reported chronic low-level viremia in 31% of their population, with 2.1 times higher (95% CI 1.3–3.6) risk of mortality when compared with PLHIV without a history of low-level viremia [20].

There is an effective and life-saving second-line ART regimen, but delayed switch is particularly problematic in patients with advanced HIV disease. Current recommendations for the management of virological failure rely on a public health approach. Programs

in resource-limited settings use a threshold of ≥1,000 copies/mL to identify failure and recommend switching to second-line ART when virological failure is confirmed in a second sample [40]. Some have argued that in settings with no access to drug-resistance testing, such approaches might delay introduction of effective and life-saving second-line ART regimens and might increase risk of resistance accumulation, which in turn with further compromise effectiveness of second-line treatment; this would be particularly problematic in patients with AHD and it has been argued that in some circumstances switching to second-line treatment could be considered in patients with a single VL showing viremia above 1,000 copies/mL [41].

Guidelines on virological monitoring and the management of treatment failure have been changing over time [41–43]. In our study, until 2016 most of our patients had a VL done based on immunological and/or clinical criteria. Only after 2012 did a threshold of VL ≥1,000 copies/mL become an indication for switching to second-line ART. Nevertheless, in this study cohort since 2009 61.5% of patients with viremia ≥1,000 copies/mL received a follow-up VL. Virological failure was confirmed among 57.1% of those with a follow-up VL, with 66.5% of the latter being switched to second-line ART. The implementation of VL monitoring in resource-limited settings is a challenge. A study from Swaziland reported an increase of follow-up VL coverage to 84% in recent years, however, the proportion of patients with confirmed virological failure switched to second-line ART remained low (43.2%) [44]. Similarly, in South Africa and Lesotho only 25–30% of patients in need were switched to second-line treatment in a timely manner [45, 46]. Even though enhanced adherence counseling has been reported as an effective strategy to identify those truly in need of second-line ART in settings with limited access to drug-resistance testing, only 53.4% (95% CI 40.1% to 66.8%) of those who received such counseling and were identified as in need of second-line ART were switched, according to a systematic review from 2019 [47]. A previous study from Myanmar highlights the importance of timely switching to second-line ART, as one-third of those who did not switch died or were LFU from care [5].

In short, routine VL monitoring reduces mortality when used together with adherence support [47] and a timely switch to effective treatment [48, 49], but ensuring coverage of VL and second-line ART for those with a diagnosis of virological failure remains a huge challenge. When coverage is low, the overall benefit from VL scale-up might be lower than anticipated. To improve program performance along the VL cascade, innovative approaches, such as “mHealth” [50] or “nurse-champions” [51] can be effective. Furthermore, it might be important to prioritize and differentiate VL testing in those at a higher risk of failure, in settings where barriers for scale-up exist. For instance, the management of PLHIV who re-engage in care after being LFU requires more frequent VL monitoring [26] and possibly a faster switch to second-line treatment, especially if they present with clinical signs of

advanced HIV disease. Considering the correlation between low-level viremia and treatment failure [19, 52, 53] and mortality [20], the threshold of ≥1,000 copies/mL for enrollment into enhanced adherence support and switching to second-line ART may need to be revised. A more differentiated approach to VL monitoring, guided by the increasing body of evidence on predictors of virological failure and mortality among patients with low-level viremia and/or virological failure, may result in better outcomes for those most at risk.

Our study evaluated a large cohort with a long study period. It used real-life program data with complete data on appointment delays, including LFU. However, 28.6% of the cohort had no VL during the observation period and data for various baseline characteristics were incomplete, which resulted in only a part of our cohort being included in the final multivariable model. The resulting selection bias might lower the internal validity of our study results and reduce the generalizability of our study findings. The burden of virological failure was assessed by looking at the first episode of virological failure only, despite knowing that PLHIV transit from suppressed to unsuppressed state multiple times during their time on ART. This might underestimate the total burden of failure in a cohort and multistate analysis of virological outcomes would be more appropriate. We did not investigate the reason why patients did not access VL, were delayed or LFU, or why switching to second-line ART was delayed. Further research on these topics is needed.

## 3.6 Conclusion

VL monitoring is an important tool to improve program outcomes. Suboptimal VL cascade in resource-limited settings hampers the full potential of VL monitoring and it reduces its cost-effectiveness. Our study observed higher rates of virological failure PLHIV with tuberculosis co-infection and those with history of LFU or who remain on one treatment regimen. Those subgroups might need more frequent virological and more intensive clinical monitoring. Growing evidence on the risk factors for unfavorable virological and clinical outcomes, may suggest the refinement of a differentiated approach to VL monitoring in growing and aging HIV cohorts in resource-limited settings.

## 3.7 Declarations

**Ethics approval and consent to participate** The study was approved by the Institutional Review Board, Department of Medical Research, Ministry of Health and Sports, Myanmar (Ethics/DMR/2019/153) and fulfilled the exemption criteria set by the MSF independent Ethical Review Board (ERB) [54] for a posteriori analysis of routinely collected clinical data and thus did not require MSF ERB review. It was conducted with permission from the MSF Medical Director, Operational Center Amsterdam. Exemption from review by the MSF ERB for retrospective analyses of routinely collected data requires consent to have been given by patients in MSF programs at the time of treatment for secondary use of their data. Therefore, consents of individuals for secondary analysis of the dataset were not sought.



**Availability of data and materials** Data are available on request. MSF has a managed access system for data sharing that respects MSF's legal and ethical obligations to its patients to collect, manage and protect their data responsibility. Ethical risks include, but are not limited to the nature of MSF operations and target populations being such that data collected often involves highly sensitive data. The dataset supporting the conclusions of this article is available are available on request in accordance with MSF's data sharing policy (available at: http://fieldresearch.msf.org/msf/handle/10144/306501). Requests for access to data should be made to data.sharing@msf.org.

**Competing interests** Authors have no competing interest to declare.

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**Authors' contributions** AM and AS conceptualized and designed the study. HTM, PT, TTT and MP contributed to data collection, data management and data extraction. AS performed the data analysis. AS, AM, LL, TD, MP and HTM participated in the data interpretation. AM drafted the original manuscript. AM, AS, LL and TD revised all subsequent versions of the manuscript. All authors contributed to and approved the final version of the manuscript.

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# Chapter 4|

## Viremic-time predicts mortality among people living with HIV on second-line antiretroviral treatment in Myanmar: A retrospective cohort study

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## 4.1 Abstract

**Introduction**: Despite HIV viral load (VL) monitoring being serial, most studies use a cross-sectional design to evaluate the virological status of a cohort. The objective of our study was to use a simplified approach to calculate viremic-time: the proportion of follow-up time with unsuppressed VL above the limit of detection. We estimated risk factors for higher viremic-time and whether viremic-time predicted mortality in a second-line antiretroviral treatment (ART) cohort in Myanmar.

**Methods:** We conducted a retrospective cohort analysis of people living with HIV (PLHIV) who received second-line ART for a period >6 months and who had at least two HIV VL test results between 01 January 2014 and 30 April 2018. Fractional logistic regression assessed risk factors for having higher viremic-time and Cox proportional hazards regression assessed the association between viremic-time and mortality. Kaplan-Meier curves were plotted to illustrate survival probability for different viremic-time categories.

**Results:** Among 1,352 participants, 815 (60.3%) never experienced viremia, and 172 (12.7%), 214 (15.8%), and 80 (5.9%) participants were viremic <20%, 20–49%, and 50–79% of their total follow-up time, respectively. Few (71; 5.3%) participants were ≥80% of their total follow-up time viremic. The odds for having higher viremic-time were higher among people with a history of injecting drug use (aOR 2.01, 95% CI 1.30–3.10, p=0.002), sex workers (aOR 2.10, 95% CI 1.11–4.00, p=0.02) and patients treated with lopinavir/ritonavir (vs. atazanavir; aOR 1.53, 95% CI 1.12–2.10, p=0.008). Viremic-time was strongly associated with mortality hazard among those with 50–79% and ≥80% viremic-time (aHR 2.92, 95% CI 1.21–7.10, p=0.02 and aHR 2.71, 95% CI 1.22–6.01, p=0.01). This association was not observed in those with viremic-time <50%.

**Conclusions:** Key populations were at risk for having a higher viremic-time on second-line ART. Viremic-time predicts clinical outcomes. Differentiated services should target subgroups at risk for a higher viremic-time to control both HIV transmission and mortality.

**Keywords:** HIV viremia, viremic-time, viral load, second-line antiretroviral treatment, Myanmar

## 4.2 Introduction

An increasing number of treatment-experienced people living with HIV (PLHIV) require second-line or third-line antiretroviral treatment (ART) regimens. It has been estimated that by 2030, about 4.6 million people in Sub-Saharan Africa alone will receive second-line ART [1]. For the majority of adult PLHIV, second-line ART includes two nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) combined with a ritonavir-boosted protease inhibitor (PI): atazanavir or lopinavir.

World Health Organization (WHO) guidelines recommend routine monitoring of ART effectiveness and adherence to treatment by performing HIV viral load (VL) testing at 6 months after treatment initiation and then every subsequent 12 months [2]. In resource-limited settings, access to routine HIV VL testing is still suboptimal due to the cost and often also due to a lack of awareness among healthcare providers and patients about the benefits of regular VL monitoring [3]. Coverage of VL testing and access to second- and third-line ART for PLHIV with virological failure remain challenging in many high burden settings [4–6]. Globally, at the end of 2019, UNAIDS estimated that 59% (95% CI 49–69%) of all PLHIV achieved virological suppression. The UNAIDS target of 95% virological suppression among all those on ART by 2030 seems yet out of reach [7]. Virological suppression through highly effective ART is an important component of prevention of sexual transmission of HIV [8–12]. Since 2016, The Prevention Access Campaign with the slogan "Undetectable=Untransmittable" ("U=U") has been essential in shaping public opinion, fighting stigma, and reducing future HIV infections [13]. Myanmar had an estimated 220,000 PLHIV and 77% ART coverage at the end of 2019 [14]. Despite substantially improved access to HIV care, in 2019 only 72% of PLHIV on ART had access to VL monitoring [15].

Médecins Sans Frontières (MSF) has been providing HIV care in Myanmar in close collaboration with the National AIDS Programme (NAP) since 2003. The second-line ART cohort studied here is the largest and the oldest cohort with long-term access to routine virological monitoring in Myanmar. Despite serial HIV VL monitoring being implemented in many HIV cohorts, most of the studies use a cross-sectional design to evaluate virological status. However, during HIV treatment, especially when taking second-line treatment with a high genetic barrier [16, 17], patients may transition back and forth between different virological states (suppressed vs. unsuppressed). By overlooking these transitions, one might over- or underestimate the overall virological suppression rates among patients on ART. In addition, cross-sectional measures do not show whether patients were suppressed or unsuppressed for a short or long fraction of their follow-up time. In 2010, Cole et al. used "viremia copy-years" (VCY) [18] and various studies confirmed the relationship between VCY

and unfavorable outcomes among PLHIV on ART [18–20]. In our second-line ART cohort, PLHIV were monitored by routine VL tests twice per year.

The objective of our study was to use a simplified approach to calculate viremic-time, defined as the proportion of cumulative unsuppressed time over follow-up time on second-line ART, and to investigate whether having higher viremic-time predicted mortality in a second-line ART cohort in Myanmar.

## 4.3 Methods

### 4.3.1 Design and study population

We conducted a retrospective cohort analysis of PLHIV aged above 5 years who had received second-line ART for over 6 months and had at least two HIV VL test results during the study period between 01 January 2014 and 30 April 2018.

### 4.3.2 Study setting

The study used data from the MSF HIV program in Myanmar, which provided, free of charge, a comprehensive HIV care package to more than 58,000 PLHIV. The secondary use of program data frequently serves operational research, which has been seen as a tool to improve outcomes of existing medical programs or evaluate new strategies or interventions in specific contexts. Findings often inform policy change [21]. Since 2014, routine HIV VL monitoring twice a year was introduced for PLHIV on second-line ART. Different VL assays were used during the study period: Cavidi ExaVir version 3.0 (lower limit of detection, LLD, 200 copies/mL) and Xpert® HIV-1 Viral Load (LLD 40 copies/mL). Management of virological failure in Myanmar relies on a public health approach [2]. For PLHIV with detectable plasma viremia ≥1000 copies/mL, the national guideline recommends enhanced adherence counseling (EAC), which includes identifying barriers to adherence and providing intensified psychosocial support to sustain long-term compliance [22]. In case of virological failure while on second-line ART, the switch to third-line ART is often delayed. Reasons for failure include suboptimal adherence and HIV drug resistance; only the latter is a definite indication for switching to third-line ART.

### 4.3.3 Study variables

The study used routine program data collected from standardized patient forms and encoded in the MSF HIV program database, FUCHIA (Follow-up and Care of HIV Infection and AIDS). To calculate the viremic-time, we divided the cumulative unsuppressed time by follow-up time (both in days). Cumulative unsuppressed time was the time during which we assumed that a patient had plasma HIV VL > 200 copies/mL (unsuppressed VL). Cumulative suppressed time was the time during which we assumed that a patient had undetectable (suppressed)

HIV VL. Follow-up time was defined as a sum of cumulative unsuppressed and suppressed time. When two consecutive VL tests showed the same result, either viremia or suppression, the time in between both tests was considered unsuppressed or suppressed, respectively. When two consecutive VL tests showed different results, the time in between both tests was divided in half, adding both unsuppressed and suppressed time. Patients were supposed to have VL tests twice a year; however, if the time between two VL tests was more than 365 days, a maximum of 183 days was added to either unsuppressed or suppressed time (Figure 4-1). Follow-up time started on the date of the first VL test and ended on the date of the last VL test plus a maximum of 183 days, to ensure that each VL result was included. For assessing the mortality hazard during second-line ART, observation time was calculated as the time between the date of the second VL test and the date of the primary outcome (death). Follow-up started on the date of the second VL test to avoid immortal time bias [23] since those without two VL tests were excluded from the analysis (Figure 4-2). For patients that did not experience the outcome, censoring occurred on the dates of transfer out (to the NAP), switch to third-line ART, or the last visit during the study period.



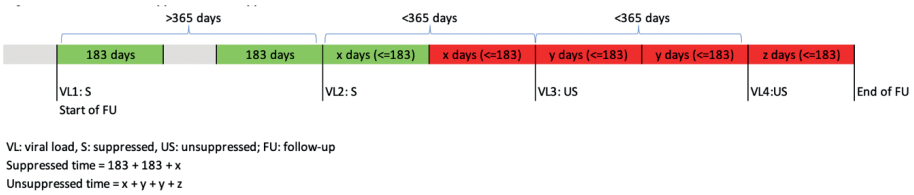



**Figure 4-1|** Example of Allocation of unsuppressed and suppressed time

## 4.3.4 Data analysis

The normal distribution of continuous variables was assessed by Skewness/Kurtosis tests for Normality and plotting histograms for each of the continuous variables. When the distribution was not normal, we calculated medians and interquartile ranges (IQR). To calculate the odds ratios (OR) and respective 95% confidence intervals (CI) for having an unsuppressed VL we performed a fractional logistic regression. To compute hazard ratios (HR) and respective 95% CI for mortality we performed a Cox proportional hazards regression. For both regressions, forward stepwise selection was used to construct the final multivariable model. First, variables known for their clinical importance (age, gender) were included, regardless of their association with the outcome. Additional variables were stepwise included in the multivariable model if a) they were associated with outcome ($p<0.10$) in the univariable analysis, and b) if they significantly improved the model ($p<0.05$, with Wald test for logistic regressions and likelihood ratio tests for Cox regressions). The

proportional hazards assumption was tested using scaled Schoenfeld residuals. All analyses were carried out using STATA statistical software version 14.0 (STATACorp, Texas, USA).

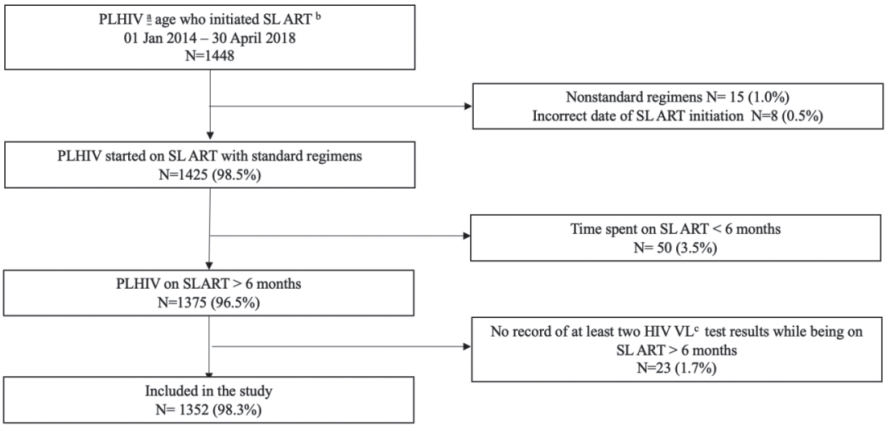
### 4.3.5 Ethics approval

The study was approved by the Institutional Review Board, Department of Medical Research, Ministry of Health and Sports, Myanmar (Ethics/DMR/2019/153). The study also fulfilled the exemption criteria set by the MSF independent Ethical Review Board (ERB) for ***a posteriori*** analyses of routinely collected clinical data—which requires patients in MSF programs at the time of entering MSF care to have given informed written consent for secondary use of their data, including research—thus did not require MSF ERB review [24]. All medical records and data were fully anonymized before we included them in this analysis.

## 4.4 Results

### 4.4.1 Study population

During the study period, 1,448 PLHIV aged >5 years started second-line ART and 1,352 (93.4%) were included in the study (Fig 2). Their median age was 34.8 (IQR 28.4–40.6) years. The median baseline CD4 count and BMI were 162 (IQR 68–309) cells/mm$^3$ and 20.5 (IQR 18.3–23.6) kg/m$^2$, respectively. The median time on first-line and second-line ART was 49.0 (IQR 28.6–79.7) and 54.5 (IQR 44.6–65.1) months. Additional characteristics of the study population are presented in Table 4-1.




**Legend:** [a]PLHIV: People living with HIV, [b]SL ART: Second-line antiretroviral treatment, [c]HIV VL: HIV viral load

**Figure 4-2|** Inclusion flowchart

**Table 4-1|** Demographic and clinical characteristics of the study population at the time of second-line treatment initiation (N=1,352)

| Variable | Characteristics | N | % |
|---|---|---|---|
| Gender | Male | 768 | 56.8 |
| | Female | 584 | 43.2 |
| Age group (years) | 5–18 | 224 | 16.5 |
| | 19–25 | 41 | 3.0 |
| | 25–45 | 918 | 68.0 |
| | >45 | 169 | 12.5 |
| Profession | Employed | 832 | 61.5 |
| | Student | 49 | 3.6 |
| | Unemployed | 354 | 26.2 |
| | Missing | 117 | 8.7 |
| Marital Status | Married | 656 | 48.6 |
| | Separated | 99 | 7.3 |
| | Single | 421 | 31.1 |
| | Widow | 129 | 9.5 |
| | Missing | 47 | 3.5 |
| Men having sex with men[a] | Yes | 8 | 0.6 |
| History of injecting drugs | Yes | 63 | 4.7 |
| History of sex work | Yes | 26 | 1.9 |
| Baseline CD4 (cells/mm$^3$) | <200 | 661 | 48.9 |
| | ≥200 | 362 | 26.8 |
| | Missing | 329 | 24.3 |
| Baseline BMI (kg/m$^2$)[b] | <18.5 | 360 | 26.6 |
| | ≥18.5 | 932 | 69.0 |
| | Missing | 60 | 4.4 |
| Baseline WHO stage | 1 or 2 | 154 | 11.4 |
| | 3 or 4 | 1194 | 88.3 |
| | Missing | 4 | 0.3 |
| Tuberculosis | Yes | 203 | 15.0 |
| Second-line regimen[c] | Atv/r-based | 1134 | 83.9 |
| | Lop/r-based | 218 | 16.1 |
| Second-line treatment duration (months) | <24 | 23 | 1.7 |
| | 24–60 | 842 | 62.3 |
| | ≥60 | 487 | 36.0 |
| First-line treatment duration (months) | <24 | 274 | 20.3 |
| | 24–60 | 528 | 39.1 |
| | ≥60 | 525 | 38.8 |
| | Missing[d] | 25 | 1.8 |

[a]Among male population; [b]BMI: body mass index; [c]ATV/r: Atazanavir/ritonavir, Lop/r: Lopinavir/ritonavir; [d]This group of participants started second-line ART without prior first-treatment either due to co-morbidities (tuberculosis), intolerance, or previous exposure to first-line treatment; Note: Baseline- at the time of second line antiretroviral initiation.

## 4.4.2 Viremic-time

There were 5,048 VL results recorded during the overall follow-up time of 1,103,817 days for 1,352 participants (median 4 VL tests per patient, IQR 2–6). In only 244 occasions, the time between two consecutive VL tests was >365 days, resulting in a reduction of 23,338 days, based on the established maximum of allocated time per VL result (365 days: with a maximum of 183 days either suppressed or unsuppressed time before and after the date of the VL test; Figure 4-1). As presented in Table 4-2, in our study population on second-line treatment, 815 (60.3%) participants never experienced viremia, while in 172 (12.7%), 214 (15.8%), and 80 (5.9%) participants the viremic-time was <20%, 20–49%, and 50–79% of the total follow-up time, respectively. In 71 (5.3%) participants the viremic-time was ≥80%, of which 51 (3.8%) participants had viremia throughout the total follow-up time (Figure 4-3).

**Table 4-2|** Proportion of time with viremia >200 copies/mL while on second-line treatment (N=1,352)

| Viremic-time (%)[a] | N | % | Median time on second-line ART (months)[b] | IQR[c] |
|---|---|---|---|---|
| No viremia | 815 | 60.3 | 54.0 | 44.9, 64.8 |
| 1–19 | 172 | 12.7 | 59.2 | 49.9, 69.2 |
| 20–49 | 214 | 15.8 | 56.8 | 49.3, 56.8 |
| 50–79 | 80 | 5.9 | 48.5 | 40.9, 60.4 |
| ≥80 | 71 | 5.3 | 42.7 | 32.2, 54.5 |

[a] Viremic-time is calculated as estimated time with VL >200 copies/mL over total follow-up time on second-line ART; [b] Calculated from the start of second-line ART until the end of the study period or censoring (death, switch to third-line ART or transfer out); [c] IQR: Interquartile range (months)

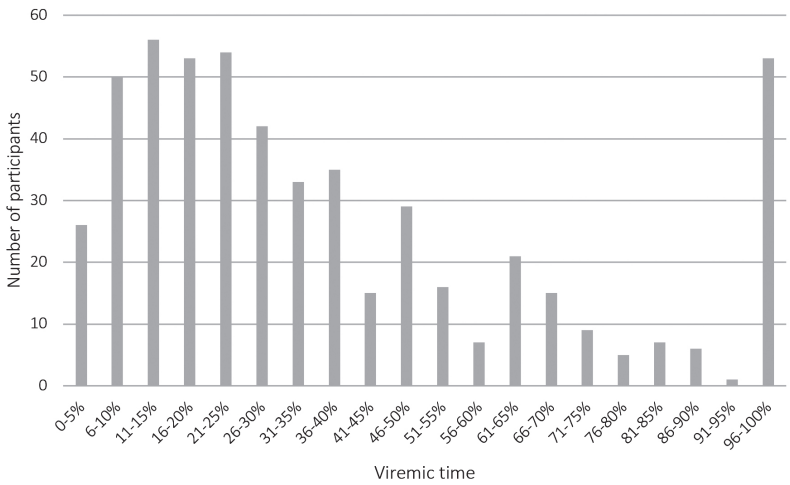



**Figure 4-3|** Distribution of participants by proportion of follow-up time with unsuppressed (>200 copies/mL) viremia among those who experienced viremia (N=537)

### 4.4.3 Risk factors for viremia

The odds for experiencing viremic-time were higher among people with a history of injecting drug use (aOR 2.01, 95% CI 1.30–3.10, p=0.002), sex workers (aOR 2.10, 95% CI 1.11–4.00, p=0.02) and patients treated with a second-line lopinavir/ritonavir-based regimen (vs. atazanavir; aOR 1.53, 95% CI 1.12–2.10, p=0.008). When compared to married participants, those who were separated had a higher odds for viremic-time (aOR 1.59, 95% CI 1 01–2.38, p=0.02). Age, gender and profession were not significantly associated with viremia in our study, as presented in Table 4-3.

### 4.4.4 Factors associated with mortality

At the end of the study period, 61 (4.5%) participants had died, 565 (41.8%) were transferred-out to the NAP, and 726 (53.7%) were still in care in the MSF program; 5 participants had a brief history of loss to follow-up but all returned to care in the MSF program during the study period (after a medium time of 112 days (IQR 65–145)). Twenty-two (1.63%) PLHIV switched to third-line ART during the study period. Patients with viremic-time >50% had a higher mortality hazard (Table 4-4). PLHIV with viremic-time 50–79% or >80% had an almost three-fold higher mortality hazard compared to those who were not viremic during their follow-up time (aHR 2.92, 95% CI 1.21–7.10, p=0.02; aHR 2.71, 95% CI 1.22–6.01, p=0.01, respectively). Among PLHIV with viremic-time <50%, the mortality hazard was not higher compared to those without viremia during their follow-up period. Participants on lopinavir/ritonavir-based second-line ART had a 4.53 times higher mortality hazard compared to participants who were on an atazanavir/ritonavir-based regimen (95% CI 2.58–8.00; p<0.001). For every year increase in age, the mortality hazard increased (aHR 1.04, 95% CI 1.06–1.08, p<0.01). Gender, marital status and baseline BMI were not significantly associated with mortality in our study population (Table 4-4).

The cumulative mortality hazard at two years of follow-up on second-line treatment since the second VL was 6.2% (95% CI 4.2–9.1%) for PLHIV with no viremic-time, and 1.3% (95% CI 0.3–5.5), 3.8% (95% CI 1.5–9.5%), 19.01% (95% CI 9.2–39.6%) and 26.7% (95% CI 13.2–54.9%) for those with 1–19%, 20–49%, 50–79%, or ≥80% viremic-time (p<0.001), respectively. Kaplan-Meier plot estimating the survival function is presented in the Figure 4-4.

**Table 4-3|** Univariable and multivariable fractional logistic regression to show the association between explanatory variables and viremia > 200 copies/mL (N=1,352)

| Variable | Category | Odds ratio (95% CI) | p-value | Adjusted Odds Ratio[a] | p-value |
|---|---|---|---|---|---|
| Gender | Female | 1.17 (0.94–1.45) | 0.16 | 1.20 (0.94–1.54) | 0.15 |
| Age | | 0.98 (0.97–0.99) | <0.001 | 0.99 (0.98–1.00) | 0.41 |
| Profession | Employed | Reference | | | |
| | Student | 1.38 (0.81–2.34) | 0.23 | 1.02 (0.57–1.81) | 0.96 |
| | Unemployed | 1.22 (0.96–1.55) | 0.10 | 0.99 (0.75–1.31) | 0.95 |
| Marital Status | Married | Reference | | | |
| | Separated | 1.61(1.09–2.38) | 0.02 | 1.59 (1.01–2.38) | 0.02 |
| | Single | 1.50 (1.16–1.86) | 0.002 | 1.31 (0.96–1.78) | 0.09 |
| | Widow | 0.95 (0.63–1.43) | 0.81 | 0.90 (0.59–1.35) | 0.62 |
| Man having sex with men | Yes | 0.51 (0.18–1.46) | 0.21 | | |
| History of injecting drugs | Yes | 1.76 (1.16–2.66) | 0.007 | 2.01 (1.30–3.10) | 0.002 |
| History of sex work | Yes | 2.41(1.28–4.51) | 0.006 | 2.10 (1.11–4.00) | 0.02 |
| Baseline WHO stage | 1or 2 | Reference | | | |
| | 3 or 4 | 1.21 (0.86–1.71) | 0.26 | | |
| Second-line regimen[b] | Atv/r[c] | reference | | | |
| | Lop/r[c] | 1.75 (1.33–2.31) | <0.001 | 1.53 (1.12–2.10) | 0.008 |
| Baseline tuberculosis | Yes | 1.19 (0.90–1.57) | 0.23 | | |
| Baseline CD4 (cells/mm$^3$) | | 1.00 (1.00–1.01) | 0.017 | 1.00 (0.99–1.00) | 0.10 |
| Baseline BMI[c] (kg/m$^2$) | | 1.01 (0.98–1.03) | 0.32 | | |
| First-line treatment duration (months) | | 1.00 (0.99–1.00) | 0.32 | | |

[a] Forward stepwise selection was used to construct the final multivariable model. First, variables known for their clinical importance (age, gender) were included, regardless of their association with the outcome. Additional variables were stepwise included in the multivariable model if they were associated with outcome (p<0.10) in the univariable analysis, and b) if they significantly improved the model (p<0.05). [b]Atv/r: atazanavir/ritonavir, Lop/r: lopinavir/ritonavir, [c]BMI: Body mass index; Note: Baseline- at the time of second line antiretroviral initiation.

**Table 4-4** |Univariable and multivariable Cox regression to show the association between explanatory variables and mortality

| Variable | Category | Hazard ratio (95% CI) | p-value | Adjusted hazard ratio[a] (95% CI) | p-value |
|---|---|---|---|---|---|
| Gender | Male | | | | |
| | Female | 1.40 (0.85–2.32) | 0.19 | 1.44 (0.89–1.63) | 0.44 |
| Age | | 1.04 (1.02–1.06) | <0.001 | 1.06 (1.03–1.08) | <0.001 |
| Profession | Employed | | | | |
| | Student | 1.15 (0.28–4.78) | 0.85 | | |
| | Unemployed | 1.01 (0.58–1.77) | 0.97 | | |
| Marital Status | Married | | | | |
| | Separated | 0.67 (0.20–2.20) | 0.51 | 0.87 (0.26–2.93) | 0.82 |
| | Single | 0.80 (0.43–1.49) | 0.48 | 1.79 (0.84–3.80) | 0.13 |
| | Widow | 2.00 (1.02–3.94) | 0.04 | 1.04 (0.49–2.24) | 0.90 |
| Man having sex with men | Yes | NA | NA | | |
| History of injecting drugs | Yes | 1.60 (0.50–5.12) | 0.43 | | |
| History of sex work | Yes | 1.63 (0.40–6.67) | 0.50 | | |
| Baseline CD4 (cells/mm$^3$) | | 0.99 (0.99–1.00) | 0.37 | | |
| Baseline BMI[b] (kg/m$^2$) | | 0.94 (0.88–1.00) | 0.04 | 0.96 (0.90–1.02) | 0.18 |
| Baseline WHO stage | 1 or 2 | | | | |
| | 3 or 4 | 3.05 (0.75–12.50) | 0.12 | | |
| Baseline Tuberculosis | Yes | 1.43 (0.77–2.63) | 0.25 | | |
| Second-line regimen | Atv/r[c] | | | | |
| | Lop/r[c] | 4.13 (2.48–6.86) | <0.001 | 4.53 (2.58–8.00) | <0.001 |
| Duration of first-line treatment (months) | | 1.00 (0.99–1.00) | 0.72 | | |
| Viremic-time (%) | 0 | | | | |
| | 1–19 | 0.53 (0.21–1.38) | 0.20 | 0.60 (0.23–1.58) | 0.30 |
| | 20–49 | 0.76 (0.34–1.73) | 0.51 | 0.88 (0.38–2.04) | 0.78 |
| | 50–79 | 3.06 (1.41–6.67) | 0.005 | 2.92 (1.21–7.10) | 0.02 |
| | ≥80 | 5.05 (2.46–10.39) | <0.001 | 2.71 (1.22–6.01) | 0.01 |

[a] Forward stepwise selection was used to construct the final multivariable model. First, variables known for their clinical importance (age, gender) were included, regardless of their association with the outcome. Additional variables were stepwise included in the multivariable model if they were associated with outcome (p<0.10) in the univariable analysis, and b) if they significantly improved the model (p<0.05); [b]BMI: Body mass index; [c]Atv/r: atazanavir/ritonavir, Lop/r: lopinavir/ritonavir; Note: Baseline- at the time of second line antiretroviral initiation.

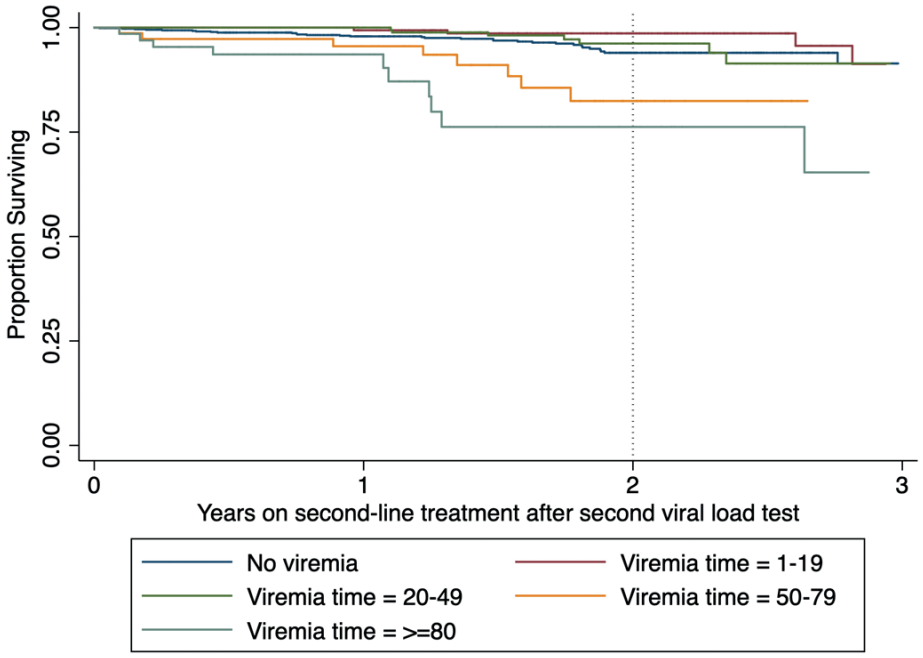



**Figure 4-4|** Kaplan-Meier survival estimates by viremic-time

## 4.5 Discussion

The study of our second-line ART cohort in Myanmar demonstrated a close to three-fold increase in mortality hazard in PLHIV who were more than half of their follow-up time viremic, after controlling for other relevant factors. Those who were viremic, but less than half of their follow-up time, were not at elevated risk of mortality, as compared to those not being viremic. HIV is a chronic disease. Being viremic does not equal immediate symptomatic morbidity and this may explain why mortality increases only when patients are viremic for a longer period of time [25]. Studies show that treatment interruptions might lead to a drop in CD4 counts, increased incidence of opportunistic infections, and mortality [26], while others argue that guided treatment interruptions might be a successful strategy in long-term HIV care [27]. This practice may work—without resulting in an increased mortality risk—as long as the immune system remains intact, and no resistance is acquired to the prescribed ART drugs. However, this has important implications since transmission is not halted. Multiple studies have shown that the risk of transmission increases with increased HIV VL [28–30]. We speculate that those who were viremic, and not at risk of dying, continued with their daily life and could contribute to HIV transmission in the community, especially when their HIV VL >1000 copies/mL [31].

As a measure for unsuppressed VL, we used any viremia that was above 200 cells/mm$^3$. The WHO now recommends intensive adherence support and three-monthly VL monitoring for PLHIV with detectable viremia <1000 copies/mL [32] and there is an increasing amount of evidence on low-level viremia being associated with unfavorable treatment outcomes [33, 34]. A recently published study from the same setting confirmed low-level viremia as a predictor of virological failure in patients on first-line ART [35]. Further studies should evaluate which cut-off is epidemiologically and clinically the most relevant.

To calculate viremic-time, we used a simplified approach that could be applied in programmatic settings. Multiple studies used VCY as a measure of the proportion of follow-up time with an unsuppressed VL and reported an association between VCY and having an unfavorable outcome, either morbidity [18, 36, 37] or mortality [18, 19, 38]. Further studies are needed to assess the best use of viremic-time as a prognostic factor in routine clinical practice. Multiple studies emphasize that prolonged exposure to HIV replication leads to immune system activation [19], also involved in the pathogenesis of non-communicable diseases (NCDs) [36, 39], and increases risks of opportunistic infections [26, 40]. Viremic-time as a predictor of morbidity was not studied in our cohort and should be subjected to further research. To successfully meet HIV control targets, 95% of all PLHIV should have a suppressed VL. Programs measure this indicator at a given moment in time, and do not distinguish between having all PLHIV suppressed for 95% of the time or aiming at having 95% PLHIV suppressed and accepting that 5% are virologically failing until they die and "disappear" from the equation. It seems obvious that programs aim for the best for all their patients, but the distinction cannot be made the way VL data are reported in programmatic settings. While clinicians tend to interpret VL longitudinally, usually cross-sectional designs are used to evaluate the virological response to HIV treatment within a cohort [41–43]. We believe that cumulative assessments reflect the health status and HIV control of the entire cohort better than cross-sectionally measured indicators.

The risk of having higher viremic-time was double in people with a history of injecting drug use or sex work. Key populations are disproportionately affected by the HIV epidemic and are known to play a fundamental role in HIV transmission in many settings, including Myanmar [44]. In 2019, the estimated HIV prevalence among people who inject drugs, sex workers, and men having sex with men in Myanmar was 28.5%, 25.0%, and 20.0%, respectively [14]. In addition to poor access to care, non-sustained suppression can partially explain the high HIV incidence among those populations [45]. In the context of the present study, key populations are often mobile, and their working hours or practices impede easy access to care. Additionally, stigma, discrimination, and criminalization of their practices interfere with adherence, thus increase viremic-time and consequently results in HIV transmission. To address the specific needs of key populations, differentiated service

delivery models, including a comprehensive package of preventative and treatment services have been recommended to achieve “treatment as prevention” [46]. To simultaneously improve access and retention in care and also address health and social needs, communities and peers may need to be empowered to take an active role [47]. The National HIV Strategic Plan recommends such strategies to be implemented in Myanmar [22].

Our results show that PLHIV with higher viremic-time should benefit from differentiated care, including more frequent clinical visits, better adherence support, HIV drug-resistance monitoring, and eventually an early switch to third-line treatment when resistance to second-line drugs emerges. Additionally, the periodicity of VL monitoring may need to increase. In 2015, Marks et al. demonstrated that when VL monitoring was done less frequently, patients were at risk for longer periods with viremia. They argued that more frequent virological monitoring might reduce viremic-time, transmission risk, and improve individual health of PLHIV [30]. In the future, novel tools that allow point-of-care (POC) VL testing will revolutionize HIV control [48]. Meanwhile, subgroups at risk for higher viremic-time should be prioritized for more frequent VL monitoring. In our study cohort with access to frequent routine VL monitoring, 40% of PLHIV experienced viremia while being on second-line ART. Only a minority of PLHIV were switched to third-line ART because only confirmed HIV drug resistance was an indication for treatment change. Indeed, HIV drug-resistance testing is recommended to distinguish between viremia caused by treatment failure due to suboptimal adherence and treatment failure due to HIV drug resistance. For the first type of patients, third-line ART is not needed and may even cause harm, as in the long run a precious treatment option might be lost. Only for the latter group, a switch to third-line ART is justified. As access to drug-resistance testing as part of routine clinical care and/or access to third-line medications remain very limited, many patients continue second-line treatment despite viremia [49]. Hermans et al. have recently recommended using ART-drug serum-level measurements as a strategy to differentiate causes of treatment failure and accelerate clinical decision-making [50]. An early switch to effective treatment after first-line treatment failure was modeled to be a lifesaving opportunity, especially for those with advanced HIV disease [51]. Similar studies should assess if the same approach would benefit those with second-line treatment failure, keeping in mind increased HIV transmission risk.

PLHIV on a lopinavir/ritonavir-based regimen experienced higher viremic-time in our cohort, consistent with previously reported findings [52]. Long-term previous exposure to first-line ART was not associated with a higher viremic-time once patients were on second-line treatment. However, routine virological monitoring for patients on first-line ART in our cohort was introduced only after 2016. In patients with first-line virological failure who were not switched in time resistance accumulates to the NRTIs [53], the backbone of second-line

ART regimens. Some studies suggest this leads to a less effective second-line regimen and more-frequent second-line failures [54, 55]. However, this is not supported by the findings from the clinical trials, which demonstrated that NRTI mutations do not compromise second line ART and that paradoxically patients with more NRTI mutations have better outcomes on second line treatment [56]. To overcome such challenges in the future, there is a need to scale up access to relatively new antiretrovirals, such as dolutegravir or darunavir/cobicistat, known to be safe and highly effective, and at the same time to have a higher genetic barrier and longevity in comparison with currently used treatments [57–61].

Our study identified other hazards for mortality among PLHIV on second-line ART. Our results show an increase in mortality hazard for every year increase in age. The older, the higher risk of NCDs or some type of opportunistic infections. However, careful mortality ascertainment was not done and known causes of death among adults were not included in the regression model. PLHIV who received lopinavir/ritonavir had a higher risk of mortality when compared to those on atazanavir/ritonavir. The association between the type of protease inhibitor and mortality is probably not related to the drug itself, but the underlying indication for its use. Unfortunately, data on such indications (e.g. an episode of tuberculosis during second-line treatment) were not included in the study.



Our study represents the reality of a large long-term HIV program in the Southeast Asian context with an exceptionally high coverage of routine VL testing. However, there are several limitations. Sampling bias caused by irregular VL testing has been discussed as a limitation of cumulative indicators of viremia [60]. In our study, only a minority of VL tests were more than six months delayed. Moreover, we limited time allocation to a VL result to a maximum of 365 days, with a maximum of 183 days before and 183 days after the date of VL testing. Assessment of sensitive information, such as sexual preferences (gay men or men having sex with men), involvement in sex work, and injecting drug status was done at baseline only. Possible changes over time were not recorded. Furthermore, reporting bias might have occurred as PLHIV in this setting tend to underreport risk behavior due to stigma and criminalization of these activities. This may have resulted in an underestimation of the frequency of such risk behaviors and may have affected their association with outcomes. Because treatment adherence was not recorded in the database it could not be assessed as a predictor. This may have caused residual confounding. The study includes patients from Myanmar and is unlikely to be representative of geographically different groups. Conversely, findings are likely generalizable to other second-line ART cohorts in Myanmar, given that the MSF HIV program included a quarter of the estimated total population of PLHIV in the country.

## 4.6 Conclusions

Among PLHIV on second-line ART in Myanmar, having less than 50% viremic-time was not associated with mortality but could be considered as a risk factor for ongoing HIV transmission, especially among key populations. Viremic-time >50% was associated with mortality. Cross-sectional analysis of VL data does not allow clinicians and program managers to assess the clinical and public health impact of higher viremic-time. Cumulative assessments of HIV viremia might better reflect the health status and the level of HIV control of the entire cohort than cross-sectional indicators. To reduce the risk of HIV transmission and mortality among those who are failing second-line HIV treatment, differentiated services including innovative approaches for the management of viremia and models of care tailored to the specific needs of at-risk groups should be scaled up.

## 4.7 Declarations

**Competing interests** Authors have no competing interests to declare.

**Authors' contributions** AM and TD conceptualized and designed the study. HTM, AAK, TTT, and MP contributed to data collection, data management, and data extraction. AM and TD performed the data analysis. AM, TD, LL, BKMJ, MS, TTT, MP, and HTM participated in the data interpretation. AM drafted the original manuscript. AM, TD, and LL revised all subsequent versions of the manuscript. All authors contributed to and approved the final version of the manuscript.

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# Chater 5 |

## Systematic review on cumulative HIV viremia among people living with HIV receiving antiretroviral treatment and its association with mortality and morbidity

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## 5.1 Abstract

**Objectives:** We performed a systematic review to generate evidence on cumulative HIV viremia and its association with various health outcomes.

**Methods:** Quantitative studies reporting on HIV cumulative viremia (CV) and its association with health outcomes among people living with HIV (PLHIV) on antiretroviral treatment (ART) were included. We searched MEDLINE via PubMed, Embase, Scopus and Web of Science, and conference abstracts from January 1, 2008, to August 1, 2022. Study characteristics, definitions, and the measure of CV, as well as strength of the association between CV and mortality or morbidity were summarized in the tables.

**Results:** The systematic review included 26 studies. The association between CV and mortality depended on the study population, methods used to calculate CV and its level. Higher CV was not consistently associated with greater risk of AIDS-defining clinical conditions. However, four studies present a strong relationship between CV and cardiovascular disease. The risk was not confirmed in relation to increased hazards of stroke. Studies that assessed the effect of CV on the risk of cancer reported a positive association between CV and malignancy, although the effect may differ for different types of cancer.

**Conclusions:** CV is associated with adverse health outcomes in PLHIV on ART, especially at higher levels. However, its role in clinical and programmatic monitoring and management of PLHIV on ART is yet to be established.

**Keywords:** HIV viremia, viral load, cumulative viremia, viremia copy-years

## 5.2 Introduction

Virological suppression is the best measure of treatment success during HIV infection. Multiple studies have demonstrated the prognostic value of plasma HIV RNA levels or HIV viral load (VL) for mortality, disease progression [1–6], HIV transmission [7–9], and immune system activation. The latter may lead to chronic non-communicable health conditions [2, 10–13]. Most programs use a cross-sectional approach when studying virological outcomes, usually relying on the most recent VL [14]. However, VL suppression might not be stable, and cross-sectional approaches do not show how long a patient had suppressed VL. During HIV treatment, people living with HIV (PLHIV) may transition between suppressed and unsuppressed viremia. By overlooking these transitions, a cross-sectional approach might misrepresent the level of suppression in HIV cohorts [15, 16]. Overestimated VL suppression may result in missed opportunities to improve individual health, and result in ongoing HIV transmission in a given context. In the last two decades, the association between longitudinal measurements of viremia and health outcomes has emerged as an area of interest. In 2009 and 2010, Zoufaly et al. [17] and Cole et al. [18] introduced the concept "HIV cumulative viremia (CV)", defined by a person's cumulative exposure to unsuppressed VL. No previous review has systematically summarized evidence on different indicators of CV and their association with mortality and morbidity in HIV cohorts. We, therefore, carried out a systematic review to define indicators of CV and the strength of association with various health outcomes.



## 5.3 Methods

### 5.3.1 Eligibility

We included quantitative studies reporting HIV CV and its association with health outcomes among PLHIV on antiretroviral treatment (ART). Studies reporting HIV CV among ART-naïve PLHIV or those that did not clearly specify the ART history of study participants were excluded from the review.

### 5.3.2 Search strategy and selection criteria

The systematic review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement updated in 2020 [19, 20] and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021283891). We searched MEDLINE via PubMed, Embase, Scopus, and Web of Science from January 1, 2008 to August 1, 2022 using a search strategy (Supplement 5-1) that combined terms for HIV infection, viremia, ART, and health outcomes, without age or geographical restriction. The language was restricted to English. An automatic PubMed alert with the same terms was used until August 1, 2022. We also hand-screened

references of all included full-text articles. We searched conference abstracts from the International AIDS Society, Conferences on Retroviruses and Opportunistic Infections, and International Conference on AIDS and Sexually Transmitted Infections in Africa from 2008 onwards to identify studies not yet published as full-text articles. After reports were identified, they were uploaded to Rayyan, a browser-based tool for support of the literature review [21]. Two authors (AM and LL) independently screened titles and abstracts. They read full articles and assessed selected articles for risk of bias with the Newcastle-Ottawa tool for observational studies [22]. Disagreements about inclusion were resolved by discussion and arbitration with a third researcher (TD).

### 5.3.3 Data analysis

Two reviewers (AM and LL) extracted data independently in accordance with a predefined data extraction sheet. Outcomes of interest were CV and any health outcomes related to PLHIV on ART. We also extracted data about study settings, population, methods used to calculate CV, time when viremia was estimated, and the periodicity of VL testing. Due to the heterogeneity among included studies regarding study population, definitions of CV, and studied outcomes, we did not conduct a meta-analysis. We have summarized study characteristics, definitions of CV, and the measure of CV, as well as the association between CV and various health outcomes in tables. When data were not available, we indicated non-applicable (N/A).

## 5.4 Results

### 5.4.1 Search and screening results

The database searches, after deduplication, yielded 162 records that underwent title and abstract screening. Totally, 35 full-text articles were assessed for eligibility and 20 were included in the analysis. Manual searches of the references of included articles and screening of conference abstracts resulted in another 13 records, of which 6 were included, resulting in 26 records being included in the analysis (Figure 5-1).

### 5.4.2 Included studies

Among the 26 included studies, one was a randomized clinical trial and 25 were observational cohort studies (Table 5-1). Thirteen studies were conducted in the United States of America (USA), seven in Europe, two in Latin America, two in Sub-Saharan Africa, one in Australia, and one in Southeast Asia. The size of the study population ranged from 140 to 112,243 participants. Participants received ART in combinations recommended by the guidelines used during the respective study periods. Follow-up time on ART was reported by 21 studies and ranged from a median from 1 to 10 years. The periodicity of VL monitoring varied from

one VL test every 2 years (median 2.0 (interquartile range [IQR] 2.0–8.0) [23] to one every 4 months (average 3.1 VL tests per participant per year) [24].

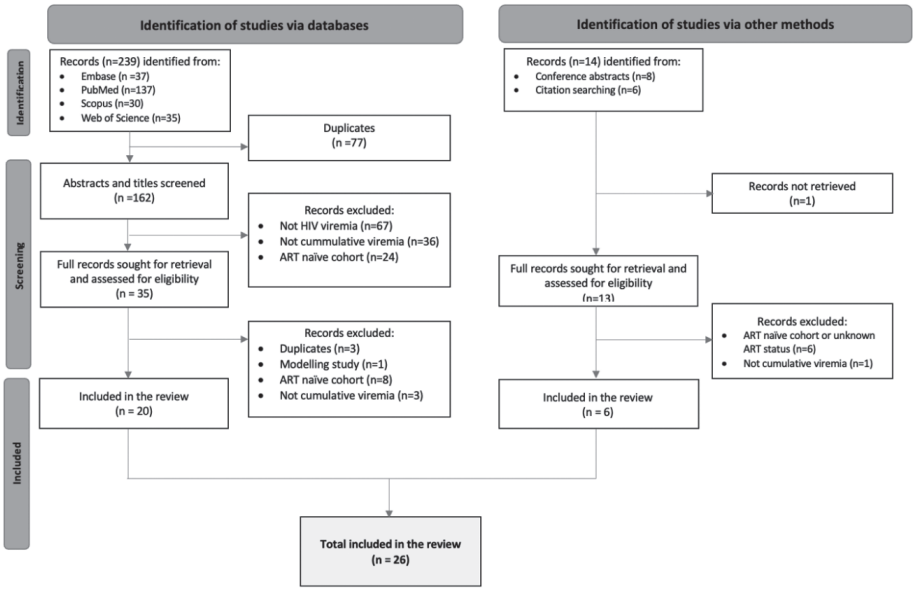
### 5.4.3 Risk of bias

Included studies were considered to have a low risk of bias (Supplement 5-2). The quality assessment showed a good to fair result despite some concerns about the representativeness of study populations [16, 23, 25–29], rates of lost to follow-up in observational cohorts [24, 26–28, 30–42], and duration of follow-up, which may have been too short to reliably measure outcomes of interest in selected studies [33, 34, 38–40].

### 5.4.4 Cumulative viremia

Cumulative viremia was defined as a proportion of follow-up time on ART under or above a certain VL threshold [16, 17, 26, 27, 29, 35–37, 43], or both [16, 17, 26, 27, 36, 37] or as viremia copy-years (VCY; or a variation of this definition), which estimates the area under a patient's VL curve [23, 24, 28, 32, 33, 35, 38–42, 44–46] (Table 5-1). The method was first presented by Cole et al. in 2010 [18]. Some studies obtained a logarithmic value of CV ($Log_{10}$ copy-years/mL) by summing the area under the VL curve and then taking the logarithm, or by summing the area under the logarithmic VL curve [17, 38, 42, 45]. Most studies calculated CV 4–12 months after ART initiation, allowing the first evaluation of virological suppression [16, 27–29, 32, 33, 35, 37–39, 41, 42, 45]. Various approaches were used to deal with values below the lower limit of detection (LLD): those were either considered equal to the LLD [36, 38, 40], half the LLD [35, 39, 46], or set to zero [17, 29, 32, 37, 41, 42, 45]. Studies that used proportion of time under or above a given VL threshold, defined this VL threshold either as the LLD (20–500 copies/mL) [16, 17, 26, 27, 29, 36, 37] or set to 1,500 copies/mL when transmission risk was studied [43]. The lowest CV was reported by Elvstam et al. (median 0.22 (IQR 0.0–2.4) $Log_{10}$ copy-years/mL for 5.5 years on ART) [45] and the highest was reported by Chirouze et al. (median 7.8 (IQR 2.4–16.6) $Log_{10}$ copy-years/mL for a median 10 years on ART) [32]. In the latter study, CV was lower (median 2.7 $Log_{10}$ copy-years/mL during the same observation period) in participants who were ART naïve at the start of the study. Studies showed higher CV in patients who were on ART for a longer period. Wright et al. showed a mean VCY of 2.31 (95% confidence interval [CI] 2.26–2.36) at one year of ART and a mean of 4.3 (95% CI 4.22–4.39) VCY at ten years of ART [30]. Wang et al. reported 2.2 (IQR 1.5–4.1) and 3.1 (IQR 1.8–4.3) $Log_{10}$ copy-years/mL at two and three years of ART, respectively [16]. Lima et al. reported higher CV for those on an efavirenz-based regimen (median 1.56 (IQR 1.46–1.68) $Log_{10}$ copy-years/mL from baseline) compared to those on a boosted lopinavir-based regimen (median 1.75 (IQR 1.51–1.92) $Log_{10}$ copy-years/mL from baseline) [38]. Pascom et al. reported that CV was significantly lower with a dolutegravir-based regimen as compared to lopinavir/ritonavir- or efavirenz-based regimens

[40] (mean 689.5 (standard deviation [SD] 269.6) $Log_{10}$ copy-days/mL for dolutegravir- vs. 728.0 (SD 306.8) $Log_{10}$ copy-days/mL for efavirenz- and 743.9 (SD 312.2) $Log_{10}$ copy-days/mL for atazanavir-based regimens).




Note: Citation searching records identified as references of the studies identified via databases and included in the systematic review.

**Figure 5-1|** Study inclusion flow diagram

**Table 5-1|** Characteristics of the studies reporting cumulative viremia (n=26)

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Cates et al., USA [35] | 1998–2013 | Prospective observational cohort | Pregnant women-initiated ART prior conception and with minimum two VL results | 149 | N/A | Semi-annually | VCY# from ART initiation and excluding the first VL result | 4.4 (IQR 3.8–4.9) median $Log_{10}$ copy-years/mL |
| Chirouze et al., France [32] | 1997–1999 | Prospective observational cohort | PLHIV on protease inhibitor treatment with baseline plasma VL >500 copies/mL and at least two VL tests | 979 | 10 (IQR 5.0–12.0) median years | Median number of VL tests:<br>12 (IQR 4.0–23.0) if below lower limit of detection<br>5 (IQR: 2.0–11.0) if above lower limit of detection | VCY from eight months of follow up | Median $Log_{10}$ copy-years/mL:<br>4.8 (IQR 1.3–13.5) overall<br>2.7 (IQR 1.0–1.1) in the ART-naïve population<br>7.8 (IQR 2.4–16.6) in the ART-experienced population |
| Falasca et al., Italy [31] | 2011–2015 | Retrospective observational cohort | PLHIV on ART with at least 6 VL tests during 54 months of follow-up | 850 | 54 months | 7.5 (SD 1.4) mean number of VL tests | VCY | Median $Log_{10}$ copy-years/mL:<br>1.3 (IQR 0.9–1.7) if pre-study viremia suppressed<br>1.7 (IQR 1.7–2.2) if pre-study viremia <37 copies/mL<br>2.5 (IQR 1.9–3.3) if pre-study viremia 37–200 copies/mL |
| Kukoyi et al., Ghana [23] | 2009–2013 | Prospective observational cohort | Age 0–13 years with minimum two VL tests | 140 | 4.3 (SD 2.4) mean years | 2.0 (IQR 2.0–8.0) median number of VL tests | VCY | 36% with <2 $Log_{10}$ copy-years/mL<br>19.2% with 2–4 $Log_{10}$ copy-years/m<br>44.3% with >4 $Log_{10}$ copy-years/mL |
| Mugavero et al., USA [39] | 2000–2008 | Prospective observational cohort | PLHIV initiated on ART with minimum two VL tests | 2,027 | 2.7 (IQR 1.6–4.6) median years | 8.0 (IQR 4.0–15.0) median number of VL tests | VCY from 24 weeks of ART | 5.3 (IQR, 4.9–6.3) median $Log_{10}$ copy-years/mL |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Pascom et al., Brazil [40] | 2014–2017 | Retrospective observational cohort | PLHIV age >12 years initiated on ART with at least two VL tests | 112,243 | 1 year | 2 VL tests minimum | VC days in one year | Mean $Log_{10}$ copy-days/mL:<br>722.4 (SD 301.5) overall<br>689.5 (SD 269.6) for DTG regimen<br>728.0 (SD 306.8) for EFV regimen<br>743.9 (SD 312.2) for ATV/r regimen |
| Quiros-Roldan et al., Italy [41] | 1998–2012 | Retrospective observational cohort | PLHIV starting ART during the study period with minimum three VL tests | 3,271 | 4.1 median years | 4.5 median number of VL tests | Overall VCY (VCY-o) from start of ART until the end of follow-up<br>Early VCY (VCY-e) in the first 8 months<br>Late VCY (VCY-l) after at least 8 months of ART; categorical variable: VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD) | Median $Log_{10}$ copy-years/mL:<br>6.16 (IQR 5.58–6.71) VCY-o<br>6.15 (IQR 5.57–6.71) VCY-e<br>1.47 (IQR 0–3.72) VCY-l/FUD |
| Salinas et al., USA [28] | 1996–2012 | Prospective observational cohort | PLHIV started on ART | 8,168 | N/A | N/A | VCY from 180 days after ART initiation | N/A |
| Sempa et al., Uganda [42] | 2004–2014 | Prospective observational cohort | PLHIV started on ART | 489 | 8.3 (IQR 2.3–8.8) median years | Semi-annually | Cumulative VL from 24 weeks of ART accumulated on linear scale (cVL1) and logarithmic scale (cVL2) | N/A |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Wright et al., Australia [30] | 1996–2004 | Prospective observational cohort | PLHIV on ART >24 months | 2,073 | N/A | N/A | VCY from six months of ART | Mean $Log_{10}$copy-years/mL<br>2.31 (95% CI 2.26 - 2.36) at 1 year ART<br>3.27 (95% CI 3.21– 3.33) at 3 years ART<br>3.71 (95% CI 3.65–3.78) at 5 years ART<br>4.31 (95% CI 4.22–4.39) at 10 years ART<br>Mean copy-years/mL:<br>204 (95% CI 182–229) at 1 year ART<br>1862 (95% CI 1622–2138) at 3 years ART<br>5129 (95% CI 4467–6026) at 5 years ART<br>19,953 (95% CI16,596 -24,547) at 10 years ART |
| Cozzi-Lepri et al., Italy [44] | N/A | Retrospective observational cohort | PLHIV who initiated ART | 5,512 | N/A | N/A | VCY from ART initiation | 5.27 (2.69–11.19) median $Log_{10}$ copies/mL |
| Coburn et al., USA [34] | 1997–2016 | Retrospective observational cohort | Women age >25 years on ART | 5,279 | 5 (IQR 2–9) median years | N/A | VCY from ART initiation | 17,306 (IQR: 1419, 101,338) median copy-years/mL |
| Lima et al., Mexico [38] | 2005–2007 | Clinical Trial | PLHIV age >18 years initiated on ART efavirenz or lopinavir\r | 189 | 48 weeks | 5 VL tests | VCY from ART initiation and after six months of ART | Median $Log_{10}$ copy-years/mL on EFV regimen:<br>1.56 (IQR1.46–1.68) from baseline<br>0.26 (IQR 0.26–0.30) from 6 months<br>Median $Log_{10}$ copy-years/mL on Lop/r regimen:<br>1.75 (IQR 1.51–1.92) from baseline<br>0.28 (IQR 0.26–0.32) from 6 months |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Marconi et al, USA [24] | 2008–2011 | Retrospective observational cohort | PLHIV | 1,949 | 5.6 (SD 3.98) mean years | 3.1 mean VL tests per participant per year | VC months | 16.3 (IQR 7.14–24.94) median $Log_{10}$ copy-months/mL |
| Delaney et al., USA [33] | 1996–2006 | Prospective observational cohort | PLHIV starting ART | 11,324 | 4.4 median years | N/A | Cumulative VL ($Log_2$ transformation) from six months after enrolment | 36.1 (SD 140) mean million copy-days/mL |
| Elvstam et al., (Sweden) [45] | 1996–2017 | Prospective observational cohort | PLHIV on ART | 6,562 | 5.5 median years | N/A | VCY from the date of the first VL ≥12 months after initiation of ART by viremia category: overall, virologic suppression <50 copies/mL, LLV of 50–199 copies/mL, LLV of 200–999 copies/mL, high-level viremia ≥1,000 copies/mL | Median $Log_{10}$ copy-years/mL for overall 0.22 (IQR 0– 2.40) Median $Log_{10}$ copy-years/mL for virologic suppression 0 (IQR 0–0.11) Median $Log_{10}$ copy-years/mL for LLV of 50–199 copies/mL 1.11 (IQR 0.50– 1.72) Median $Log_{10}$ copy-years/mL for LLV of 200–999 copies/mL 1.98 (IQR 1.14– 3.16) Median $Log_{10}$ copy-years/mL for high viremia 6.39 IQR (2.69– 13.75) |
| Harding et al., (USA) [46] | 2006–2014 | Prospective observational cohort | PLHIV on ART | 15,974 | N/A | Average 12 VL measurements | VC days | 1.1 (IQR 0.047–3,092) million median copy–days/mL |
| Kowalkowski et al., USA [26] | 1985–2010 | Retrospective observational cohort | Male PLHIV ever receiving ART | 31,576 | 9.0 (SD 5.0) mean years | 3.2 (SD 3.1) mean number of VL tests | VCY % of time being undetectable | 212,743 (SD 467,984) mean copy-years/mL 49% (SD 34%) mean proportion of time being undetectable |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Laut et al., EuroSida# [37] | 2011–2015 | Prospective observational cohort | PLHIV with minimum three VL test results | 11,860 | 4.5 (IQR 3.2–5.9) median years | Semi-annually | VCY after four months of ART<br>Consecutive months with VL ≥50 copies/mL<br>% of time on ART spent fully suppressed | N/A |
| Wang et al., USA [16] | 1995–2004 | Prospective observational cohort | MSM PLHIV starting ART | 841 | 10 years follow up | Semi-annually | VCY during various periods after ART initiation<br>% participants being supressed | Median $Log_{10}$ copy-years/mL:<br>4.3 (IQR 3.6–4.9) overall<br>2.2 (IQR 1.5–4.1) in the recent two years<br>3.1 (IQR 1.8–4.3) in the recent three years<br>% of participants supressed:<br>61% in the recent two years<br>55% in the recent three years<br>33% during the whole study period |
| Pallela et al., USA [27] | 1995–2017 | Prospective observational cohort | PLHIV on ART at least 6 months and with minimum two VL test results | 1,645 | N/A | 14 (IQR 7.0–24) median number of VL tests | VCY from six months after ART initiation<br>% time with VL>50 copies/mL<br>% time with VL<200 copies/ml | 3.0 (IQR 2.3–4.2) median $Log_{10}$ copy-years/mL<br>25.5% median of person-years with VL>50 copies/mL<br>9.7% median of person-years with VL>200 copies/mL |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Zoufaly et al., Germany [17] | 1999–2006 | Prospective observational cohort | PLHIV on ART with minimum two VL test results and no lymphoma on baseline | 6,022 | 754 (IQR 327–1847) median days of ART duration; lymphoma group<br>1520 (IQR 730.5–2645) median days of ART duration; non-lymphoma group | 3.97 (SD 2.17) mean number of VL tests | VCY<br>% of all VL >500 copies/mL, | N/A |
| Hughes et al., USA [36] | 2012–2014 | Prospective observational cohort | PLHIV on ART with minimum two VL test results | 650 | Two years | 5.0 median number of VL tests | VCY<br>Person time spent unsuppressed (<200 copies/mL)<br>Person time spent transmissible (<1500 copies/mL) | 2.2 (IQR 1.96–2.0) median 2-years $Log_{10}$ copy-years/mL<br>9.2% (IQR 7.2–11.1%) median time unsuppressed<br>6.2% (IQR 4.7–7.7%) median time transmissible |
| Chiao et al., USA [25] | 1985–2009 | Retrospective observational cohort | Male veterans on ART | 28,806 | 166,362 person years of follow up | 17.0 median number of VL tests | % time being supressed <500 copies/mL | Proportion of observation time being supressed:<br>≤20%: 22.3%,<br>21–40%: 11.0%<br>41–60%: 12.3%<br>61–80%: 15.1%<br>>=80%: 39.2% |

| Author, Country | Study period | Study design | Study population | Sample size (n) | Duration of follow up on ART | Frequency of viral load monitoring | Measure of cumulative viremia | Cumulative viremia |
|---|---|---|---|---|---|---|---|---|
| Lesko et al., USA [43] | 2010–2015 | Retrospective observational cohort | PLHIV engaged in HIV care and on ART | 3,021 | Median 5.7 (IQR 3.9, 5.7) years of observation time | 10 (IQR 5, 15) median number of VL tests | % follow-up time with VL>1,500 copies/mL after ART initiation | 12.5% person years in care with >1500 copies/mL<br>12.6% person years in care with >1500 copies/mL when time spent lost to clinic assumed <1,500 copies/mL<br>27.2% person years in care with >1500 copies/mL when time spent lost to clinic assumed >1,500 copies/mL |
| Mesic et al., (Myanmar) [29] | 2014–2018 | Retrospective observational cohort | PLHIV on ART | 1,352 | Median 54.5 (IQR 44.6–65.1) months | 4 (IQR 2–6) median number of VL tests | % of follow-time with VL>200 copies/mL from the second VL (minimum six) months after ART initiation | Proportion of participants being un-suppressed (>200 copies/mL):<br>Never: 60.3%<br>1–19% of follow-up time: 12.7%<br>20–49% of follow-up time: 15.8%<br>50–79% of follow-up time: 5.9%<br>>=80% of follow-up time: 5.3% |

#VCY: Viremia Copy-years is a measure of cumulative HIV burden that estimates the area under a patient's longitudinal VL curve. The method was first presented by Cole et al. [18] in 2010. The trapezoidal rule is used to approximate the integral representing the area under each patient's longitudinal VL curve. Viral load burden for time interval between 2 consecutive VL values is calculated by multiplying the mean of the 2 VL values by the time interval. The copy-years/mL for each segment of a patient's VL curve are then summed to calculate viremia copy-years—the number of copies of HIV RNA per mL of plasma over time. Studies report logarithmic value of cumulative viremia obtained by either summing the area under the VL curve and then taking the logarithm or, more rarely, by summing the area under the log VL curve.

**Abbreviations:** ART: antiretroviral treatment; cVL: cumulative viral load; IQR: Interquartile range; LLV: low-level viremia; PLHIV: people living with HIV; SD: standard deviation; VL: viral load; VCY: viremia copy-years; USA: United States of America; N/A: Data not available in the full-text article.

## 5.4.5 Association between cumulative viremia and mortality

Eleven studies studied the association between CV and mortality among PLHIV on ART (Table 5-2). Mugavero et al. [39] showed a 44% increase of mortality risk by one CV unit (adjusted hazard ratio [aHR] 1.44 per $Log_{10}$ copy-years/mL; 95% CI 1.07–1.94), independent of the last VL and CD4 cell count values. Salinas et al. [28] categorized CV: compared to <1,000 copy-years/mL, CV of 1,000–14,999 copy-years/mL (aHR 1.36; 95% CI 1.16–1.59), 15,000–99,999 copy-years/mL (aHR 1.89; 95% CI 1.61–2.21), and ≥100,000 copy-years/mL (aHR 4.09; 95% CI 1.61–2.21) were associated with mortality. Similarly, Wright et al. [30] demonstrated that VCY higher than $10^5$ copy-years/mL predicted mortality (HR 1.52; 95% CI; 1.09–2.13, p=0.01) independent of the last VL and CD4 cell count values, but failed to confirm the same when CV was included as a continuous variable in the model (aHR 1.14; 95% CI 0.94–1.38; p=0.19). Sempa et al. [42] studied VL accumulated on the linear scale (cVL1) or logarithmic scale (cVL2). The latter (but not the former) predicted mortality up to 12 weeks after the last VL result (aHR 1.63; 95% CI 1.02–2.60 vs. aHR 0.97; 95% CI 0.65–1.44; p<0.05 for each $Log_{10}$ copy-years/mL increase).

The effect of CV on mortality depended on its level. A study from Myanmar reported that among PLHIV with viremic-time 50–79% or >80%, mortality hazard was almost three-folds higher compared to those who were not viremic during their follow-up time (aHR 2.92, 95% CI 1.21–7.10, p=0.02; aHR 2.71, 95% CI 1.22–6.01, p=0.01, respectively) [29] (Chapter 4). In the same study, mortality hazard was not increased in participants with viremic-time <50% of their follow up. Similarly, Quiros-Roldan et al. [41] demonstrated that among participants who maintained levels of CV <3 $Log_{10}$ copy-years/mL or <2.3 $Log_{10}$ copy-years/mL of VCY, risk of death was similar to participants with permanently suppressed VL. However, they reported that risk of mortality doubled among participants with >15% of VL results of >500 copies/mL compared to those without. One study demonstrated that the association between CV and mortality depended on the ART status of the population. Chirouze et al. [32] reported that CV was associated with 10 years mortality (aHR 2.0; 95% CI 1.2–3.5 for VCY>1.4 $Log_{10}$ copy-years/mL) among their entire study population. This association was not shown in ART-naïve participants (aHR 1.3; 95% CI 0.6–2.8 for VCY>1.4 $Log_{10}$ copy-years/mL). Three studies compared the prognostic value of CV with cross-sectional measures. Pallela et al. [27] studied multiple viremia exposure measures and showed that all measures individually and in combination predicted mortality. However, the most predictive model used a combination of the most recent VL and time spent with VL>200 copies/mL (aHR 1.15; 95% CI 1.07–1.23). In their EuroSida cohort study, Laut et al. reported a poor discriminative ability of VCY (p=0.77), consecutive months with VL≥50 copies/mL (p=0.15), and percentage of time on ART spent fully suppressed (p=0.33) when compared with “current VL” as a reference to predict mortality after five years on ART [37]. Wang et al. [16] concluded that

VCY calculated during the three most recent years on ART better predicted mortality than VCY for the entire period on ART or cross-sectional VL measures.

### 5.4.6 Association between cumulative viremia and morbidity

We identified 14 studies that assessed the relationship between CV and different morbidities (Table 5-3). Higher CV was not consistently associated with greater risk of an AIDS-defining clinical conditions. Marconi et al. and Laut et al. [24, 37] demonstrated increased risk of AIDS in participants with higher CV; however, Sempa et al. and Kukoyi et al. failed to identify an association between CV and incidence of opportunistic infections [23, 42]. Nonetheless, Kukoyi et al. reported that those with CV >4 $Log_{10}$ copy-years/mL had more frequent outpatient encounters compared to participants with <4 $Log_{10}$ copy-years/mL (p=0.03). Cumulative viremia was investigated as a predictor of non-communicable diseases. Three studies [28, 33, 45] confirmed a strong relationship between CV and acute myocardial infarction (AMI). This was particularly strong for type-2 AMI, showing that CV increasing from the 25$^{th}$ to the 75$^{th}$ percentile was associated with more than double hazards (aHR 2.31; 95% CI 1.59–3.35) [33]. Elvstam et al. reported an association between CV and cardiovascular disease (CVD) (adjusted subhazard ratio [aSHR] 1.03; 95% CI 1.01–1.05). When analyzed as viremia categories, participants with high-level viremia (>1,000 copies/mL) had higher hazards of CVD compared with those who had virological suppression (aSHR, 1.45; 95% CI 1.03–2.05), and low-level viremia (LLV; unsuppressed <1,000 copies/mL) was not associated with risk of CVDs [45]. In contrast, a study from the USA showed that CV was not associated with increased hazards of stroke [46]. Studies that assessed the effect of CV on the risk of cancer reported positive association between CV and malignancy, although the effect may differ for different types of cancer. In the study by Zoufaly et al. [17], CV was associated with incidence of AIDS-lymphoma (aHR 1.67; 95% CI 1.27–2.20; p<0.001). The strongest association was for Burkitt-type lymphoma (aHR 3.45; (95% CI 1.52–7.85, p<0.003) but there was no association between CV and central nervous system lymphoma (aHR 1.00; 95% CI 0.39–2.57, p=1.00). Another study confirmed the effect of CV on HIV-associated anal carcinoma [25]. Kowalkowski et al. [26] investigated the relationship between CV and non-AIDS-defining malignancies. A positive association was found for Hodgkin lymphoma (aHR 1.22; 95% CI 1.06–1.40, p=0.005) and squamous cell anal carcinoma (aHR 1.36; 95% CI 1.21–1.52, p<0.001), but not for hepatocellular carcinoma (aHR1.02; 95% CI 0.93–1.13, p=0.67). In contrast, Coburn et al. [34] could not demonstrate an association between CV and an increased risk of breast cancer (aHR 0.91; 95% CI 0.63–1.32 per $Log_{10}$ increase in the current VCY.

**Table 5-2|** Association between cumulative viremia and mortality (n=11)

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Chirouze et al., France [32] | All-cause 10 year mortality | VCY REF >1.4 $Log_{10}$ copy-years/mL<br>VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD) >2.8 $Log_{10}$ copy-years/mL<br>VCY at year 1<br>VCY at year 5 | Whole study population:<br>2.0 (95% CI 1.2–3.5) HR for VCY>1.4 $Log_{10}$ copy-years/mL<br>1.8 (95% CI 1.1–3.0) HR for VCY/FUD >2.8 $Log_{10}$ copy-years/mL<br>1.2 (95% CI 1.1–1.4) RR for each $Log_{10}$ copy-years/mL increase and when adjusted for the last VL<br>ART-naïve study population:<br>1.3 (95% CI 0.6–2.8) HR for VCY>1.4 $Log_{10}$ copy-years/mL<br>2.4 (95% CI 1.1–5.3) HR for VCY ($Log_{10}$ copy-years/mL) at 5 years<br>2.3 (95% CI 0.8–1.2) HR for VCY ($Log_{10}$ copy-years/mL) at 1 year |
| Mugavero et al., USA [39] | All-cause mortality | VCY $Log_{10}$ copy-years/mL as a continuous variable | 1.65 (95% C 1.32–2.06, p<0.001) aHR for each $Log_{10}$ copy-years/mL increase<br>1.44 (95% CI 1.07–1.94, p=0.02) aHR for each $Log_{10}$ copy-years/mL increase, adjusted for cross-sectional VL and time updated CD4 |
| Quiros-Roldan et al., Italy [41] | Mortality after at least 8 months on ART | Overall VCY (VCY-o) from start of ART until the end of follow-up; continuous variable or dichotomized at median (<6.16 and ≥6.16 $Log_{10}$ copy-years/mL<br>Early VCY (VCY-e) in the first 8 months; Continuous variable or dichotomized at median (<6.15 and ≥6.15 $Log_{10}$ copy-years/mL<br>Late VCY (VCY-l) after 8 months of ART; categorical variable:<br>VCY-l suppressed (VL values equal to or below the limit of detection of 50 copies/mL after 8 months of ART and maintained during all the follow-up);<br>VCY-l low-level ( <3 $Log_{10}$ copy-years/mL)<br>VCY-l ≥3 $Log_{10}$ copy-years/mL<br>VCY/FUD (VCY REF divided by the corresponding follow-up duration, FUD); categorical variable:<br>VCY-l/FUD suppressed (VL values equal to or below the limit of detection of 50 copies/mL after 8 months of ART and maintained during all the follow-up);<br>VCY-l/FUD low level (<2.3 $Log_{10}$ copies/mL)<br>VCY-l/FUD ≥2.3 $Log_{10}$ copies/mL per year of follow-up | VCY-o:<br>1.40 (95% CI 1.03–1.90, p=0.033) HR for VCY-o >6.16 $Log_{10}$ copy-years/mL<br>1.48 (95% CI 1.23–1.79, p<0.001) HR for each $Log_{10}$ copy-years/mL increase<br>VCY-e:<br>1.39 (95% CI 1.11–2.01, p=0.036) HR for VCY-e >6.15 $Log_{10}$ copy-years/mL<br>1.47 (95% CI 1.22–1.78, p<0.001) HR for each $Log_{10}$ copy-years/mL increase<br>VCY-l:<br>0.86 (95% CI 0.56–1.31, p=0.447) HR for VCY-l low level $Log_{10}$ copy-years/mL<br>1.68 HR (95% CI 1.16–2.44, p=0.006) HR for VCY-l ≥3 $Log_{10}$ copy-years/mL<br>VCY-l/FUD:<br>0.78 (95% CI 0.54–1.12, p=0.182) HR for VCY-l/FUD low level<br>19.5 (95% CI 11.10 – 34.26, p<0.001) HR for VCY-l/FUD >=2.3 $Log_{10}$ copies/mL |

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Salinas et al., USA [28] | Mortality | VCY copy-years/mL categorized:<br><1,000<br>1,000–14,999<br>15,000–99,999<br>≥100,000 | Compared to <1,000 copy-years/mL:<br>1.36 (95% CI 1.16–1.59) aHR for 1,000–14,999 copy-years/mL<br>1.89 (95% CI 1.61–2.21) aHR for 15,000–99,999 copy-years/mL<br>4.09 (95% CI 1.61–2.21) aHR for ≥100,000 copy-years/mL |
| Sempa et al., Uganda [42] | Mortality 12 and 24 weeks after the last VL | cVL1: calculated by summing the area under the VL curve and then taking the logarithm<br>cVL2: calculated by summing the area under the log VL curve | Predicting 0–12 weeks ahead:<br>0.97 (95% CI 0.65–1.44) aHR for each $Log_{10}$ copy-years/mL increase (cVL1)<br>1.63 (95% CI 1.02–2.60) aHR for each $Log_{10}$ copy-years/mL increase (cVL2)<br>Predicting 0–24 weeks ahead:<br>0.98 (95% CI 0.80–1.22) aHR for each $Log_{10}$ copy-years/mL increase (cVL1)<br>0.50 (95% CI 0.17–1.4) aHR for each $Log_{10}$ copy-years/mL increase (cVL2) |
| Wright et al., Australia [30] | Mortality | VCY $Log_{10}$ copy-years/mL as continuous variable<br>VCY $Log_{10}$ copy-years/mL as categorical variable (105 copy-years) | 1.14 (95% CI 0.94 -1.38, p=0.19) aHR for each $Log_{10}$ copy-years/mL increase<br>1.52 (95% CI 1.09–2.13, p=0.0) aHR for high VCY (105 copy-years) |
| Laut et al., EuroSida# [37] | Mortality | VCY copy-years/mL as categorical variable:<br>Consecutive number of months with VL ≥50 copies/ml as categorical variable<br>% of time on ART fully supressed as categorical variable | Poor discriminative ability to predict mortality after 5 years on ART:<br>P=0.77 for VCY<br>P=0.15 for consecutive months with VL>=50 copies/mL<br>P=0.33 for percentage of time on ART spent fully suppressed<br>Note: *P values refer to the discriminative ability of VCY compared with the "current VL" reference* |
| Wang et al., USA [16] | Mortality | VCY $Log_{10}$ copy-years/mL as continuous variable derived from VLs assessed during different time periods (the most recent 1–10 years and initial 1–10 years following ART initiation) | All participants:<br>-4 (95% CI -36, 27) adjusted % change in survival time for overall VCY<br>-1 (95% CI -33, 30) adjusted % change in survival time for VCY in first 10 years<br>-21 (95% CI -37, -6) adjusted %change in survival time for VCY in most recent 3 years<br>Baseline CD4 count <200 cells/$mm^3$:<br>-21 (95% CI -36,-5) adjusted %change in survival time for VCY in most recent 3 years<br>-12 (95% CI -37, 12) adjusted % change in survival time for VCY in most recent 10 years<br>Baseline CD4 count ≥200 cells/$mm^3$<br>-24 (-47,-7) adjusted % change in survival time for VCY in most recent 3 years<br>-31 (-57,-5) adjusted % change in survival time for VCY in most recent 10 years |

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Pallela et al., USA [27] | Mortality | VCY $Log_{10}$ copy-years/mL as a continuous variable<br>% of person years with VL>200 copies/mL<br>% person years with VL>50 copies/mL | 1.69 (95% CI 1.46–1.97) HR for each $Log_{10}$ copy-years/mL increase<br>1.22 (95% CI 1.16–1.28) HR for 10% increment (%PY with VL >200 copies/mL)<br>1.20 (95% CI 1.14–1.27) HR for mortality per 10% increment (%PY with VL >50 copies/mL) |
| Cozzi-Lepri et al., Italy [44] | AIDS or death due to any cause<br>Severe non-AIDS (SNAE) or death due to any cause | VCY $Log_{10}$ copy-years/mL as continuous variable<br>Shape of the VCY area under curve assessed:<br>Cohorts with spikes and dips shape<br>Cohorts with stable VL trajectories | 0.77 (95% CI 0.60–0.98) aHR and 1.20 (95%1.13–1.27, p<0.001) aHR for AIDS/ death in cohorts with spikes and dips shape and those with more stable VL trajectories<br>0.75 (95% CI 0.60–0.94) aHR and 1.10 (95% 1.04–1.16, p=0.013) aHR for SNAE/death in cohorts with spikes and dips shape and those with more stable VL trajectories |
| Mesic et al., Myanmar [29] | Mortality | % of time being un-supressed as a categorical variable: never (0%),<br>1–19%, 20–49%, 50–79%, ≥80% | When to compared to participants who were never unsuppressed:<br>0.60 (95% CI 0.23–1.58, p=0.30) aHR for participants with 1–19% of un-suppressed time<br>0.88 (95% CI 0.38–2.04, p-0.78) aHR for participants with 20–49% % of un-suppressed time<br>2.92 (95% CI 1.21–7.10, p=0.02) aHR for participants with 50–79% of un-suppressed time<br>2.71 (95% CI 1.22–6.01, p=0.01) aHR for participants with ≥80% of un-suppressed time |

**Abbreviations**: AIDS: Acquired Immunodeficiency Syndrome; ART: antiretroviral treatment; aHR: adjusted hazard ratio; aRR: adjusted relative risk; CI: confidence interval; cVL: cumulative viral load; HR: hazard ratio; RR: relative risk; SNAE: severe non-AIDS event; VCY: viremia copy-years; VL: viral load;

**Table 5-3|** Association between cumulative viremia and morbidity (n=14)

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Cates et al., USA [35] | Miscarriage or still birth | VCY $Log_{10}$ copy-years/mL as continuous variable | 0.80 (95% CI 0.69–0.92) aRR for each $Log_{10}$ copy-years/mL increase<br>0.10 (95% CI 0.14–0.05) a risk difference for each $Log_{10}$ copy-years/mL increase |
| Falasca et al., Italy [31] | Virological failure | VCY $Log_{10}$ copy-years/mL as continuous variable | 1.01 (95% CI 1.01–1.02, p<0.001) HR for each $Log_{10}$ copy-years/mL increase |
| Kukoyi et al., Ghana [23] | Frequency of hospital admissions, opportunistic infections, and outpatient sick visits | VCY $Log_{10}$ copy-years/mL categorized<br><2 $Log_{10}$ copy-years/mL<br>2–4 $Log_{10}$ copy-years/mL<br>>4 $Log_{10}$ copy-years/mL | Participants with >4 $Log_{10}$ copy-years/mL had increased outpatient encounters compared with participants with <$Log_{10}$ copy-years/mL (85.5% (53/62) vs. 70.5% (55/78), p=0.03).<br>There was no association between VCY and the frequency of opportunistic infections or hospital admissions (data not shared). |
| Salinas et al., USA [28] | Acute myocardial infraction | $Log_{10}$ copy-years/mL categorized:<br><1,000<br>1,000–14,999<br>15,000–99,999<br>≥100,000 | Compared to <1,000 copy-years/mL:<br>1.61 (95% CI 1.06–2.44) aHR for 1,000–14,999 copy-years/mL<br>1.67 (95% CI 1.07–2.61) aHR for 15,000–99,999 copy-years/mL<br>2.02 (95% CI 1.30–3.14) aHR for ≥100,000 copy-years/mL |
| Sempa et al., Uganda [42] | Opportunistic infections | cVL1: calculated by summing the area under the VL curve and then taking the logarithm<br>cVL2: calculated by summing the area under the log VL curve | Predicting 0–12 weeks ahead:<br>0.97 (95% CI 0.86–1.09) aHR for each $Log_{10}$ copy-years/mL increase (cVL1)<br>0.78 (95% CI 0.52–1.15) aHR for each $Log_{10}$ copy-years/mL increase (cVL2)<br>Predicting 0–24 weeks ahead:<br>1.00 (0.91–1.10) aHR for each $Log_{10}$ copy-years/mL increase (cVL1)<br>1.00 (95% CI 0.68–1.48) aHR for each $Log_{10}$ copy-years/mL increase (cVL2) |
| Coburn et al., USA [34] | Breast cancer | $Log_{10}$ VCY as a continuous variable<br>VCY on ART was lagged 1–5 years to account for cancer latency | 0.91 (95% CI 0.63–1.32) aHR for each $Log_{10}$ copy-years/mL increase in the current VCY<br>0.78 (95% CI 0.55–1.10) aHR for each $Log_{10}$ copy-years/mL increase when VCY lagged 1–5 years on ART |

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Marconi et al, USA [24] | AIDS events and CD4 recovery | VC-months dichotomized based on the median | 2.38 (95% CI 1.56–3.62, p<0.001) RR for AIDS when CV higher than median<br>1.96 (95% CI 1.24–3.13, p=0.004) RR for AIDS when CV higher than median and when VL suppression achieved at 6 months<br>2.33 (95% CI 1.44–3.80, p=0.001) RR for AIDS when CV higher than median and when VL suppression achieved at 12 months<br>1.78 (SE 24.11, p=0.941) coefficient for overall CD4 gain in association with CV<br>52.19 (SE 10.87, p<0.001) coefficient for CD4 gain after two years of ART in association with CV |
| Delaney et al., USA [33] | Myocardial infarction type 1 (atheroembolic) and type 2 (vasospasm induced) | $Log_2$ VCY as a continuous variable—distribution of cumulative VL at 5 years was used | Doubling of CV:<br>1.06 (95% CI 1.02–1.10) aHR for both types of myocardial infarction<br>1.02 (95% CI 0.97–1.08) aHR for myocardial infarction type 1<br>1.10 (95% CI 1.06–1.15) aHR for myocardial infarction type 2<br>Increase of CV from 25$^{th}$ to 75$^{th}$ percentile:<br>1.65 (95% CI 1.22–2.23) aHR for both types of myocardial infarction<br>1.22 (95% CI 0.78–1.91) aHR for myocardial infarction type 1<br>2.31 (95% CI 1.59–3.35) aHR for myocardial infarction type 2 |
| Elvstam et al., Sweden [45] | CVD (myocardial infarction, stroke, heart failure) | VCY $Log_{10}$ copy-years/mL as continuous variable for overall, virologic suppression <50 copies/mL, LLV of 50–199 copies/mL, LLV of 200–999 copies/mL, high-level viremia ≥1,000 copies/mL | Overall:<br>1.03 (95% CI 1.01–1.05) for each $Log_{10}$ copy-years/mL increase<br><br>When compared to those with virologic suppression (<50 copies/mL):<br>0.95 (95% CI 0.45–2.01) for LLV 50–199 copies/mL for each $Log_{10}$ copy-years/mL increase<br>1.11 (95% CI 0.53–2.35) for LLV 200–999 copies/mL for each $Log_{10}$ copy-years/mL increase<br>1.45 (95% CI 1.03–2.05) for high-level ≥1000 copies/mL viremia for each $Log_{10}$ copy-years/mL increase |
| Harding et al., USA [46] | Stroke | VCY as copy-days/mL | Compared to participants with CV in 25th percentile:<br>0.91 (95% CI 0.45–1.9) HR for participants with CV in 75th percentile for any stoke<br>0.97 (95% CI 0.46–2.1) HR for participants with CV in 75th percentile for ischaemic stroke |

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Kowalkowski et al., USA [26] | Non-AIDS defining malignancy | VCY $Log_{10}$ copy-years/mL as a continuous variable<br>% of time undetectable as a categorical variable:<br><20%, 20–39%, 40–59%, 60–79%, and ≥80% | 1.22 (95% CI 1.06–1.40, p=-0.005) aHR for HL for each $Log_{10}$ copy-years/mL increase<br>1.36 (95% CI 1.21–1.52, p<0.001) aHR for SCCA for each $Log_{10}$ copy-years/mL increase<br>1.02 (95% CI 0.93–1.13, p=0.67) aHR for HCC for each $Log_{10}$ copy-years/mL increase<br>Compared to participants with <20% time undetectable VL:<br>0.62 (95% CI 0.37–1.02, p=0.06) aHR for HL in participants with undetectable HIV VL >=80% of time<br>0.64 (95% CI 0.44–0.93, p=0.02) aHR for SCCA in participants with undetectable HIV VL >=80% of time<br>1.39 (95% CI 0.98–1.99, p=0.07) aHR for HCC in participants with undetectable HIV VL >=80% of time |
| Laut et al., EuroSida# [37] | Failure and HIV resistance<br>AIDS/non-AIDS clinical events | VCY copy-years/mL as categorical variable:<br>Consecutive number of months with VL ≥50 copies/ml as categorical variable<br>% of time on ART fully supressed as categorical variable | Poor discriminative ability to predict clinical events after 5 years on ART<br>VCY:<br>P=0.33 for any AIDS/non-AIDS clinical event<br>P<0.01 for resistance<br>P=0.42 for triple class failure<br>Consecutive months with VL>=50 copies/mL:<br>P=0.01 for any AIDS/non-AIDS clinical event<br>P=0.17 for resistance<br>P=0.65 for triple class failure<br>Percentage of time on ART spent fully suppressed:<br>P=0.22 for any AIDS/non-AIDS clinical event<br>P<0.02 for resistance<br>P=0.65 for triple class failure<br>Note: *P values refer to the discriminative ability of VCY compared with the "current VL" reference* |

| Author, Country | Outcome | Main exposure variable | Effect estimate |
|---|---|---|---|
| Zoufaly et al., Germany [17] | Incidence of AIDS-lymphoma | VCY $Log_{10}$ as a continuous variable | All lymphomas:<br>1.67 (95% CI 1.27–2.20, p<0.001) aHR per 2000 days $Log_{10}$ copies/mL (reference group,0 days $Log_{10}$ copies/mL<br>1.81 (95% CI 1.32–2.49, p<0.001) aHR CV in the past 3 years<br>Burkitt NHL:<br>3.45 (95% CI 1.52–7.85, p<0.003) aHR per 2000 days $Log_{10}$ copies/mL (reference group,0 days $Log_{10}$ copies/mL<br>Non-Burkitt high-grade B cell NHL:<br>2.02 (95% CI 1.37–2.98, p<0.001) aHR per 2000 days $Log_{10}$ copies/mL (reference group,0 days $Log_{10}$ copies/mL<br>Primary CNS lymphoma:<br>1.00 (95% CI 0.39–2.57, p=1.00) aHR per 2000 days $Log_{10}$ copies/mL (reference group,0 days $Log_{10}$ copies/mL |
| Chiao et al., USA | Incidence of SCAC | % Undetectable VL | Compared to participants with ≤20% of undetectable VL:<br>0.85 (95% CI 0.59–1.22; p=0.371) aHR for SCAC among participants with 21–40% undetectable VL<br>0.86 (95% CI 0.59–1.23; p=0.389) aHR for SCAC among participants with 41–60% undetectable VL<br>0.56 (95% CI 0.37–0.83; p=0.004) aHR for SCAC among participants with 61–80% undetectable VL<br>0.55 (95% CI 0.40–0.77; p=0.0004) aHR for SCAC among participants with undetectable VL >80% VL |

**Abbreviations**: AIDS: Acquired Immunodeficiency Syndrome; ART: antiretroviral treatment; aHR: adjusted hazard ratio; aRR: adjusted relative risk; CI: confidence interval; CNS: Central Nervous System; CV: cumulative viremia; CVD: cardiovascular disease; cVL: cumulative viral load; HCC: Hepatocellular carcinoma; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma; VCY: viremia copy-years; VL: viral load; SCCA- Squamous cell anal carcinoma; SE: standard error; LLV: low-level viremia

## 5.5 Discussion

The systematic review summarized findings from 26 studies that had investigated cumulative HIV viremia among PLHIV on ART and its association with morbidity and mortality. The prognostic effect of CV on health outcomes depended on the methods used, study populations, and the timing when it was measured. Several studies reported a firm and independent association between CV and all-cause mortality [16, 28, 30, 39, 44]. This finding is consistent with the landmark study by Cole et al. [18], which is not included in the review as it measured VCY from the time of HIV seroconversion. However, the study first reported a cumulative indicator providing prognostic information beyond cross-sectional measures of viremia [18]. HIV replication is related to chronic inflammation and immune reactivation, both causing clinical deterioration and mortality [47, 48]. In the randomized clinical trial "Strategic Management of Antiretroviral Therapy" (SMART), increased risk of death and other adverse outcomes in PLHIV—who received ART intermittently—persisted even after ART was re-introduced [49]. In this trial, investigators reported increased levels of inflammatory biomarkers (interleukin-6 and D-dimers) in the experimental arm, known to be associated with all-cause mortality [12]. Starting ART in PLHIV with a CD4 cell count higher than 500 cells/mm$^3$ was proven to have benefits over delaying ART until the CD4 cell count is below 350 cells/mm$^3$ [50]. Therefore, the biological plausibility that long duration of unsuppressed VL leads to unfavorable health outcomes exists. While a high viremia burden predicted mortality, this was not always the case for PLHIV with lower CV burden, when compared to those who were continuously suppressed [29, 41]. Increased inflammatory markers are not always observed in patients with LLV [51, 52], which might partially explain the lack of increased risk of mortality [41] or morbidity in this subgroup [45].

The prognostic value of CV depended on when it was measured. The impact of timing was demonstrated by Wang et al. who reported greater mortality prognostic value of VCY calculated on the recent three years than that of the overall VCY or cross-sectional VL [16]. The lack of prognostic value of distant viremia could partially be explained by ART reversing the risk of opportunistic infections [53] or immune activation [54].

Higher CV was associated with AIDS [24, 37, 44] and virological failure [31], but not the overall incidence of opportunistic infections [23, 42]. The type of participants and methods used to calculate CV varied among those studies, limiting their comparison. ART increased life expectancy among PLHIV. As a consequence, age-related morbidity, such as CVDs [55, 56] or malignancies [57] are now prevalent in HIV cohorts. HIV replication is an important factor of chronic inflammation [58], influencing atherosclerosis [59] and oncogenesis [60]. We found that CV strongly predicted AMI and CVD [28, 33, 45], especially when the viremia burden is high. It has been known that HIV viremia contributes to the risk of stroke

through HIV-associated and traditional stroke risk factors [61]. However, a study from USA reported that increased hazards of stroke were not associated with CV; rather, they were predicted by baseline and time-updated VLs [46], suggesting that acute VL increases might cause inflammatory responses, which in turn result in higher risk of stroke. Those immune responses might be reverted by effective ART and subsequent viral suppression, reducing the risk of morbidity [62]. CV was reported as an independent risk factor for Burkitt, Hodgkin-lymphoma and squamous cell anal cancer, but not CNS related lymphoma, breast, or hepatocellular carcinoma [17, 25, 26, 34], emphasizing the complexity of oncogenesis and the yet not fully understood role of HIV replication in it.

Pallela et al. [27] presented that all longitudinal and cross-sectional viremia measured individually and in combination predicted mortality very well, while others reported poor discriminative ability of CV indicators to predict mortality or morbidity when compared with the cross-sectional VL reference [32, 37]. Cross-sectional VL is a simple indicator that should remain the basis for monitoring the effectiveness of ART and adherence in an individual but can fail to predict certain morbidity.

Despite the challenges, the main advantage of CV is that it represents the overall viremia status of a patient and as such is a good tool to simultaneously evaluate the individual and public health benefit of ART. Not all levels of CV may be associated with mortality. However, any unsuppressed VL may result in transmission, thus a risk for public health. As demonstrated by Hughes et al., a cohort in the USA spent on average almost one month per year at a transmittable VL (>1,500 copies/mL) [36].

Reviewed studies applied different methods to measure CV and as Sempa et al. argue, this has an impact on its predictive value. In their study, CV predicted mortality up to 12 weeks from the last VL, only when calculated on a logarithmic scale. Most of the studies included in this review measured CV by first summing VL values on a linear scale, followed by log-transformation of the cumulative measure, which according to Sempa et al. is a method prone to confounding and does not reflect the log-linear nature of the relationship between CV and clinical events. Furthermore, when using a limited number of VL tests, often spread over time, assumptions are made about the VL status between the two measurements. As demonstrated by Lesosky et al. [63], CV for PLHIV with more spaced VL measures tends to be biased upwards. They demonstrated that sampling frequency bias led to inaccuracy, which could especially affect study populations with longer exposure to ART and more frequent periods with reduced treatment adherence. Over the last decades, technologies to measure VL have improved, demonstrating better sensitivity for viremia detection. Therefore, the LLD of viremia in included studies varied from 20 copies/mL to 500 copies/mL. Studies described various imputing strategies regarding the LLD, some setting the value to zero, while others

included any VL value in the calculation of CV. Estimating the level of CV burden in HIV cohorts could facilitate the identification of patients who would benefit from differentiated care models, including more frequent clinical visits with VL monitoring and enhanced adherence support, as well as screening for co-morbidities including CVD and malignancy. However, without standardized methodology to estimate CV, the comparison of its burden or its effect on health outcomes among different HIV cohorts remains challenging.

Our review was systematic, and it used a replicable search strategy. It also has several limitations. Most of the studies were conducted in well-resourced settings with high frequency of VL monitoring. This may not reflect the reality of high HIV-burden countries with limited resources. Most of the studies included in the review were observational, which reduce their capacity to demonstrate causality and we cannot exclude residual confounding. The duration of follow-up may have been insufficient to demonstrate the long-term impact of viremia on health outcomes. Our review was not able to answer two fundamental questions: firstly, is CV better than cross-sectional indicators in measuring the risk of unfavorable treatment outcomes. Secondly, which level of CV is tolerated, and from which level onwards does the risk of mortality increase. Further research into standardized methodology of cumulative HIV viremia is necessary.



## 5.6 Conclusions

This review reconfirms that achieving and maintaining full VL suppression is crucial to prevent high CV. CV is associated with adverse health outcomes in PLHIV on ART, especially at higher levels. As indicated above, cross-sectional measures of viremia play an important role during the monitoring of treatment response, but may fail to predict some health outcomes, including morbidity caused by long-term inflammation. However, the role of CV in clinical and programmatic management is yet to be established and may increase as cohorts grow older.

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# Chapter 6 |

## Advanced HIV disease and associated attrition after re-engagement in HIV care in Myanmar between 2003 and 2019: a retrospective cohort study

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## 6.1 Abstract

**Introduction:** The burden of advanced HIV disease (AHD) and predictors of outcomes among people living with HIV (PLHIV) re-engaging in care are not well known.

**Methods:** We conducted a retrospective cohort study of PLHIV who re-engaged in care after being lost to follow-up (LFU), between 2003 and 2019, in Myanmar. We calculated the incidence rates of attrition after re-engagement and performed Cox regression to identify risk factors for attrition.

**Results:** Of 44,131 PLHIV who started antiretroviral treatment, 12,338 (28.0%) were LFU at least once: 7,608 (61.6%) re-engaged in care, 4,672 (61.4%) with AHD at re-engagement. The death and LFU rates were 2.21-fold (95% CI 1.82–2.67) and 1.46-fold (95% CI 1.33–1.61) higher among patients who re-engaged with AHD ($p<0.001$). Death in patients who re-engaged with AHD was associated with male sex (aHR 2.63; 95% CI 1.31–5.26; p=0.006), tuberculosis co-infection (aHR 2.26; 95% CI 1.23–4.14; p=0.008) and sex work (aHR 7.49, 95% CI 2.29–22.52; $p<0.001$). History of intravenous drug use was identified as a predictor of being LFU.

**Conclusions:** Re-engagement in HIV care in Myanmar is frequent and those who re-engage carry a high burden of AHD. As AHD at re-engagement is associated with higher attrition rates, implementation of differentiated interventions that enable earlier linkage to care, and prompt identification and management of AHD in this population is necessary.

**Keywords:** Advanced HIV disease, Attrition, Key populations, Myanmar, Re-engagement

## 6.2 Introduction

The world has achieved progress in controlling the HIV epidemic and out of 38 million people living with HIV (PLHIV), 73% (56–88%) were receiving antiretroviral treatment (ART) by the end of 2020 [1]. Since 2015, countries started to implement the "Test and Treat" strategy that recommends starting ART regardless of the CD4 cell count. Still, 680,000 (480,000–1.0 million) people died of HIV in 2020 [1]. HIV-related mortality was declining but plateaued due to a persistent burden of advanced HIV disease (AHD), defined as having either a CD4 cell count <200 cells/mm$^3$ or clinical stage III or IV disease, or being a child under the age of five years with HIV infection [2]. Data from various contexts show that more than a third of PLHIV start ART with AHD [3–5]. In the early stage of ART roll-out, patients with AHD were mostly ART-naïve "late presenters", who were diagnosed with HIV and started ART in an advanced stage of their infection. At present, an increasing proportion of patients who present with AHD had started ART, interrupted treatment, and then re-engaged in care [3]. A South African study showed that the proportion of ART-experienced patients returning to care with a CD4 cell count <50 cells/mm$^3$ increased from 14.3% to 56.7% [5]. Patients with AHD are at a higher risk of dying [2]. Two reported leading causes of death are tuberculosis and cryptococcal meningitis, although data on the specific cause of mortality is usually not reported [6]. Since 2017, the World Health Organization (WHO) recommended a package of interventions that includes enhanced prophylaxis, screening, and diagnosis of the most prevalent opportunistic infections, rapid (re)initiation of ART in patients with AHD and adherence support [2]. However, most programs do not have clear targets for the implementation of these specific recommendations. Furthermore, the lack of standardised indicators to systematically monitor and evaluate the burden of AHD or the effect of intervention on morbidity or mortality associated with the presence of AHD. Some experts therefore recommend adding AHD indicators to the already existing "95-95-95" Joint United Nations Programme on HIV/AIDS (UNAIDS) targets [7].

Myanmar has the second highest HIV prevalence in Southeast Asia. About 0.57% of the general population was estimated to be infected with HIV, although key populations and their partners were the most affected; the HIV prevalence among people who inject drugs (PWID), sex workers (SWs), and men having sex with men (MSM) was 28.5%, 25%, and 20%, respectively [8]. In 2018, Myanmar counted an estimated 220,000 PLHIV [1]. The National AIDS Programme, Ministry of Health and Sports, Myanmar (NAP) had successfully scaled up ART reaching 77% coverage by the end of 2019 [9]. However, a study published in 2018 by Aung et al. reported a 58% burden of AHD at enrollment to HIV care and high rates of early mortality and loss to follow-up. This study identified AHD as one of the risk factors for unfavorable treatment outcomes in the large Myanmar cohort [10].

Since 2003, Médecins Sans Frontières (MSF) in collaboration with the NAP has been providing HIV care at the primary health care level in Yangon, Kachin, and Shan States in Myanmar. Before 2014, due to the high volume of patients in need of starting ART, only those with severe immunosuppression (CD4 cell count <200 cells/mm$^3$) were enrolled on treatment. From 2014 onwards, after the NAP successfully scaled up access to ART through decentralization, and following updates from the WHO and national guidelines, ART enrollment criteria became more inclusive. The threshold to start ART increased stepwise, from CD4 cell count <200 cells/mm$^3$ to "Test and Treat" in 2016. By December 31, 2018, 58,470 PLHIV older than five years of age were enrolled in HIV care in MSF programs. Since 2014, to provide good quality of care in a setting with a health workforce gap and to maximally focus clinical care on the needs of patients with AHD, MSF implemented differentiated service delivery, spacing appointments for patients stable on ART and introducing the concept of task sharing [11]. Since 2009, AHD management included the full package of systematic prophylaxis, screening, and treatment of opportunistic infections as recommended by the WHO [2]. Studies from China, Cambodia, and Myanmar report that despite the gradual improvement observed in earlier ART initiation, a large proportion of patients starting ART have AHD [10, 12, 13]. Re-engagement with healthcare after treatment interruption has been studied in a limited number of contexts and studies report that 11–77% of patients enrolled in HIV care temporarily disengage [14–16]. However, the burden of AHD after re-engagement has not yet been studied in detail.

In the present study, we describe the proportion of PLHIV presenting with AHD at the time of re-engagement in HIV care in MSF's program in Myanmar. We compare attrition after re-engagement in those with and without AHD and assess predictors of attrition among those with AHD.

## 6.3 Methods

### 6.3.1 Design and study population

This was a retrospective cohort study of PLHIV older than five years of age at the time of ART initiation, who received ART in the Myanmar MSF HIV program from January 01, 2003 to January 01, 2019, and who re-engaged in care after being declared lost to follow-up (LFU).

### 6.3.2 Data collection and analysis

The study used routine program data collected from standardized patient forms and encoded in the MSF HIV program database "FUCHIA" (Follow-up and Care of HIV Infection and AIDS). The dataset was exported into the statistical software RStudio (version 3.5.1; RStudio, Boston, MA, USA) for statistical analysis. Independent variables included age, gender, marital status, profession, binary variables to show belonging to a subgroup

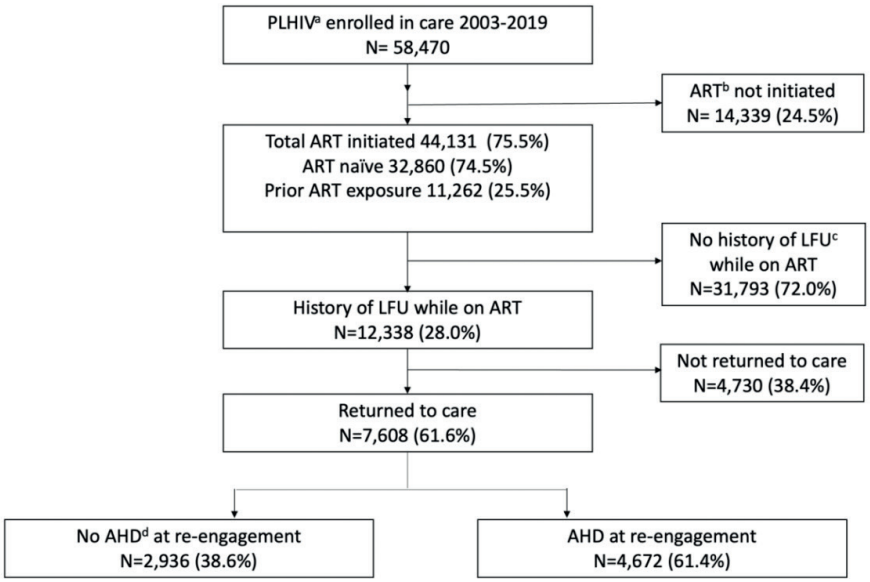
(SWs, PWID, MSM, imprisonment, economic migration, mother-to-child transmission, blood transfusion), having an HIV positive partner, opportunistic infections (cryptococcal meningitis, tuberculosis, talaromycosis (formerly penicilliosis), cytomegalovirus infection), baseline CD4 cell count (cells/mm$^3$), and baseline WHO clinical stage. Outcome variables included LFU (disengaged from care from the next planned appointment for >60 days), death (all-cause mortality while on ART), and attrition (either LFU or death). Prevalence of severe opportunistic infections was reported for the first 60 days after the day of re-engagement. Baseline characteristics were described using frequencies and percentages for categorical variables. For continuous variables, the distribution of data was assessed by histograms. When the distribution was normal, means with their standard deviations (SD) were calculated, otherwise medians with interquartile range would be presented. The follow-up time was expressed in person-years and defined as difference between the date of ART start and the date the patient had an event (either LFU or death) or the date the patient was censored (date of transfer out or, if active on ART, the date of the end of the observation period). Incidence rates of death and LFU were calculated as the number of participants who experienced the event (death, LFU) divided by total person-years of follow-up time. Incidence rate ratios were calculated as ratios of incidence rates in exposed (with AHD) and non-exposed (without AHD) populations. Kaplan-Meier survival analyses were performed to assess time to death, LFU, and attrition, yielding survival probabilities for AHD patients versus those without AHD. The log-rank test was used to determine if the difference between survival curves was significant. In separate survival analyses LFU and death were considered as censoring events. To identify predictors of attrition among patients with AHD after re-engaging in care, univariable Cox regression was used to assess the association between exposure variables and attrition and those where association resulted in $p<0.10$ together with gender and age were included in the multivariable Cox regression model. First, we created a saturated multivariable model, including all explanatory variables. The model was then simplified by stepwise backwards elimination until only variables that improved fit of the model were included in the final analysis.



## 6.4 Results

Between 2003 and 2019, 58,470 PLHIV older than five years of age were enrolled in care and 44,131 (75.5%) were initiated on ART: 32,869 (74.5%) were ART-naïve and 11,271 (25.5%) had been exposed to ART before enrollment in the MSF program. Among ART-naïve patients, 24,791 (75.4%) had AHD. Of 44,131 PLHIV who started ART, 12,338 (28%) were LFU at least once: 7,608 (61.6%) re-engaged in care, among whom 4,672 (61.4%) had AHD at the time of re-engagement (Figure 6-1). Among those who re-engaged and were diagnosed with AHD, 460 (9.84%) had not been diagnosed with AHD before, and they progressed to AHD while being LFU.

Demographic and clinical characteristics of PLHIV re-engaging in care are presented in Table 6-1. Among PLHIV who re-engaged with AHD, 547 (11.7%) and 86 (1.84%) did not have a baseline CD4 cell count or WHO clinical stage reported, respectively. Among those for whom data were available, 1,839 (44.5% of 4,125) had a CD4 cell count <200 cells/mm$^3$ and 3,995 (87.1% of 4,586) presented with WHO clinical stage III or IV disease. Among PLHIV with AHD, 1,800 (38.5%) had a CD4 cell count and WHO stage status showing AHD, 39 (0.83%) had AHD based on having a CD4 cell count <200 cells/mm$^3$, and 2,833 (60.6%) of PLHIV were diagnosed based on their WHO clinical status. Tuberculosis, cryptococcal meningitis, cytomegalovirus, and talaromycosis were diagnosed in 30%, 1.7%, 1.2%, and 0.1% of patients re-engaging in care with AHD, respectively.




Legend: [a] People living with HIV; [b] Antiretroviral treatment; [c] Lost to follow up; [d] Advanced HIV Disease

**Figure 6-1|** Flowchart of inclusion pathway in the study

**Table 6-1|** Demographic characteristics of the study population (n=7,608)

| Characteristics | Categories | n | % |
|---|---|---|---|
| Gender | Male | 4218 | 55.4 |
| | Female | 3390 | 44.6 |
| Age categories (years) | 6–15 | 380 | 5.0 |
| | 16–40 | 5424 | 71.3 |
| | 41–65 | 1794 | 23.6 |
| | >65 | 10 | 0.10 |
| Marital status | Married | 4551 | 59.7 |
| | Separated | 514 | 6.8 |
| | Single | 1686 | 22.2 |
| | Widow | 654 | 8.6 |
| | Missing | 203 | 2.7 |
| Profession | Business | 813 | 10.7 |
| | Transportation | 228 | 3.0 |
| | Administration | 220 | 2.9 |
| | Manual labor | 1131 | 14.9 |
| | Student | 118 | 1.6 |
| | Unemployed | 1598 | 20.9 |
| | Other | 2943 | 38.7 |
| | Missing | 557 | 7.3 |
| SW[a] | No | 4774 | 62.7 |
| | Yes | 129 | 1.7 |
| | Missing | 2705 | 35.6 |
| PWID[b] | No | 4213 | 55.4 |
| | Yes | 947 | 12.4 |
| | Missing | 2448 | 32.2 |
| MSM[c] | No | 4769 | 62.7 |
| | Yes | 57 | 0.75 |
| | Missing | 2782 | 36.5 |
| Economical migrant | No | 7468 | 98.2 |
| | Yes | 140 | 1.8 |
| Imprisonment | No | 7468 | 98.2 |
| | Yes | 140 | 1.8 |
| History of blood transfusion | No | 7508 | 98.7 |
| | Yes | 100 | 1.3 |
| Mother-to-child prevention | No | 7458 | 98.0 |
| | Yes | 150 | 2.0 |
| HIV positive partner | No | 6967 | 91.6 |
| | Yes | 641 | 8.4 |

[a] Sex Worker; [b] People who inject drugs; [c] Men having sex with men

## 6.4.1 Attrition after re-engagement

The mean time to re-engagement was shorter among PLHIV with AHD than among those without AHD (541.4 days (SD 579.7) vs. 907.8 days (SD 804.3); p<0.001). Of 7,608 patients who re-engaged in care, 2,617 (34.4%) either died (N=605; 8.0%) or were subsequently lost to follow-up again (N=2,012; 26.4%) (Table 6-2). The death rates in patients with and without AHD were 2.95 (95% CI 2.70–3.22) and 1.33 (95% CI 1.13–1.58) per 100 person-years, respectively. The LFU rates in patients with and without AHD were 8.81 (95% CI 8.38–9.26) and 6.01 (95% CI 5.56–6.49). The death and LFU rate were 2.21-fold (95% CI 1.82–2.67) and 1.46-fold (95% CI 1.33–1.61) higher among patients who re-engaged with AHD (p>0.001). Based on Kaplan Meier estimates after re-engagement in care, retention in care at 1, 2, 4, and 6 years in patients with and without AHD was 78.1% (95% CI 77.9–78.3%) vs. 88% (95% CI 87.6–88.2%), 69.4% (95% CI 68.8–70.2%) vs. 81.4% (95% CI 81.1–81.9%), 60.6% (95% CI 59.9–61.3%) vs. 74.1% (95% CI 73.5–74.6%) and 54.2% (95% CI 53.1%-55.0%) vs. 69.8% (95% CI 68.8–70.9%) (p<0.001) as demonstrated in Figure 6-2.

**Table 6-2|** Attrition, lost to follow-up and death rates per 100 person-years, by advanced HIV disease status

| | AHD[a] at re-engagement (15983 person-years) | | No AHD[b] at re-engagement (10051 person-years) | | Incidence rate ratio (95%CI) | *P* value |
|---|---|---|---|---|---|---|
| | N | Rate (95% CI) | N | Rate (95% CI) | | |
| **Death** | 471 | 2.95 (2.70–3.22) | 134 | 1.33 (1.13–1.58) | 2.21 (1.82–2.67) | <0.001 |
| **LFU[c]** | 1408 | 8.81 (8.38–9.26) | 604 | 6.01 (5.56–6.49) | 1.46 (1.33–1.61) | <0.001 |
| **Attrition** | 1879 | 11.76 (11.27–12.26) | 738 | 7.34 (6.85–7.87) | 1.61 (1.47–1.74) | <0.001 |

[a] Advanced HIV Disease (N=4,672); [b] No Advanced HIV Disease (N= 2,963); [c] Lost to follow-up after re-engagement

## 6.4.2 Predictors of attrition among patients who re-engage with AHD

Among PLHIV who re-engaged in care with AHD, being male (adjusted hazard ratio (aHR) 2.63, 95% CI 1.31–5.26; p=0.006), working as a SW (aHR 7.49, 95% CI 2.29–22.52; p<0.001), or having a diagnosis of tuberculosis when re-engaging in care (aHR 2.26, 95% CI 1.23–4.14; p=0.008) predicted mortality (Table 6-3). Those with a history of intravenous drug use were identified as having an almost 2-fold higher hazard of being LFU (aHR 1.94; 95% CI 1.54–2.46; p<0.001) compared to those with no history of intravenous drug use (Table 6-4). In comparison with those who were 16–40 years old, children who re-engaged with AHD at 6–15 years of age and those re-engaging at 41–65 years of age had a lower hazard of being LFU (aHR 0.24, 95% CI 0.009–0.66 and aHR 0.77, 95% CI 0.62–0.95; p=0.016).

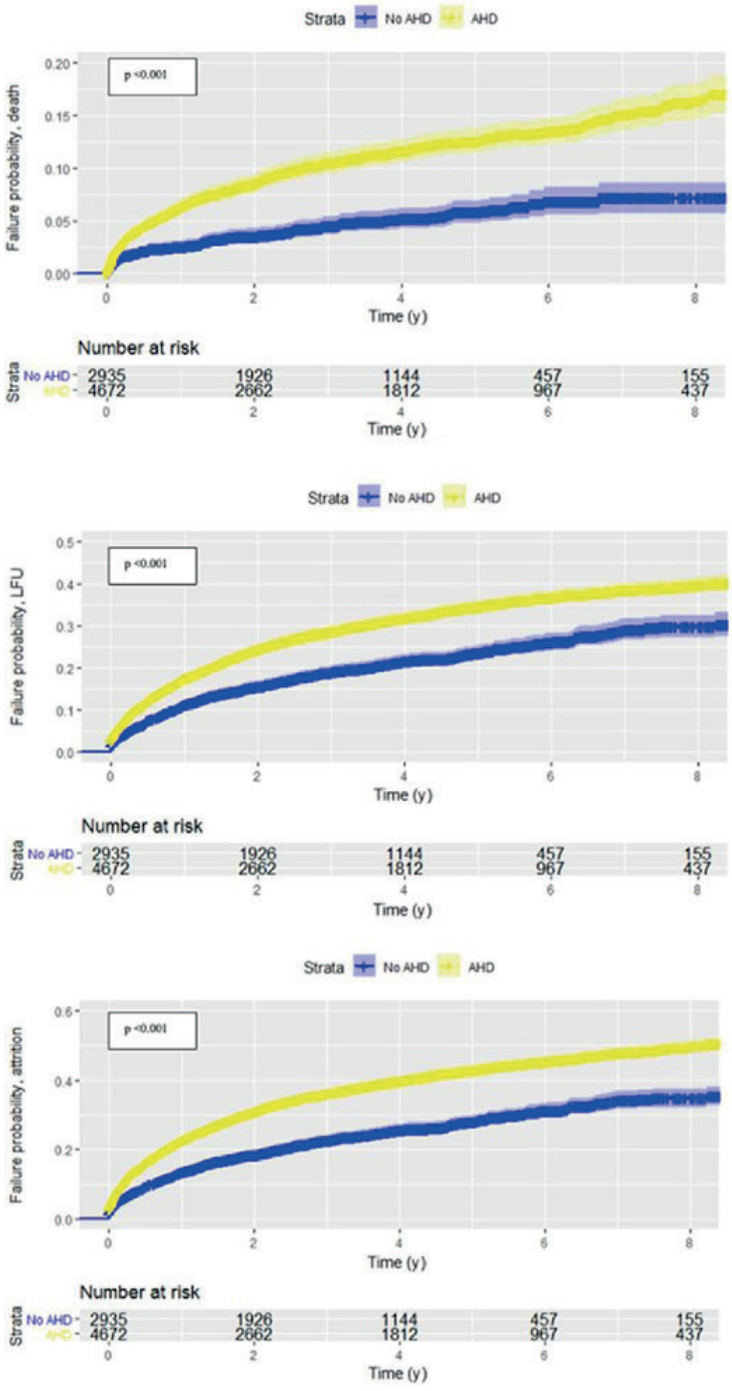



**Figure 6-2|** Kaplan-Meier curves for death (top), lost to follow-up (middle) and attrition (bottom) by advanced HIV disease status (n=7,608)

**Table 6-3|** Risk factors for dying among PLHIV re-engaged in care with advanced HIV disease

| | Died (n=471)[a] | | Cox regression | | Multivariable Cox regression | |
|---|---|---|---|---|---|---|
| | n | % | Hazard ratio | P value | Adjusted Hazard ratio | P value |
| Gender | | | | | | |
| Female | 129 | 7.5 | Reference | | Reference | |
| Male | 342 | 11.6 | 1.72 (1.41–2.13) | <0.001 | 2.63 (1.31–5.26) | 0.006 |
| Age Group (years) | | | | | | |
| 6–15 | 4 | 2.7 | 0.24 (0.09–0.63) | | NA[b] | |
| 16–40 | 333 | 10.0 | Reference | | Reference | |
| 41–65 | 1,172 | 11.4 | 1.21 (0.99–1.48) | <0.001 | 1.82 (1.01–3.28) | NS[c] |
| >65 | 0 | 0.0 | NA[b] | | NA[b] | |
| Marital Status | | | | | | |
| Married | 258 | 9.9 | Reference | | Reference | |
| Separated | 51 | 12.9 | 1.43 (1.06–1.94) | | 1.11 (0.43–2.87) | |
| Single | 105 | 9.4 | 1.02 (0.81–1.28) | 0.059 | 1.02 (0.53–1.95) | NS[c] |
| Widow | 45 | 9.8 | 0.93 (0.68–1.28) | | 0.52 (0.16–1.75) | |
| Profession | | | | | | |
| Business | 50 | 9.9 | Reference | | | |
| Transportation | 17 | 10.5 | 1.12 (0.65–1.95) | | | |
| Administration | 16 | 11.7 | 1.30 (0.74–2.28) | | | |
| Manual labor | 90 | 11.7 | 1.38 (0.98–1.95) | 0.179 | NA[d] | |
| Student | 3 | 4.9 | 0.48 (0.15–1.54) | | | |
| Unemployed | 90 | 9.9 | 1.03 (0.73–1.45) | | | |
| Other | 171 | 9.4 | 1.05 (0.77–1.44) | | | |
| PWID[e,f] | 20 | 3.0 | 2.08 (1.23–3.50) | 0.006 | 0.66 (0.27–1.61) | NS[c] |
| Imprisonment[e] | 3 | 2.8 | 0.26 (0.08–0.80) | 0.019 | 1.74 (0.40–7.50) | NS[c] |
| SW[e,g] | 14 | 17.1 | 10.84 (6.03–19.5) | <0.001 | 7.49 (2.29–22.52) | <0.001 |

| | Died (n=471)[a] | | Cox regression | | Multivariable Cox regression | |
|---|---|---|---|---|---|---|
| | n | % | Hazard ratio | P value | Adjusted Hazard ratio | P value |
| Economical migrant[e] | 5 | 5.2 | 0.54 (0.23–1.31) | 0.175 | NA[d] | |
| Blood transfusion[e] | 2 | 3.6 | 0.31 (0.08–1.23) | 0.095 | 0.85 (0.12–6.32) | NS[c] |
| HIV positive partner[e] | 3 | 0.9 | 0.07 (0.02–0.22) | <0.001 | 0.56 (0.16–1.94) | NS[c] |
| Tuberculosis[e] | 118 | 15.8 | 1.82 (1.48–2.24) | <0.001 | 2.26 (1.23–4.14) | 0.008 |
| Cryptococcosis[e] | 3 | 14.3 | 2.74 (1.02–7.32) | 0.045 | NA[b] | |
| Cytomegalovirus[e] | 4 | 26.7 | 1.56 (0.50–4.84) | 0.446 | NA[d] | |

[a] Death was not observed among participants with talaromycosis, men having sex with men, and those registered through the mother-to-child prevention program; [b] Not applicable due to small number of events; [c] Not significant (p>0.05); [d] Not applicable due to p>0.10; [e] Binary variable; [f] People who inject drugs; [g] Sex Worker

**Table 6-4|** Risk factors for being lost to follow-up among PLHIV re-engaged in care with advanced HIV disease

| | Lost to follow up (N=1,408)[a] | | Cox regression | | Multivariable Cox regression | |
|---|---|---|---|---|---|---|
| | n | % | Hazard ratio | P value | Adjusted Hazard Ratio | P value |
| Gender | | | | | | |
| Female | 462 | 26.9 | Reference | | Reference | |
| Male | 946 | 32.0 | 1.32 (1.18–1.48) | <0.001 | 1.05 (0.85–1.29) | NS[b] |
| Age Group (years) | | | | | | |
| 6–15 | 23 | 15.3 | 0.42 (0.28–0.63) | | 0.24 (0.09–0.66) | |
| 16–40 | 1,091 | 32.6 | Reference | | | |
| 41–65 | 293 | 25.0 | 0.8 (0.7–0.91) | <0.001 | 0.77 (0.62–0.95) | 0.016 |
| >65 | 1 | 25.0 | NA[c] | | NA[c] | |
| Marital Status | | | | | | |
| Married | 746 | 28.7 | Reference | | Reference | |
| Separated | 150 | 38.0 | 1.45 (1.22–1.73) | | 1.46 (1.09–1.95) | |
| Single | 368 | 32.9 | 1.24 (1.09–1.4) | <0.001 | 1.15 (0.94–1.42) | NS[b] |
| Widow | 120 | 26.1 | 0.87 (0.72–1.06) | | 0.84 (0.61–1.15) | |
| Profession | | | | | | |
| Business | 134 | 26.5 | Reference | | Reference | |
| Transportation | 43 | 26.5 | 1.05 (0.74–1.48) | | 0.61 (0.31–1.21) | |
| Administration | 37 | 27.0 | 1.11 (0.77–1.6) | | 0.99 (0.55–1.81) | |
| Manual labor | 252 | 32.6 | 1.43 (1.16–1.76) | 0.04 | 1.17 (0.84–1.62) | NS[b] |
| Student | 13 | 21.3 | 0.77 (0.43–1.36) | | 0.61 (0.21–1.71) | |
| Unemployed | 256 | 28.2 | 1.09 (0.88–1.34) | | 1.06 (0.77–1.45) | |
| Other | 591 | 65.0 | 1.33 (1.1–1.61) | | 1.20 (0.89–1.61) | |
| PWID[d,e] | 250 | 38.1 | 2.6 (2,23–3.04) | <0.001 | 1.95 (1.54–2.46) | <0.001 |
| Imprisonment[d] | 25 | 22.9 | 0.71 (0.48–1.06) | 0.093 | 0.77 (0.48–1.28) | NS[b] |
| MSM[b,d] | 9 | 28.1 | 1.27 (0.66–2.45) | 0.48 | NA[d] | |
| SW[d,f] | 26 | 31.7 | 1.64 (1.11–2.43) | 0.013 | 1.22 (0.54–2.76) | NS[b] |
| Economical migrant[d] | 36 | 37.1 | 1.33 (0,96–1.85) | 0.091 | | |
| Blood transfusion[d] | 9 | 16.4 | 0.47 (0.24–0.9) | 0.022 | 0.71 (0.35–1.45) | NS[b] |
| Mother-to-child prevention[d] | 4 | 6.1 | 0.16 (0.06–0.44) | <0.001 | NA[c] | |
| HIV positive partner[d] | 68 | 19.9 | 0.55 (0.43–0.7) | <0.001 | 0.69 (0.22–2.15) | NS[b] |
| Tuberculosis[d] | 241 | 32.3 | 1.12 (0.98–1.29) | 0.100 | 0.98 (0.76–1.25) | NS[b] |
| Cryptococcosis[d] | 6 | 28.6 | 1.03 (0.46–2.29) | 0.949 | NA[g] | |
| Cytomegalovirus[d] | 3 | 20.0 | 0.67 (0.22–2.09) | 0.446 | NA[g] | |

[a] There were no events observed among participants with talaromycosis; [b] Not significant (p<0.05); [c] Not applicable due to small number of events; [d] Binary variable; [e] People who inject drugs; [f] Sex Worker; [g] Not applicable due to p>0.10

## 6.5 Discussion

Almost one-third of PLHIV in our cohort were LFU at least once during the 15 years of follow-up period. More than half of the LFU cohort re-engaged in care. At the time of the re-engagement, they were presenting with high burden of AHD. Our study results demonstrate consistently higher attrition rates over time for those re-engaging with AHD. Death and LFU rates among PLHIV who re-engaged with AHD were significantly higher when compared to those who re-engaged in a better immunological and clinical condition.

In most HIV programs, the frequency of treatment interruptions is very likely underestimated. A study from South Africa showed that one-fourth of PLHIV disengaged from care at least once during a study period of more than ten years, and that one-third re-engaged in care [14]. In Uganda, during seven years of follow-up, disengagement from care was less frequent (11.2%) and more than 70% returned to care. The authors explain the high proportion of re-engagement by the performant tracing system [17]. Similarly, in our setting, tracing of LFU patients was established from the start of the program and it contributed to re-engagement. A study from a rural community in Kenya reported that 77% of PLHIV disengaged at least once from care, with some patients interrupting treatment up to seven times [15]. In our study, we observed up to two episodes of being LFU. After re-engaging in care, about one-fourth disengaged from care again. The majority of the study participants were diagnosed with AHD before interrupting care. Another 10% experienced clinical and/or immunological deterioration after disengaging from care, which on average lasted over 500 days. Repetitive disengagement and a high burden of AHD show that barriers to care are not yet well addressed. Patients on lifelong ART need to overcome psychosocial and structural barriers to pill intake on a daily basis [18]. Even when appointments are spaced, patients still must invest time and money to stay in care. Besides health-system-driven interventions, such as spacing and tracing, programs may also need to consider patient-driven interventions that build on social networks within communities [19]. Experiences from high HIV prevalence settings show that retention in community-based HIV programs is high [20, 21]. Various interventions have been suggested as enablers for linkage to HIV care among those diagnosed with HIV, but there is a lack of evidence on the specific interventions for those who disengaged from care [22]. Additional evidence is needed to identify reasons for delayed re-engagement. Tailored but feasible and cost-effective approaches for earlier linkage to care need to be evaluated. In a study from Zambia, Zanolini et al. reported a negative impact of health providers' attitudes, described as unfriendly or disrespectful, on retention and re-engagement in care [23]. Therefore, some programs started with the implementation of "Welcome Back" differentiated services targeting specifically those who are re-engaging in care [4, 24]. Among those who re-engaged with AHD, key populations were at risk of having an unfavorable outcome. People with a history of drug use had an

almost two times higher hazard of being LFU after re-engagement and SWs were seven times more at risk of dying. Stigma, discrimination, criminalization of sex work and drug use challenge adherence and may delay re-engagement among those LFU, and consequently increase the risk of AHD and higher attrition after re-engagement, as recently reported in a review by Chen, Q., et al [25]. Our program was not designed to provide differentiated care adapted to the specific needs of key populations. Furthermore, in our context, key populations are often mobile and their working hours impede easy access to care. There is a longstanding debate whether HIV care for key populations should be provided integrated, as part of HIV services for the general population, or whether they would be better served by a vertical set-up, involving peer health care workers and providing care at a venue where they feel the most comfortable [26]. Myanmar reports a high burden of HIV among key populations [26]. The National HIV Strategic Plan recommends differentiated service delivery models adapted to both health and social needs of key populations, while building on community engagement and peer support [27]. Implementation of those interventions should be seen as a priority by the national program and its partners in Myanmar.

Effective AHD management requires diagnostic capacity. CD4 testing remains critical for the diagnosis of AHD and subsequent screening, prophylaxis, diagnosis, and treatment of opportunistic infections. Since the implementation of "Treat All", access to CD4 testing has reduced in many HIV programs [4]. A study from Uganda reported a persistent high burden of AHD, which can only be identified by measuring the number of CD4 cells (24% of tested with a CD4 cell count <200 cells/$mm^3$ and 83% presenting with WHO stage I or II). Unfortunately, CD4 testing coverage at enrollment decreased from 73% in 2013 to 21% in 2018, following the introduction of the "Test and Treat" policy [28]. In our cohort of PLHIV re-engaging with care with AHD and available baseline results, 44.5% had a CD4 cell count <200 cells/$mm^3$, but the majority were diagnosed with WHO stage III or IV at the same time, which could be explained by the ART experience and WHO stage diagnosis from the first ART initiation.

In order to achieve "95-95-95" UNAIDS targets, it is important to continue scale up of access to decentralized HIV care in Myanmar and to expand access to AHD care services. As ART cohorts in Myanmar grow and age, differentiated service delivery will allow stable patients to access ART closer to home, while clinic-based care can prioritize AHD management [3, 29].

In our cohort, one-third of PLHIV were diagnosed with tuberculosis at the time of their re-engagement. Tuberculosis is known to be the most frequent cause of mortality among PLHIV and in our study, the mortality hazard was two-fold higher in those co-infected with tuberculosis [3, 6]. Cryptococcal meningitis, another important cause of mortality, was registered in a small number of study participants, lower than what was reported in other

resource-limited settings [5, 6]. We speculate that the real prevalence in our cohort was much higher than reported. It is probable that this diagnosis was not rigorously recorded in the electronic database. In order to monitor and evaluate and subsequently adapt HIV services, it is necessary for the national programs to set targets and develop indicators focusing on the implementation of AHD package of care [7].

Our study has some important strengths. The findings represent the reality of a large long-term HIV program in the Southeast Asian context. We focus our reporting outcomes of PLHIV re-engaging in care, which was not extensively studied in this region. However, there are also several limitations. Firstly, our retrospective study used routinely collected program data, which may have introduced information bias. This was mitigated by involving a team of data clerks in data management, including prospective data encoding and periodic data cleaning. Reporting bias might have occurred as PLHIV in this setting tend to underreport certain risk behaviors due to stigma and criminalization of these activities. This may have resulted in an underestimation of the frequency of such risk behaviors, which in turn may have affected our regression analyses. Data collection on opportunistic infections was disproportionally affected by missingness. We may have underestimated disengagement from care, as short interruptions were not identified, and we may have underestimated re-engagement in care, as those who silently returned to care in the same health facility (as newly registered patients) or self-transferred to another health provider were not accounted for. The study highlights areas of future research to investigate predictors of AHD among PLHIV who re-engage in care, to help identify at-risk groups who can be targeted or prioritized in provision of AHD package of care. Furthermore, studies to assess specific reasons for unfavorable outcomes within these specific populations (children, elderly, key populations) to gain information how to tailor AHD and re-engagement interventions would support health providers.



## 6.6 Conclusions

Adequate response to AHD remains an important component of the HIV epidemic control. Our study shows that re-engagement in HIV care, after a period of temporary disengagement, is frequent, and that those who re-engage carry a high burden of AHD in this context. In this population, interventions that enable earlier linkage to care, followed by prompt identification and management of AHD, are necessary since having AHD is associated with a higher risk of attrition. As key populations may be disproportionally affected by HIV, in settings where the HIV prevalence is high in this group, HIV care needs to include differentiated approaches, adapted to their specific needs. Such approaches will need to include a comprehensive clinical and social care package for the prevention, diagnosis and management of AHD.

## 6.7 Declarations

Authors' contributions: AM, TH, AL, and TD conceptualized and designed the study. AM and TH contributed to study implementation. AM, TH, PT, HTM, TTT, AAK, MP, and SS contributed to implementation of the study. TH was responsible for the data analysis. All authors participated in the data interpretation. AM drafted the original manuscript. All authors had major contributions to manuscript writing and all approved the final version of the manuscript.

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Competing interests: Authors have no competing interests to declare.

Ethical approval: The study was approved by the Institutional Review Board, Ministry of Public Health and Sports, Myanmar (Ethics/DMR/202/128). It fulfilled the exemption criteria set by the MSF independent Ethical Review Board (ERB) [30] for a posteriori analyses of routinely collected clinical data and thus did not require MSF ERB review. Exemption from the review by the MSF ERB for retrospective analyses of routinely collected data requires informed consent for secondary use of their data to have been given by patients in MSF program at the time of the enrollment in care. All medical records and data were fully anonymized before we accessed them for this analysis.

Data availability statement: The study was set up in the Médecins Sans Frontières' (MSF) HIV Program in Myanmar. MSF's ability to work in all settings, including unstable and conflict-affected countries, is based on impartiality and trust. Relinquishing control of sensitive patient data from named countries/regions to be used in non-approved ways, with no oversight around how this data may be interpreted, may jeopardize MSF relationships and thus our ability to access all contexts. Furthermore, MSF are a data controller subject to the EU GDPR and UK GDPR. This regulation requires that MSF adhere to the principles of data protection, including: fair, lawful and transparent processing, and purpose limitation. In order to adhere to these requirements, all processing must have a lawful basis (and condition for special categories data), which need to be assessed on a case-by-case basis prior to sharing any information. The principle of purpose limitation requires that any further processing of the data collected needs to have a similar purpose/objective to the

original project/purpose. Again, this requires an assessment on a case-by-case basis. In order to adhere to the "transparent" aspect of the first principle, MSF need to communicate to data subjects how their information will be shared, and open access repositories are not included in the information about potential data sharing. This study used data from the MSF HIV Program in Myanmar – a vulnerable population in a named program, involving highly sensitive data that has the potential to cause real harm to individuals if it was to get into the wrong hands. Whilst we have taken steps to fully anonymize the dataset, this anonymization process has different levels and has not been undertaken with the aim of making these datasets open access. MSF is committed to evidence-based practice, and strongly believes in ethical and lawful data sharing if that sharing will ultimately benefit wider society, which will need to be assessed per request. Requests for this data can be made via data.sharing@msf.org. The requestor will be required to complete a form detailing the proposed use of the data, and this will be reviewed by the MSF Research Committee on a case-by-case basis.

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# Chapter 7 |

## General Discussion

In this chapter, I have summarized the findings of all the studies included in the thesis and discussed the implications for programmatic and clinical monitoring in HIV cohorts with a special focus on Myanmar. Further, I have presented the strengths and limitations of the work done, and finally, outlined ideas for future research.

## 7.1 Monitoring of virological outcomes

Achievement of the virological suppression is key to the success of ART in an individual and for public health. Therefore, VL monitoring is considered as the main tool to assess if the desired response is achieved. Most frequently, programs report virological outcomes as part of the last "95" of the global 95-95-95 targets. I investigated virological outcomes among PLHIV receiving first- and second-line ART by standard and alternative methodologies. The thesis provides recommendations on how to adapt clinical and programmatic virological monitoring in cohorts with high burden and limited resources.

### 7.1.1 Viral load cascade

According to the WHO guidelines, all PLHIV on ART should receive a VL test six months after they initiated ART and then yearly [1]. If the VL test shows detectable viremia >1,000 copies/mL, enhanced adherence support should be applied, followed by repeated VL testing after three to six months. If the second VL confirms viremia >1,000 copies/mL, switching the ART regimen should be considered. Regular access to VL testing for PLHIV on ART, timely review of the test results by clinicians, followed by appropriate actions taken, are necessary to achieve the full potential of applying the VL cascade. In the studied first-line ART cohort in Myanmar, multiple gaps across the VL cascade were identified [2]. Among 71% of PLHIV who accessed VL testing, 14% experienced at least one episode of viremia >1,000 copies/mL, but only 62% of those received a second VL test. However, a high proportion of confirmed virological failure occurred among those who had their follow-up test (57%). According to the current guidelines, all the latter should be switched to second-line treatment, but in the studied cohort this occurred only in 66% of the cases. In 2009, VL testing targeted only those with immunological and/or clinical failure [3]. From 2016 onwards, yearly routine monitoring was recommended for all PLHIV on ART. Additionally, the threshold to declare failure has been changing over time. From 2009 until 2012 the threshold was defined as viremia >5,000 copies/mL and only after 2012 the threshold of >1,000 copies/mL was introduced [4]. Described gaps of the VL cascade in the studied ART cohort in Myanmar showed that the national and international guidelines on virological monitoring in place before 2016 fell short of reaching their targets.

The VL cascade is not just about the coverage. Utilization of test results and appropriate actions taken are equally important. In Chapter 4, where we described CV among PLHIV

on second-line ART, we identified that 40% of PLHIV who experienced a CV (***viremic time)*** [5]. Only a minority of those were switched to third-line ART in the studied cohort, despite repeated VL test results with high viremia. Findings from our studies are supported by similar examples. A study from Swaziland reported an increase of follow-up VL coverage to 84% in recent years; however, the proportion of patients with confirmed virological failure switched to second-line ART remained low (43.2%) [6]. A study from sub-Saharan Africa identified poor access to VL testing as the main reason for a delayed switch to second-line treatment. Moreover, when the results were available, they were poorly utilized: 40% of patients with virological failure were not switched to second-line ART, whereas 30% had been switched without proof of failure [7]. A recent review of the literature reported 66% (38–77%) uptake of follow-up VL tests among PLHIV with initially elevated results, 62% (50–75%) of confirmed treatment failure among those with a follow-up test and only 45% (36–71%) switching rate among those with confirmed treatment failure [8]. In Myanmar, studies performed by the NAP reported high rates of virological failure, but low rates of switching to second-line treatment [9]. A qualitative study explored risk factors for having a suboptimal VL cascade in the public system in Myanmar and attributed it to both patient and health system factors: lack of knowledge about the benefits of VL monitoring, concerns about adherence or pill burden, financial or social challenges to reach the testing site as well as lack of training among health care providers, delayed reporting of the results and centralized decision-making [10]. The cost of second-line treatment was also prohibitive in the past, being 2.5 times more expensive than first-line therapy at the time [11].



Improper management of patients with treatment failure leads to poor treatment outcomes, accumulation of mutations conferring resistance, transmission of resistant-HIV strains and increases cost of HIV care delivery. A study from Myanmar reported that one-third of PLHIV who did not switch their treatment after being diagnosed with virological failure, died or were LFU from care, highlighting well the importance of timely switching [9]. Making a clinical decision about switching the regimen, especially among patients who receive treatment with a high genetic barrier to resistance[1] (e.g. based protease inhibitors or dolutegravir), is very challenging. There is evidence that PLHIV might successfully re-suppress after enhanced adherence counselling; however, in many programs, this part of the VL cascade is not well recorded [12]. Only confirmed HIV drug resistance should be an indication for treatment change. HIV drug-resistance testing is recommended to distinguish between viremia caused by treatment failure due to suboptimal adherence and treatment failure due to HIV drug resistance. For the first type of patients, ART regimen change is not needed and may even cause harm, as in the long run, a precious treatment option might be lost. Only for the latter group, a switch of ART regimen is justified. Because of

1 The genetic barrier to resistance is considered as the number of mutations in a therapeutic target required to confer a clinically meaningful loss of susceptibility to the specific drug.

very limited access to HIV drug-resistance testing as part of the routine clinical care, even for PLHIV on second-line treatment, many patients continue the same treatment regimen, despite long-term viremia [13]. Innovative tools, which measure exposure to antiretroviral drugs in serum or in urine, were studied in South Africa to predict the selection of HIV drug resistance. These novel screening strategies can effectively be used to differentiate causes of treatment failure (suboptimal adherence versus HIV drug resistance) and to help improve clinical decision-making about the need to perform HIV drug-resistance testing and treatment regimen change [14-16].

To be able to adapt clinical and programmatic virological monitoring, it is necessary to know which subpopulations are at the highest risk of unfavorable virological outcomes. Risk factors for virological failure and CV among PLHIV on ART [2, 5] have been presented in Chapters 3 and 4 of this thesis, respectively. The definition of virological failure differs between high-resource and low-resource settings. The former defines virological failure based on a threshold of viremia ranging between 50–200 copies/mL [17, 18], while a higher threshold of VL >1,000 copies/mL is recommended by WHO for the public health approach in low-resource settings [3]. Having a history of low-level viremia (defined as detectable viremia <1,000 copies/mL) was associated with a higher risk of virological failure in our study. In the studied HIV cohorts, a high proportion of PLHIV on ART experienced low-level viremia. There is an increasing body of evidence that low-level viremia is associated with unfavorable treatment outcomes [19-22]. Based on these findings, the last WHO guidelines recommended enhanced adherence support and more frequent monitoring for PLHIV who experience low-level viremia. PLHIV with tuberculosis co-infection were identified with higher hazards of virological failure in the first-line ART cohort. Moreover, the odds of having CV were four times higher among those on lopinavir/ritonavir treatment in comparison with those on atazanavir/ritonavir second-line ART [5]. In addition to more frequent adverse events and higher pill burden in the lopinavir/ritonavir cohort, which can contribute to higher viremic time, this specific treatment is indicated for those with tuberculosis co-infection [23]. Our findings about tuberculosis co-infection as a predictor of virological failure and CV are consistent with existing evidence that advanced HIV disease strongly predicts treatment failure [24-27].

Countries have been implementing VL monitoring since the last two decades; however, the findings of this thesis demonstrate that implementation of the VL cascade continues to be a major challenge. Scale up of ART in the public sector in Myanmar started in 2014, hence with a delay as compared to many other countries and global achievements. Due to lack of infrastructure and health care workers the NAP has been struggling to implement routine VL testing, with the highest burden of HIV among key populations and in the remote areas of the northern states. VL testing is still limited to centralized laboratories based in the

two major cities, Mandalay and Yangon. Myanmar has a comparable HIV epidemic profile with some of its neighboring countries (e.g. Thailand, Vietnam, Cambodia) that started HIV response earlier and could provide lessons learnt for innovative and decentralized approaches necessary to improve VL coverage in Myanmar. In remote settings in Vietnam, using dried blood spot (DBS) sampling for specimen collection improved access for VL testing among key populations [28]. Additionally, to expand access to VL monitoring, the WHO has recommended point-of-care (POC) testing in priority groups [29]. A recently published study from Yangon showed that POC testing could improve indicators along the VL cascade in Myanmar. POC testing could be replicable in the less-accessible areas of the country [30].

As access to routine VL testing remains suboptimal, it is not sufficient to only report the proportion of PLHIV with a suppressed VL (standard indicator as part of the global targets). VL coverage, for example, might vary among different sub-populations and each program should collect more granulated information about access to VL testing. A recent review highlighted that certain subgroups might be more affected when the VL monitoring fails, and these same subgroups are often at a higher risk of having unfavorable virological outcomes [8]. From the studies conducted in low- and middle-income countries, the review reported a VL coverage between 25% and 95% among adults, 2–94% among children, adolescents and young people, and 32–84% among pregnant women [8]. Only with in-depth information, programs can develop strategies to improve coverage, which can include targeted resources to specific subpopulations, decentralization, or POC services. This thesis highlights the importance of conducting the VL cascade analysis, which can support efforts to improve quality of care, including awareness among PLHIV and health care providers, clinical training for improved utilization of VL test results, better access to various ART regimens and use of innovative tools that can support clinical decision-making.



The frequency of VL monitoring plays a role in detection of viremia and actions taken to control it. Less frequent assessment of virological status is related to longer periods of viremia and missed opportunities to improve adherence, which in turn lead to deterioration of health, increased risk of HIV drug-resistance and increased transmission risk [31, 32]. Understanding the risk factors for unfavorable outcomes (virological failure and/or CV) in each cohort can support clinicians and programs to organize care for those at higher risk differently, including provision of differentiated approach for VL monitoring that can include more frequent VL tests, enhanced adherence, and psychosocial support and, if necessary, immediate switch of ART regimen. Increasing evidence about the impact of the most recent low-level viremia on health outcomes questions the currently used threshold for the definition of virological failure in resource-limited setting and further studies should evaluate which cut-off is epidemiologically and clinically the most relevant.

### 7.1.2 HIV viremia: cross-sectional versus longitudinal measures

In Chapter 3 we presented a study in which we measured the burden of HIV viremia by using standard indicators: proportion and incidence of virological failure (HIV viremia >1,000 copies/mL) [2]. The results presented were: 14% of study participants experienced virological failure, with an overall incidence of 2.5 per 100 person-years. These results are comparable with the findings from other settings [16, 24, 33, 34] and from other HIV cohorts in Myanmar [35]. However, these standard indicators of HIV viremia do not reflect the entire period that an individual is in a state of suppressed or unsuppressed viremia. This is a major shortcoming of the cross-sectional viremia indicators, as they do not consider the fact that PLHIV, while being on treatment, may transition from being suppressed to being unsuppressed and vice versa. To overcome this issue, CV indicators were introduced two decades ago.

Chapter 4, ***viremic time***, describes the use of our own method to calculate CV in a cohort of PLHIV on second-line ART. In this cohort 60% of PLHIV never experienced viremia during their follow-up time [5]. Among those who did, 12.5%, 15.8%, 5.9% and 5.35% experienced viremia during 1–19%, 20–49%, 50–79% and ≥80% of their follow-up time on second-line ART, respectively. Moreover, there were 51 participants who were viremic on each of their VL test results (100% of their follow-up time). Unpublished programmatic data of the same cohort reported a level of suppression at 95% (MSF project report December 2019, internal document). The cross-sectional programmatic indicator, which looked at the proportion of people with suppressed viremia on their last VL result, failed to reflect that some of the PLHIV transition from one viremic state to another and created an impression of a better overall suppression rate in the cohort. Overestimated virological suppression has individual and public health consequences. It may result in missed opportunities to improve individual health, and may result in ongoing HIV transmission [36, 37].

Others have also studied CV in their settings. Chapter 5 presented synthetized published evidence on the burden of cumulative HIV viremia [38]. A recurrent finding, across the 26 studies included in the systematic review, was that despite the most recent VL result, a vast majority of the PLHIV experience some level of CV while being on ART. Furthermore, CV was studied as a predictor of health outcomes. Chapter 4 presented results of the association between mortality and CV (***viremic time***) in the Myanmar cohort and showed that PLHIV who experience viremia >50% of their follow-up time on ART carry an almost three times higher risk of mortality, when compared to those who do not experience viremia [5]. Multiple studies included in the systematic review, as presented in Chapter 5, reported an association between CV and all-cause mortality, although our review did not confirm that CV outperforms predictability of a current or last VL result [38]. CV predicted mortality when it was high or when it was calculated using VL results from the most recent period

(not longer than three years). The lack of prognostic value of distant viremia could partially be explained by the effect of highly active ART in patients with HIV susceptible to the regimen prescribed, reversing the risk of opportunistic infections or immune activation [39, 40]. Similarly, when the viremia calculation only included viremia <1,000 copies/mL, it did not predict mortality [41, 42]. One possible underlying hypothesis why low-level CV is probably not associated with mortality is frequent lack of increased inflammatory markers in patients with low-level CV [43, 44]. While shorter periods of CV do not increase the risk of death, those who are viremic may successfully continue their daily life and contribute to HIV transmission in their communities, especially in periods when their viremia exceeds 1,000 copies/mL [45]. On the basis that HIV replication is an important factor of chronic inflammation, HIV has an impact on atherosclerosis and oncogenesis in aging PLHIV [46, 47]. Chapter 5 reported that CV strongly predicted cardiovascular diseases. Moreover, it acted as an independent risk factor for Burkitt, Hodgkin lymphoma and squamous cell anal cancer, but not CNS-related lymphoma, breast, or hepatocellular carcinoma. The lack of an association with having any type of malignancy emphasized the complexity of oncogenesis and the yet not fully understood role of HIV replication in it.

The most frequently used methods to express CV are variations of VCY, which estimates the area under a patient's VL curve [48] and a proportion of follow-up time on ART under or above a certain VL threshold [5, 49]. VCY is defined as the number of copies of HIV-1 RNA per mL per year circulating in plasma and integrated over the number of years from ART initiation (or another specific point of time) and is calculated based on trapezoidal estimation. It represents the area under patients' longitudinal VL curve; therefore, it combines level of viremia and its duration.



As being the most used method to express CV, its limitations are also well studied. Firstly, the term of CV was utilized differently by different researchers in terms of using copies/mL versus $\log_{10}$ copies/mL, different handling of lower and upper limit of viremia detection and non-standardized follow-up duration. Secondly, most of the studies measured CV by first summing VL values on a linear scale, followed by a log-transformation of the cumulative measure, which is a method prone to confounding and does not reflect the log-linear nature of the relationship between CV and clinical events [50]. Lesosky et al., demonstrated that CV for PLHIV with more spaced VL measures tends to be biased upwards [51]. They demonstrated that sampling frequency bias led to inaccuracy, which could especially affect study populations with longer exposure to ART and more frequent periods with reduced treatment adherence [51]. The authors argue that even within a single study, CV is more reflective of sampling frequency bias than any underlying biological mechanism, unless VL testing is done with the same timing and frequency for every individual. Therefore, any comparison of CV among the studies needs to be undertaken with caution.

To overcome complex calculation methods, we applied a simplified method for calculation of CV, by using data available in the real-life setting. We defined CV as a proportion of the follow-up time that the patient was viremic (>200 copies/mL), a concept which may be more directly interpretable in the program setting. To avoid frequency bias, and to limit the power of assumptions related to the long periods of time between two VL tests, each VL result was assigned a period of six months maximum. By the same method, we controlled assumptions about viremia during LFU period [5]. However, limitations of our method have not yet been studied. In addition, we did not compare if viremic-time outweighs the mortality-predictive value of the last VL result, nor did we compare its performance with any other method. Nonetheless, since our data come from the cohort, which in the studied setting received priority in VL monitoring, we cannot completely exclude frequency bias, described as a limitation of CV calculation.

To summarize, CV is a measure, which captures the full VL trajectory over time and as such could be used by the programs to assess the overall success of the ART. Moreover, it could improve identification of those who need to be targeted for prevention, screening, and early management of different co-morbidities. Longitudinal quantification of HIV viremia could be a long-desired indicator for quality of HIV care. However, future work is necessary before deciding whether and which specific CV indicator is indeed a better prognostic measure in clinical and programmatic settings in comparison with cross-sectional VL results. Unfortunately, methods to express HIV CV are not yet adapted for use in a programmatic setting. They are complex, prone to biases and confounding and moreover different, which limits the comparability of the results. The vast majority of studies on HIV CV were performed in high-resource settings and in a research environment. Methodological approaches to calculate CV need to be improved, simplified, and standardized for systematic use in program setting, while in the meantime, we continue to use “current VL result” for clinical decision-making and programmatic monitoring.

## 7.2 Monitoring of disengagement from and re-engagement with HIV care

PLHIV who regularly attend their clinical, laboratory or ART collection appointments are usually considered as retained in HIV care while on ART. With the increasing lifespan of HIV cohorts, cyclical nature of the HIV-care retention is more common: PLHIV disengage from care for a short or long period, followed by re-engagement. HIV care for these populations can be challenging due to pre-existing ART exposure and HIV drug resistance, and frequent re-engagement with AHD. Studies examining retention in HIV care often capture cross-sectional status and there is limited evidence on the effect of the cyclical

nature of retention on health outcomes. In the thesis (Chapters 3 and 6), I first investigated how frequently PLHIV disengage from and re-engage with HIV care in the Myanmar cohort and then I assessed what is the association between disengagement and health outcomes after re-engagement. The thesis provides recommendations on how to adapt clinical and programmatic monitoring to improve care for those who re-engage with HIV care.

### 7.2.1 Frequency of disengagement from and re-engagement with HIV care

A high burden of disengagement from care was seen in the studied Myanmar cohorts. Chapter 3 demonstrated the frequency of disengagement from HIV care by proportion of PLHIV with a history of LFU and as a cumulative disengagement from care [2]. The study included PLHIV in the Myanmar cohort who had access to VL testing. The proportion of PLHIV with a history of LFU is an indicator reported by most of the HIV programs, where LFU is defined as being disengaged from care >60 days from the next-appointment date. Ten percent of the cohort with a history of LFU, and 0.4% PLHIV experienced three or more episodes of LFU during the observation time. Furthermore, in the daily clinical practice we observed that many PLHIV present late for their scheduled appointments, but the delay is short and does not qualify for the programmatic definition of the LFU. Such delays are not part of the standard monitoring and are usually not reported. In the study, we presented an indicator to measure these shorter, but often more frequent, temporary disengagements from HIV care. ***Cumulative appointment delay*** was presented as a sum of the number of days of delay between the date of an appointment and an actual date the visit took place. In the studied cohort, 87% of PLHIV experienced some cumulative delay. A quarter of the cohort was cumulatively delayed for their appointments 60 days or longer, while 6.6% of the cohort had cumulative delay >365 days.

Further, the study presented in the Chapter 5 included a larger population of the Myanmar cohort and it reported almost one-third of the overall cohort with a history of at least one episode of LFU, while being on ART [52]. In this study, we were further interested in the frequency of re-engagement with care and reported that 62% of the disengaged cohort returned to care. Among the latter, one-quarter was LFU again. Programs report disengagement from care between 11–77% [53-56], but the lack of standardized definitions impedes comparisons between these studies [57]. In addition, the results demonstrated that retention, described by a cross-sectional measurement of the number and proportion of LFU, very likely underestimates the total burden of disengagement from HIV care, because PLHIV frequently re-enter care or they experience shorter disengagements. A study from a rural community program in Kenya reported 77% of PLHIV disengaged at least once from care, with some patients interrupting care seven times [56]. Experience from a large long-term HIV program in South Africa showed that almost a one-quarter of PLHIV disengaged from care at least once during a two-year follow-up period, with a third that subsequently

re-engaged in care [53]. In Uganda, rates of LFU were lower at 11.2% and more than 70% of the cohort re-entered HIV care again [54]. A study from USA that explored beyond binary retention in HIV care presented that among PLHIV disengaged for 1, 2, and ≥3 episodes, 34%, 14%, and 3% returned to care, respectively [58]. In our study, re-engagement with care was high because of well-set-up tracing system for LFU patients, established from the start of the program.

Our findings highlighted a need to correctly estimate the burden of disengagement from care, as currently used cross-sectional indicators of LFU rates might not be able to reflect the real situation. By knowing how frequently PLHIV exit HIV care, for how long they remain disengaged, how many return to care and what is their health status at re-engagement will help programs to develop strategies for improved retention in care and earlier linkage to care after disengagement.

### 7.2.2 Health outcomes after re-engagement with HIV care

As a continuum of the work presented in the previous paragraph, health outcomes among those who re-entered care after a period of disengagement were explored. Firstly, the interest was to assess how disengagement from care predicts virological failure in a long-term first-line ART cohort. Results presented in Chapter 3 showed that a history of LFU was associated with increased hazards of virological failure after returning to care. Similar findings were demonstrated in other settings. People with a history of LFU have often challenges with adherence to treatment and these challenges remain after returning to care, predisposing for HIV viremia, frequently with HIV drug resistance and treatment failure [24, 25, 33, 59-61]. Secondly, based on the finding that majority of the study population experienced a delay in attending their appointments, the interest was to assess if cumulative appointment delay >60 days predicts virological failure. Even though the association was positive in the univariable analysis, in the multivariable Cox regression analysis we failed to confirm prediction role of the cumulative appointment delay. There are possible explanations for such a finding. Individual appointment delays were short and PLHIV in the Myanmar cohort were supplied extra pills to avoid any further interruption. Therefore, appointment delay did not necessarily indicate suboptimal adherence or treatment interruption. Second, a categorical variable fitted the final regression model better; however, others should consider trying a different threshold of cumulative appointment delay, which might have a different effect on treatment outcomes. Despite not being able to demonstrate the association between cumulative appointment delay and risk of treatment failure, the findings could still support the need for monitoring appointment delays in a long-term HIV cohort. Short disengagements can be associated with treatment interruption that could be avoided by better understanding the reasons for delay. Moreover, with adapted treatment delivery, patients at risk for a short appointment delay can avoid treatment interruptions

if they are identified and provided with an extra supply of the medications, as was done in Myanmar.

As demonstrated in the Chapter 6, PLHIV who re-engaged with HIV care carried a high burden of AHD (61%). In a majority of those, AHD was diagnosed before the period of disengagement; however, 10% progressed to AHD during their LFU period. The mean time to re-engagement was longer among those who had AHD in comparison with PLHIV re-engaging in better clinical and immunological state (907.8 (SD 804.3) days versus 541.5 (SD 579.7) days; p<0.001). In the early stages of the HIV epidemic, AHD was diagnosed mostly among ART-naïve PLHIV presenting to care in the late stages of their HIV infection ("late presenters"). As access to HIV testing and treatment massively scaled up and the majority of PLHIV start ART in the early stage of HIV infection, most of the PLHIV presenting to care with AHD are those who are already ART-experienced and who are re-entering care after a period of disengagement [62, 63]. In South Africa, the proportion of PLHIV returning to care with CD4 count <50 cells/$mm^3$ increased from 14.3% to 56.7% [64] in the period between 2006 and 2016. In another study from two sub-Saharan African countries, up to 97% of hospitalized PLHIV present with AHD, and only 21–35% were ART naïve [47]. To further emphasize the importance of these findings, risk of subsequent attrition among those re-engaging with and without AHD was estimated. PLHIV who re-engage with AHD have 2.2 and 1.5 higher incidence rate ratio for death and LFU respectively, when compared to those without AHD at re-engagement. Moreover, key populations, men and PLHIV co-infected with tuberculosis were identified as being at high risk of attrition after they re-engaged with AHD.



Frequent disengagement and high burden of treatment failure and AHD after re-engagement demonstrate that barriers to care are not yet well addressed, despite the increasing total global number of PLHIV on ART. To improve retention in care and reduce consequences of disengagement, HIV programs need to invest in implementation of interventions such as appointment spacing, tracing of patients LFU or additional drug supply to support PLHIV who need to overcome multiple psychosocial, financial, and structural barriers to remain in care lifelong. In addition to health-system driven interventions, interventions built on social networks within communities should be part of the care support. Experiences from high-burden settings showed that programs with community-engagement have high retention in care [65, 66]. Additionally, interventions widely implemented to enable linkage to HIV care among those who are newly diagnosed with HIV might not be effective for the population that was enrolled in care already. Reasons for delayed linkage to care among this specific population are not yet fully understood and can vary according to the setting. In a study from Zambia, health providers' attitudes, described as unfriendly or disrespectful, had a negative impact on retention and re-engagement in care and this knowledge supported

some programs to pilot "Welcome Back" differentiated services specifically targeting those who are re-engaging in care [62, 67, 68].

PLHIV who re-engage with care carry a high burden of AHD. Therefore, HIV programs should be well equipped to implement the WHO recommended package of care for AHD, not just for newly diagnosed patients, but for everyone who is starting ART. Effective AHD diagnosis requires access to CD4 testing. In our study cohort (Chapter 5) almost half of the participants diagnosed with AHD were diagnosed by a CD4 test result <200 cells/mm$^3$. Unfortunately, after the successful launch of the "Treat All" policy and emphasis on virological monitoring, access to CD4 testing reduced in many HIV programs. As an example, from Uganda, CD4 testing coverage at ART initiation decreased from 73% in 2013 to 21% in 2018. In addition to CD4 testing, screening, diagnosis and treatment of opportunistic infections in an essential part of care for those re-engaging with care. In the cohorts studied in this thesis, one-third of PLHIV were diagnosed with tuberculosis before starting ART, and this co-infection was associated with higher hazards of virological failure and it carried double the hazards of mortality among re-engaging population. Strategies for screening, early diagnosis and treatment of the most prevalent opportunistic infections have been part of the WHO guideline on AHD [69].

Virological monitoring of PLHIV who return to care should be adapted due to the increased risk of virological failure, as demonstrated in this thesis. Enhanced adherence support, frequent VL tests and HIV drug-resistance testing should be part of the differentiated care for this population. In settings with no access to HIV drug-resistance testing, delay of ART regimen change is frequent. Current guidelines advise the regimen to be switched only after two consecutive VL test results >1,000 copies/mL with at least three months of enhanced adherence counselling between the tests. Delayed switch to effective life-saving ART is particularly problematic in patients in AHD and AHD is highly prevalent among those who re-engage with care. A modelling study demonstrated that use of a single VL result >1,000 copies/mL to define virological failure in PLHIV with AHD lead to reduction of deaths [70]. Based on these findings, faster switch of the ART regimen among PLHIV who return to care, and who present with high viremia after re-introduction of ART, should be evaluated in the presence of AHD. With the scale up of treatment regimens with high genetic barrier (regimens based on dolutegravir), re-evaluation of this approach and investment in strategies that will allow improved clinical detection of HIV drug resistance would be required.

AHD is the main reason that decrease in HIV-related mortality has been much slower than anticipated [26]. Despite efforts to scale up access to adequate AHD care, programs do not have clear targets for the successful implementation. In addition, programs lack standardized

indicators to systematically monitor and evaluate the burden of AHD in their settings and its impact of mortality and morbidity among specific populations. Based on the findings from our research, adding targets for CD4 testing and for screening, diagnosis, and treatment of opportunistic infections to the global 95-95-95 targets is proposed. Implementing these targets would support HIV programs to develop country-specific interventions that would support optimal AHD care.

### 7.2.3 Key populations

Key populations (people who inject drugs, sex workers, men having sex with men) were not specifically targeted in the objectives of the thesis, nor were the studies set up in a setting with an HIV cohort that provided differentiated service delivery for these groups. Using the available programmatic data, we were not able to accurately estimate the number of patients per different key population group. This is because we recorded their key population status only at the start of ART, which could change over the study period. Furthermore, key populations might not report their status accurately, given the hostile environment in the society towards these groups. However, it was important to give additional attention to some of the results related to these vulnerable populations.

In the study that explored CV among PLHIV on second-line ART, sex workers and people who inject drugs were associated with odds of higher viremia twice as high as compared to those who did not report being engaged in sex work or injecting drugs (Chapter 4). Moreover, in the study that explored AHD among those who re-engage with HIV care, sex workers with AHD at re-engagement were associated with higher hazards of dying and people who inject drugs re-engaging with AHD were associated with higher hazards of subsequent LFU (Chapter 6).

Key populations are disproportionately affected by the HIV epidemic in Myanmar, carrying the highest burden in the country [71, 72]. Multiple social barriers and punitive laws and policies, such as criminalization of sex work, same sex activities and drug use, as well as the presence of compulsory detention centers for PWID do not provide an enabling environment for HIV response [73]. In the studied context, key populations are often mobile, and their working hours or practices impede regular access to care. In addition, stigma, discrimination, marginalization and criminalization of these populations and their practices challenges adherence to treatment, retention and re-linkage to care, and it increases their risk of unfavorable health outcomes, including treatment failure and advanced HIV disease [74]. Awareness about HIV status among key populations has been traditionally low: 27.9% among PWID, and 41% and 31% among FSW and MSM, respectively. Access to prevention services remains limited and ART coverage in these groups remains suboptimal. In 2020, 21.9%, 44.1% and 59.1% of PWID, MSM and FSW, respectively, were receiving HIV treatment

[75]. The national strategic plan increases focus on these priority populations [20]. Several efforts are being made, by the national or international NGOs, to tackle the concentrated epidemic among these groups, specifically strengthening harm reduction and preventative services, the essential services are still not widely available or easily accessible.

To be able to address specific health and psychosocial needs of the key populations, the WHO recommends differentiated service delivery models that would integrate comprehensive prevention and treatment services [76]. Services could be integrated in general HIV care or provided through a vertical approach. It is certain that peers need to play an important role in implementation and provision of care, ideally where these populations feel the most comfortable, depending on the setting. Findings presented in this thesis highlight that adapted virological monitoring should also apply to key populations, considering the higher risk of viremia among these groups. Moreover, the results indicate the need to emphasize services that will enable better retention in care among these groups as well as faster linkage to care after disengagement. With the high burden of AHD among these populations, an AHD package of care should be an essential part of any health service that targets these highly vulnerable populations.

Myanmar is surrounded by countries that share a similar HIV epidemic profile and are already engaging in tailored HIV response for key populations. Thailand, where sex work remains illegal, was the first country to introduce a 100% condom use program, with the support from authorities, public health offices, brothel owners, and sex workers. Implementation of the policy resulted in a continuous decline of HIV prevalence among this population, since the 1990s [77]. Over the last decades, the Vietnam national HIV program with their partners have developed new community outreach approaches to expand and integrate harm reduction and HIV care strategies targeting PWID. Their strategies emphasize integrated services, providing access to HIV testing, prevention, as well as harm reduction activities, such as needle exchange and opioid substitution therapy. With these, the prevalence of HIV among PWID in the country decreased from 29.3% to 9.3% during the period between 2001 and 2018 [78-80]. Experiences from these countries could be used to adapt Myanmar's HIV response in the future, although this would require strong national commitment and improved access to the international resources.

## 7.3 Programmatic implications of the thesis findings

Myanmar is the least developed country in the Southeast Asia with the lowest total health expenditure in the Asia Pacific region (1.7–2.3% of its gross domestic product between 2001 and 2014). More than 60 years of internal conflict, military rule, and international sanctions have affected the country's economic growth and development, as well as its

capacity to respond to the overwhelming public health needs [81]. HIV response between 2001 and 2014 was completely dependent on international NGOs, which experienced multiple challenges to operate under the military government. International HIV funding of the public sector at the time was very limited. With the change of political context in 2014, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) grant allowed a massive scale-up of access to HIV services in the public sector. Since 2018, the NAP Myanmar started a gradual transfer of all PLHIV from the private to the public HIV services. These milestones are important, but do not necessarily reflect the capacity of the program to absorb large numbers of patients. In addition, political commitment, available human resources, infrastructure and international funding, all necessary to support the efforts to control the HIV epidemic in the country, have been declining since the last change in the political context in 2022.

The MSF program, which provided the setting for the studies included in the thesis, is the longest-running HIV program in the country. It is also a well-resourced program, with sufficiently good data quality. Many lessons were learnt in the MSF HIV program, creating a unique opportunity for the national program to use the lessons to adapt their approaches with the aim of HIV care sustainability and improvement. Some of these lessons learnt are shared in this thesis. The findings reported in this thesis could help HIV programs in resource-limited settings, like Myanmar, to adapt their programmatic and clinical monitoring strategies with the purpose of overcoming some of the main challenges faced by the HIV care providers: provision of lifelong good quality HIV care and differentiation of services to respond to the needs of specific subpopulations. Implications of these findings are summarized in Tables 7-1 and 7-2.



Assessment of the virological status of PLHIV on ART will remain the cornerstone of treatment success monitoring and evaluation of the overall program quality. To maximize the effect of VL testing, HIV programs need to adapt how they monitor their VL cascade performance and how their clinicians utilize test results. More granular information about each step of the VL cascade in different settings and among specific subpopulations will help programs to better understand the gaps and to adapt their strategies to specific needs. Strategies to include better VL coverage are usually related to increased resources, but also decentralization of VL testing. POC testing, especially if implemented together with task sharing, has shown to improve virological suppression and retention in care [82]. To further improve performance along the VL cascade, strategies are being developed that can help patients to better understand the importance of treatment adherence and virological monitoring, and that result in a more active role in the management of their disease [83, 84]. Programs should invest in understanding which setting-specific groups are at higher risks of unfavorable outcomes and why. As reported in this thesis, in Myanmar these populations

include PLHIV with AHD, key populations and those returning to care after disengagement. If resources for routine VL testing remain limited in Myanmar, the program can use this information to adapt their VL testing strategy and prioritize VL testing for groups with the highest risk of treatment failure, and other unfavorable outcomes.

Implications of our findings regarding cross-sectional versus longitudinal virological monitoring are less explicit than what we aimed for. Introduction of cumulative HIV viremia indicators would help clinicians and programs to better estimate individual and public health benefits of ART. However, these indicators are not yet validated for routine use in programmatic settings. They need to be standardized and simplified to allow for systematic utilization in the future. In the meantime, it is important to have access to timely available cross-sectional VL results for clinical decision-making and programmatic monitoring of HIV care quality.

Studies of the thesis were conducted in an era that HIV treatment regimens were based on a combination of NRTIs and NNRTIs for first-line and NRTIs and PIs for the second-line ART. Since 2018 WHO recommends the gradual introduction of an integrase strand inhibitor, DTG, as the cornerstone of first- and second-line treatment. DTG based regimens increase likelihood of achieving virological suppression, when compared to non-DTG containing ART [85]. DTG has a higher genetic barrier to resistance. Lack of viral suppression during DTG-based treatment is mostly due to adherence issues and not resistance. DTG is more robust than NNRTIs. Non-adherence resulting in viremia during NNRTI-based treatment often results in resistance. Recently presented updated results of the ADVANCE trial show that adherence support among those with viremia, while being on DTG-based regimens, lead to fast and effective re-suppression in 95% of participants, avoiding switching to another treatment regimen [86]. With these findings recommendations for virological monitoring and management of treatment failure will likely be adapted, with strong emphasis on psychosocial support and enhanced adherence counseling. However, understanding of gaps along the cascade of care and routine VL monitoring and possibly differentiated viral load monitoring will still be needed. Moreover, in the era of regimens with a strong genetic barrier it would be even more important to understand the use of cumulative viremia. How much and how long cumulative viremia can be tolerated without a major impact on resistance selection and individual and public health outcomes remains to be studied.

Lifelong retention in HIV care is globally challenging. PLHIV frequently exit and re-enter care. This non-binary retention in care has implications on individual health status, but also on services that need to be provided to this specific population. Currently used cross-sectional monitoring of disengagement from care, e.g. measuring the proportion LFU, does not reflect the reality of disengagement. Programs should monitor disengagement from care longitudinally and details on frequency and duration of any type of disengagement (delayed

for an appointment or LFU), as well as the frequency of re-engagement can highlight the real burden and provide more information for the programs to adapt their strategies for effective HIV care delivery.

Health status of PLHIV who re-enter care should be systematically monitored. This is because PLHIV who re-engage in HIV care carry a high burden of AHD, high risk of virological failure and subsequent attrition. To respond to specific needs of this population, programs will need to implement differentiated care packages that include strategies for improved engagement in HIV services and promote long-term retention in care. High burden countries with much longer and stronger HIV response have already recognized the challenge of long-term retention in care. South Africa reports a steady increase in percentage of people who had started treatment but are no longer receiving it. Based on these observations the national programme developed specific strategy to improve retention in care and to encourage re-engagement ("Welcome Back Campaign Strategy") [86]. Moreover, the full package of care for AHD for all PLHIV who (re)initiate ART needs to be available, including CD4 testing, screening, diagnosis and early treatment of opportunistic infections. Targets and indicators to monitor implementation of the package of care for AHD should be added to routine program monitoring. Furthermore, VL monitoring needs to be adapted as PLHIV with a history of disengagement often carry a high risk of suboptimal adherence, but also HIV drug resistance. Therefore, more frequent VL monitoring, adherence support, but also access to HIV drug-resistance testing and adapted regimen-switch strategies need to be included in the national guidelines for these populations.



Depending on the setting, certain populations can be more vulnerable. HIV control requires adapted strategies fitting the needs of these subgroups. In the setting of Myanmar, these are the key populations. They carry the highest HIV burden yet have the lowest ART and VL coverage in the country. They are stigmatized, marginalized and criminalized, which makes delivery of HIV services more complicated. Differentiated service delivery, driven by peers and provided within the community is key. Integration of preventive, treatment and psychosocial services is crucial when implementing HIV care for these specific groups. These strategies are part of the Myanmar National HIV Strategic Plan but are yet to be implemented.

Experiences from the neighboring countries, but also achievements from the high burden countries with generalized epidemic in Sub-Saharan Africa, demonstrated that only with a strong political commitment, strong public health sector, community engagement and collaboration with the partners (national and international NGOs), as well as commitment to generate data for evidence driven policies and guidelines, multiple challenges in the HIV response can be overcome.

**Table 7-1|** Summary of thesis findings implications for an HIV program: monitoring of viral load cascade and retention in care

| Monitoring of the viral load cascade | Differentiated viral load cascade based on risk assessment | Monitoring viremia: cross-sectional versus longitudinal | Monitoring of disengagement from care |
|---|---|---|---|
| Stratified monitoring of VL coverage by region (central versus remote) and population groups (e.g. key populations, PLHIV with AHD, PLHIV re-engaging to care).<br><br>Analyze success of each step of the VL cascade to identify the gaps: coverage, utilization of test results, ART switch practices.<br><br>Develop strategies that will improve the VL cascade: POC testing, simplified sampling, training of staff, information/education of PLHIV, improve access to second/third-line ART. | If capacity for VL monitoring is low or if high-risk groups are identified, adapt frequency of VL testing for PLHIV with high risk of unfavorable virological outcomes: PLHIV re-engaging with care, PLHIV with AHD, key populations.<br><br>Adapt ART regimen switch for PLHIV with higher risk of HIV drug resistance or mortality.<br><br>Consider use of innovative tools to improve clinical decision-making (e.g. POC tests to measure exposure to ART). | Utilize recent VL results for timely clinical decision-making.<br><br>Engage in research to study use of cumulative viremia in the program setting. | Monitor frequency and duration of any type of disengagement from care.<br><br>Monitor frequency and duration of the appointment delay for re-engagement with care.<br><br>Analyze effects of different disengagement patterns on health outcomes and adapt program strategy to mitigate those (e.g. flexible drug supply, investment in re-linkage to care services) |

*ADH: advanced HIV disease; ART: antiretroviral treatment; PLHIV: people living with HIV; VL: viral load; POC: point-of-care*

**Table 7-2|** Summary of thesis findings implications for an HIV program: specific groups

| PLHIV re-engaging with care | Key populations |
|---|---|
| Monitor cyclical nature of the retention in care.<br>Reinforce capacity of the program to diagnose and manage<br>AHD at the re-engagement (CD4 testing, OI testing).<br>Introduce indicators that would support monitoring of AHD package of care implementation (e.g. access to CD4 testing).<br>Prioritize VL monitoring after re-engagement and improve access to HIV drug-resistance testing and switching practices.<br>Develop strategies to encourage improved retention (e.g. community engagement, peer support) and earlier linkage to care after re-engagement (e.g. welcome clinics). | Monitor who are the PLHIV in your cohort: collect data on key population status and assess their specific needs.<br>Develop strategies to implement differentiated service delivery for key populations based on integration of services, community engagement and peer support.<br>Integrate the full package for AHD care in care models.<br>Prioritize VL monitoring, combined with tailored adherence and psychosocial support. |

*ADH: advanced HIV disease; PLHIV: people living with HIV; VL: viral load; OI: opportunistic infections*Strengths and limitations

## 7.4 Strengths and limitations

Research included in this thesis had its strengths and limitations. The major strength was the use of routine programmatic data, which reflects the reality of a large, long-term HIV program in the Southeast Asian resource-limited context. Observational periods in our studies were long (from 2 to 17 years), allowing sufficient time for observed outcomes to occur. Complete data on appointment delays and LFU were available, despite secondary origins. In the studied cohorts, HIV care was comprehensive and there was a high coverage of VL testing and sufficient expertise and diagnostic capacity to diagnose AHD. This allowed an in-depth analysis of unfavorable outcomes.

However, several methodological shortcomings affected the robustness of the findings. Specific methodological limitations were described in detail in Chapters 3, 4, 5 and 6. Hereby, we outline the general shortcomings. Firstly, three studies applied a retrospective cohort design; therefore, we were not able to prove causality, but only evidence for, and the strength of associations between, selected exposure variables and the studied outcomes. Originally, we aimed to set up prospective cohort studies to investigate research questions. Approvals from the NAP and ethical review board (ERB) in MSF were obtained for these studies. However, we were not able to receive the national ERB approval due to the COVID-19 pandemic, followed by the political change in the country, which led to a complete collapse of the health system, including the research institutions responsible for ERB approvals. These institutions were still not functional at the time of thesis writing and prospective research, performed by NGOs, is not allowed under the current government.

We have used programmatic data prone to missing values, which could potentially cause bias in our analyses. Each of the studies was transparent about the number of missing values for different variables. In each study, we assumed the data to be missing completely at random, and we did not observe whether missingness caused selection bias. Instead, complete-case multivariable analyses were performed. This is a frequently used strategy to deal with missingness, although it can be inefficient and biased if ***missing at random assumption*** is violated. Complete-case analyses are considered unbiased when missingness is independent of the outcome and measured covariates. An alternative approach to overcome the issue of missing data would be to use an imputation technique or the “missing indicator technique”, which uses “missing” as a category of the analysis. In consultation with statisticians and considering the large size of our study populations and the complexity of these techniques, it was decided to avoid these alternative methods and to perform complete-case analyses instead.

Routine collection of program data may have introduced information bias. This was mitigated by involving a team of data clerks in data management, including prospective data encoding and periodic data cleaning. Assessment of the specific characteristics related to lifestyle behavior—men having sex with men, sex work and people who inject drugs—was done at the baseline only and the possible change of the status over time was not recorded. Moreover, reporting bias occurred as PLHIV in this setting tend to underreport their risk factors due to stigma and criminalization of their activities. This underestimated the prevalence of specific behaviors and their association with the primary outcomes.

In programmatic settings it is often difficult to differentiate the outcomes of LFU versus mortality, because of lack of reliable death registries. Despite the strong outreach component of the programme, where the cohort studies were conducted, and the programme's aim to differentiate LFU from death in PLHIV disengaged from care, ascertainment that attrition was due to LFU rather than death was not always possible.

A number of characteristics associated with virological failure were not recorded in our database, which could be a source of residual confounding. Inability to include data on adherence and participation in enhanced adherence counseling in our analyses is likely to have resulted in unadjusted confounding affecting the results, when virological outcomes were studied. Adherence is the most important predictor of treatment failure and the inability to include it in the risk assessment in our study presents a major limitation. Furthermore, we did not adjust for clustering, as the data on household membership, community- or clinic-level were not available in the dataset.

Fractional logistic regression was used to show odds ratios for viremic time in a population of PLHIV on first-line ART, based on the assumption that "when the conditional mean of our outcome is interpretable as a probability, it is possible to transform coefficients to odds-ratios" [85]. However, the proportion of viremic time (our outcome studied) might not be directly translated to being at risk of having viremia (at any given time), as not everyone was followed-up for equally long. Only under the assumption that people's follow-up time is independent of their viremia status and the reported covariates would the interpretation be technically correct. In practice, the impact of this is likely negligible, but it was not checked in our analyses.

Lastly, of the studies included only PLHIV from Myanmar and is unlikely to be representative of more geographically dispersed groups, limiting the generalizability of the findings included in this thesis.

## 7.5 Future research

Additional research questions were identified with the purpose to support the findings presented in this thesis and to complement some of the gaps that the studies included were not able to address. Firstly, to support standardization and to improve consistency of CV indicators, methodological processes for managing sources of biases and confounding should be further studied. Studies exploring the use of more frequent VL testing should be able to obtain a more accurate estimate of CV less prone to sampling frequency biases. However, increasing the sampling frequency might be specifically challenging in settings where access to VL is limited, therefore the optimal frequency of VL monitoring to accurately estimate CV should be explored. As CV could be an important estimate to measure the success of HIV control at the community level, analysis of CV among PLHIV on ART, combined with social and behavioral data could help to estimate potential HIV transmission from people who are already in care. Lastly, as CV could be a valuable indicator in identifying people at higher risk of CVD and malignancy, the relationship between CV and inflammatory biomarkers and markers of immune system activation should be further explored. Understanding better how appointment delay is correlated with unfavorable health outcomes should increase our understanding about strategies on how to reduce the frequency of any treatment interruption. In the years to come it is essential to have a better understanding of the reasons why PLHIV disengage from care and why they delay their re-engagement. Based on these findings, specific strategies need to be developed.

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# Chapter 8 |

## Conclusion

Better access to HIV testing and improved treatment have allowed HIV programs to grow in terms of numbers of PLHIV on ART and the lifespan of their cohorts. The main challenges faced by HIV care providers have now shifted towards the provision of long-term good quality HIV care and differentiation of the public health approach to service delivery considering the needs of specific subpopulations.

HIV care continuum is usually presented as a linear path: from HIV diagnosis to maintained virological suppression, while being on ART. However, in real-life scenarios, PLHIV, while on ART, may transition between virologically suppressed and unsuppressed statuses and the VL result captured at one point of time does not account for those transitions. Longitudinal measures of the virological status could better represent individual and public health response to HIV treatment. Although promising, these measures are not yet developed for systematic use in program settings. While adapting methodological approaches to capture CV, cross-sectional VL remains the best measure of ART success in clinical and programmatic monitoring.

Similarly, retention in HIV care is often presented as a binary measure of programmatic success, while PLHIV on ART disengage from and re-engage with care frequently. Those who re-engage carry a high burden of AHD, which requires special attention in clinical and programmatic responses. Adapting a monitoring approach to capture the cyclical nature of retention will provide valuable information to the programs on how to adapt their services to the needs of PLHIV who re-engage with care.

Research presented in the thesis was set up in the Myanmar context with a high burden of HIV, concentrated epidemic pattern and exceptionally limited resources. This is also a context with delayed response to HIV epidemic in the public sector, compared to global achievements or the epidemic control in the neighboring countries. HIV response in Myanmar has been further compromised by recent changes in the political context in the country. MSF was the largest provider of HIV care in Myanmar for decades and lessons learnt in this program can, hopefully, support the NAP in scaling up HIV care with available resources. To achieve targets reflecting success of HIV epidemic control in Myanmar, the NAP will have to adapt their approaches. While continuing scale up of access to ART in the public sector and advocating for VL monitoring for all PLHIV on ART, the VL cascade will have to be adapted to the available resources, targeting those who are at the highest risk of unfavorable outcomes in this context: PLHIV with AHD, those who re-engage with care and key populations. Increasing burden of disengagement from and re-engagement with care in the country affected by political turmoil should prompt policy makers to emphasize the capacity of the program to improve their response to AHD. Furthermore, Myanmar should adapt some of the successful strategies from its neighboring countries

to improve HIV response among the key populations. This important step for the country would require strong national and international commitment. With the increasing use of DTG-based regimens gaps along the cascade still need to be monitored. A need for routine and, if needed, differentiated viral load monitoring will remain. To assure longevity of DTG-based treatment, it is important to understand how long cumulative viremia can be tolerated without a major impact on resistance selection in individuals and HIV control in communities.

# List of Tables

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# Annexes

## 9.1 Study Supplements

### 9.1.1 Supplement 3-1

**Characteristics of** patients included in multivariable analysis (n = 8,308) compared to the total population on first line ART (n = 35,356) for viral load

| Variable | Value | Included in multivariable analysis (n) | (%) | Not included in multivariable analysis (n) | (%) | *P*-value |
|---|---|---|---|---|---|---|
| Age at ART initiation >19 years | | 7487 | 90.1 | 32387 | 91.6 | <0.001 |
| Gender (Female) | | 3591 | 43.2 | 15749 | 44.5 | 0.031 |
| Divorced | | 1 | 0.0 | 10 | 0.0 | 0.757 |
| Married | | 4530 | 54.5 | 20165 | 57.0 | <0.001 |
| Separated | | 513 | 6.2 | 2178 | 6.2 | 1 |
| Single | | 2101 | 25.3 | 8163 | 23.1 | <0.001 |
| Widow | | 906 | 10.9 | 3927 | 11.1 | 1 |
| Man who has sex with men | | 74 | 0.9 | 250 | 0.7 | 0.092 |
| History of injection drug use | | 391 | 4.7 | 2785 | 7.9 | <0.001 |
| History of sex work | | 169 | 2.0 | 508 | 1.4 | <0.001 |
| Economic migrant | | 161 | 1.9 | 675 | 1.9 | 1 |
| History of imprisonment | | 135 | 1.6 | 515 | 1.5 | 0.401 |
| Baseline body mass index <18.5 kg/$m^2$ | | 1879 | 22.6 | 6829 | 19.3 | <0.001 |
| | Missing | 4714 | 56.7 | 21289 | 60.2 | |
| WHO stage at ART initiation | 1 | 3247 | 39.1 | 11501 | 32.5 | <0.001 |
| | 2 | 327 | 3.9 | 1108 | 3.1 | |
| | 3 | 2958 | 35.6 | 9710 | 27.5 | |
| | 4 | 1776 | 21.4 | 5516 | 15.6 | |
| | Missing | 0 | 0.0 | 7521 | 21.3 | |
| Baseline Tuberculosis | | 2994 | 36.0 | 8754 | 24.8 | <0.001 |
| Baseline CD4 (cells/$mm^3$) | <200 | 5262 | 63.3 | 8434 | 23.9 | <0.001 |
| | 200–500 | 2580 | 31.1 | 4668 | 13.2 | |
| | >500 | 466 | 5.6 | 928 | 2.6 | |
| | Missing | 0 | 0.0 | 21326 | 60.3 | |
| History of low viremia | | 3498 | 42.1 | 9861 | 27.9 | <0.001 |
| Frequency of low viremia | 1 | 2640 | 31.8 | 7423 | 21.0 | <0.001 |
| | ≥2 | 858 | 10.3 | 2438 | 6.9 | |
| History of no treatment change | | 1922 | 23.1 | 11355 | 32.1 | <0.001 |

| Variable | Value | Included in multivariable analysis (n) | (%) | Not included in multivariable analysis (n) | (%) | *P*-value |
|---|---|---|---|---|---|---|
| Time on ART (years) | <2 | 931 | 11.2 | 6773 | 19.2 | <0.001 |
| | 2–5 | 2368 | 28.5 | 11984 | 33.9 | |
| | >5 | 5009 | 60.3 | 16599 | 46.9 | |
| History of lost-to-follow up | | 760 | 9.1 | 3850 | 10.9 | <0.001 |
| Frequency of lost-to-follow up | 1 | 629 | 7.6 | 3176 | 9.0 | <0.001 |
| | 2 | 102 | 1.2 | 512 | 1.4 | |
| | ≥3 | 29 | 0.3 | 162 | 0.5 | |
| Cumulative appointment delay ≥60 days | | 1936 | 23.3 | 8852 | 25.0 | <0.001 |
| Cumulative appointment delay (days) | 1–59 | 5194 | 62.5 | 21507 | 60.8 | 0.03 |
| | 60–181 | 996 | 12.0 | 4492 | 12.7 | |
| | 182–364 | 375 | 4.5 | 1709 | 4.8 | |
| | ≥365 | 565 | 6.8 | 2651 | 7.5 | |

## 9.1.2 Supplement 5-1

**Search strategy**

| Database | Search 07 September 2021<br>*Filters applied: English Language, Date of publication >2007 year* |
|---|---|
| Pubmed<br>HIV: 159,860<br>ART:130,001<br>Viremia: 792<br>Outcomes: 2,436,361<br>Combined:134 | ((“cumulative viremia”) OR (“viral exposure”) OR (“cumulative viraemia”) OR (“viraemia copy-years”) OR (“viremia copy-years”) OR (“viral copy-years”) OR (“copy years viremia”) OR (“copy years viraemia”) OR (“VCY”) OR (“cumulative HIV viremia”) OR (“cumulative plasma HIV burden”) OR (“ viraemia copy years”) OR (“ cumulative viral load”) OR (“cumulative HIV exposure”) OR (“cumulative HIV care measures” [tiab]) OR (“Cumulative HIV Care Metrics” [tiab]))<br>AND<br>((“Antiretroviral Therapy, Highly Active”[Mesh]) OR (Antiretroviral Agents[tiab]) OR (“Anti-Retroviral Agents”[Mesh]) OR (Highly Active Antiretroviral Therapy[tiab]) OR (HAART[tiab]) OR (Anti Retroviral Agents[tiab]) OR (ART[tiab])))<br>AND<br>((HIV infection[MeSH Terms]) OR (HIV infection[tiab]) OR (Infection,HIV[tiab]) OR (AIDS[tiab]) OR (Acquired immunodeficiency syndrome[tiab]))<br>AND<br>((“Treatment Outcome”[Mesh]) OR (mortality[TIAB]) OR (“Lost to Follow-Up”[Mesh]) OR (“death”[mesh]) OR (survival[tiab]) OR (Lost to Follow Up[tiab]) OR (Outcome, Treatment[tiab]) OR (Patient-Relevant Outcome[tiab]) OR (efficacy[tiab]) OR (effectiveness[tiab]) OR (attrition[tiab]) OR (retention[tiab]) OR (Virolog* response[tiab]) OR treatment succes[tiab] OR treatment failure[tiab]) |
| Embase<br>HIV: 379<br>ART:524<br>Viremia: 119<br>Outcomes: 229<br>Combined: 37 | cumulative viremia OR viral exposure OR cumulative viraemia OR viraemia copy-years OR viremia copy-years OR viral copy-years OR copy years viremia OR copy years viraemia OR VCY OR cumulative HIV viremia OR cumulative plasma HIV burden OR viraemia copy years OR cumulative viral load OR cumulative HIV exposure OR cumulative HIV care measures OR Cumulative HIV Care Metrics<br>AND<br>Antiretroviral Therapy OR Antiretroviral Agents OR Anti-Retroviral Agents OR Highly Active Antiretroviral Therapy OR HAART OR Anti Retroviral Agents OR ART<br>AND<br>HIV infection OR AIDS OR Acquired immunodeficiency syndrome OR HIV<br>AND<br>Treatment Outcome OR mortality OR death OR survival OR Patient-Relevant Outcome OR efficacy OR effectiveness OR attrition OR retention OR treatment succes OR treatment failure |

| | |
|---|---|
| Web of Science<br>HIV: 558,945<br>ART: 952,741<br>Viremia:764<br>Outcomes: 5,225,407<br>Combined: 35 | (“cumulative viremia”) OR (“viral exposure”) OR (“cumulative viraemia”) OR (“viraemia copy-years”) OR (“viremia copy-years”) OR (“viral copy-years”) OR (“copy years viremia”) OR (“copy years viraemia”) OR (“VCY”) OR (“cumulative HIV viremia”) OR (“cumulative plasma HIV burden”) OR (“viraemia copy years”) OR (“cumulative viral load”) OR (“cumulative HIV exposure”) OR (“cumulative HIV care measures”) OR (“Cumulative HIV Care Metrics”)<br>AND<br>(“Antiretroviral Therapy”) OR (“Antiretroviral Agents”) OR (“Anti-Retroviral Agents”) OR (“Highly Active Antiretroviral Therapy”) OR (“HAART”) OR (“Anti Retroviral Agents”) OR (“ART”)<br>AND<br>(“HIV infection”) OR (“AIDS”) OR (“Acquired immunodeficiency syndrome”) OR (“HIV”)<br>AND<br>(“Treatment Outcome”) OR (“mortality”) OR (“death”) OR (“survival”) OR (“Patient-Relevant Outcome”) OR (“efficacy”) OR (“effectiveness”) OR (“attrition”) OR (“retention”) OR (“treatment succes”) OR (“treatment failure”) |
| Scopus<br>HIV: 1,014,962<br>ART: 141,591<br>Viremia: 1,280<br>Outcomes: 10,433,130<br>Combined: 30 | (“cumulative viremia”) OR (“viral exposure”) OR (“cumulative viraemia”) OR (“viraemia copy-years”) OR (“viremia copy-years”) OR (“viral copy-years”) OR (“copy years viremia”) OR (“copy years viraemia”) OR (“VCY”) OR (“cumulative HIV viremia”) OR (“cumulative plasma HIV burden”) OR (“viraemia copy years”) OR (“cumulative viral load”) OR (“cumulative HIV exposure”) OR (“cumulative HIV care measures”) OR (“Cumulative HIV Care Metrics”)<br>AND<br>(“Antiretroviral Therapy”) OR (“Antiretroviral Agents”) OR (“Anti-Retroviral Agents”) OR (“Highly Active Antiretroviral Therapy”) OR (“HAART”) OR (“Anti Retroviral Agents”) OR (“ART”)<br>AND<br>(“HIV infection”) OR (“AIDS”) OR (“Acquired immunodeficiency syndrome”) OR (“HIV”)<br>AND<br>(“Treatment Outcome”) OR (“mortality”) OR (“death”) OR (“survival”) OR (“Patient-Relevant Outcome”) OR (“efficacy”) OR (“effectiveness”) OR (“attrition”) OR (“retention”) OR (“treatment success”) OR (“treatment failure”) |

## 9.1.3 Supplement 5-2

*New Castle Ottawa scores for the included studies*

| Author, Year of publication | Selection (max 4)* | Comparability (max 2)* | Outcome (max 3)* |
|---|---|---|---|
| Cates et al., 2015 (27) | **** | ** | * |
| Chirouze et al.,2015 (36) | **** | ** | ** |
| Falasca et al., 2019 (35) | **** | ** | ** |
| Kukoyi et al., 2016 (26) | *** | ** | *** |
| Mugavero et al., (42) | **** | ** | * |
| Pascom et al., (43) | **** | ** | * |
| Quiros-Roldan et al.,2016 (44) | **** | ** | ** |
| Salinas et al., 2016 (32) | *** | ** | ** |
| Sempa et al., (45) | **** | ** | ** |
| Wright et al., (34) | **** | ** | ** |
| Cozzi-Lepri et al., (47) | **** | ** | ** |
| Coburn et al., (38) | **** | ** | * |
| Lima et al.,(41) | **** | ** | * |
| Marconi et al, (28) | **** | ** | ** |
| Delaney et al., (37) | **** | ** | * |
| Kowalkowski et al.,2014 (30) | *** | ** | ** |
| Laut et al.,2016 (40) | **** | ** | ** |
| Wang et al., 2016 (19) | *** | ** | *** |
| Pallela et al.,2021 (31) | *** | ** | ** |
| Zoufaly et al.,2019 (20) | **** | ** | *** |
| Hughes et al.,(39) | **** | ** | ** |
| Chiao et al.,(29) | *** | ** | ** |
| Lesko et al. (46) | **** | ** | *** |
| Elvstam et al. (48) | **** | ** | *** |
| Harding et al. (49) | **** | ** | *** |
| Mesic et al. (33) | *** | ** | *** |

*Interpretation of the score: Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

## 9.2 Abbreviations

| | |
|---|---|
| ADH | advanced HIV Disease |
| aHR | adjusted hazard ratio |
| AIDS | Acquired Immune Deficiency Syndrome |
| AMI | acute myocardial infarction |
| aOR | adjusted odds ratio |
| aRR | adjusted relative risk |
| ART | antiretroviral therapy |
| aSHR | adjusted subhazard ratio |
| ATV/r | Atazanavir/ritonavir |
| BMI | body mass index |
| CI | confidence interval |
| CNS | Central Nervous System |
| CV | cumulative viremia |
| CVD | cardiovascular disease |
| cVL | cumulative viral load |
| DBS | dried blood spot |
| DTG | Dolutegravir |
| EAC | enhanced adherence counseling |
| ERB | Ethical Review Board |
| FSW | female sex workers |
| FUCHIA | Follow-up and Care of HIV Infection and AIDS |
| GDP | gross domestic product |
| GFTAM | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| HCC | Hepatocellular carcinoma |
| HIV | Human Immunodeficiency Virus |
| HL | Hodgkin Lymphoma |
| HR | hazard ratios |
| IQR | interquartile range |
| LFU | lost to follow-up |
| LLD | lower limit of detection |
| LLV | low-level viremia |
| Lop/r | Lopinavir/ritonavir |
| MSF | Médecins Sans Frontières |
| MSM | men who have sex with men |
| N/A | non-applicable |
| NAP | National AIDS Programme |
| NCD | non-communicable disease |
| NGO | Non-Governmental Organization |
| NHL | Non-Hodgkin Lymphoma |
| OR | odds ratios |
| POC | point-of-care |
| PLHIV | people living with HIV |
| PWID | people who inject drugs |
| RR | relative risk |
| SCCA | Squamous cell anal carcinoma |
| SD | standard deviation |
| SE | standard error |
| SMART | Strategic Management of Antiretroviral Therapy |
| SNAE | severe non-AIDS event |
| UNAIDS | Joint United Nations Programme |
| VCY | viremia copy-years |
| VL | viral load |
| WHO | World Health Organization |

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