TRANSITION DYNAMICS AND TREATMENT OUTCOMES AMONG HIV-POSITIVE PATIENTS OF IFAKARA, TANZANIA: A COMPREHENSIVE ANALYSIS FOR OPTIMIZING THE EXISTING LONGITUDINAL COHORT DATA

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the Doctor of Philosophy degree

Johannesburg, 2025

DECLARATIONS

I **Aneth Vedastus Kalinjuma** declare that this Thesis Report is my own, unaided work. It is being submitted for the Degree of **Doctor of Philosophy** at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____ _____

(**Signature of candidate**)

____25_____day of__September_____2025_____in Johanesburg, South Africa

DECLARATIONS ON PUBLISHED ARTICLES

Declaration of co-authors, please see the second appendix in the appendix list

DEDICATION

To my father and mother,

Mr. and Mrs. Vedastus Kalinjuma

PRESENTATIONS ARISING FROM THIS PROJECT

I presented a poster of abstract with the title “Progress of HIV care cascade and transition dynamics along the continuum of care among persons living with HIV in Ifakara, Tanzania: A prospective study” to the 26th Internation Workshop on HIV and Hepatitis Observational Databases (IWHOD) in Portugal (in March 2024) and the National Institute Medical Research (NIMR) 32nd Annual joint scientific conference in Tanzania (May 2024).

PUBLICATIONS ARISING FROM THIS PROJECT

Kalinjuma, A. V., Glass, T. R., Masanja, H., Weisser, M., Msengwa, A. S., Vanobberghen, F., & Otwombe, K. (2023). Statistical methods applied for the assessment of the HIV cascade and continuum of care: a systematic scoping review. *BMJ open*, *13*(11), e071392. https://doi.org/10.1136/bmjopen-2022-071392

ABSTRACT

The in-and-out of care movements at various stages of HIV treatment require a specialized approach for estimating transition probabilities between stages and the association between transitions and characteristics. The multistate models are appropriate for such a problem. However, their application in the HIV cascade and continuum of care is scarce. Furthermore, there are limited assessments of engagement in care in combination with treatment outcomes such as viral load (VL), and cascade assessments at the sub-national level in Tanzania are limited. Therefore, the goal of this project was to investigate the transition dynamics and virologic outcomes among PLHIV enrolled in care at the Chronic Disease Clinic of Ifakara (CDCI), Tanzania, from 2005 to 2024.

The project had two parts: the first was the systematic scoping review of methods applied in evaluating the HIV cascade and continuum of care. In this review, descriptive statistics were used to summarize findings of the scoping review. The second part included the empirical analyses of existing data from CDCI. In these analyses, descriptive statistics, continuous-time non-parametric multistate models, and Cox proportional hazard models were used to evaluate engagement in HIV care and treatment outcomes.

The review showed 93% (279/300) of the articles reviewed applied cross-sectional design methods. Of the 21 articles that used longitudinal design methods, only 6 articles applied multistate models that addressed the cyclical nature of engagement in HIV care. In empirical analyses, the proportion of people living with HIV (PLHIV) initiated on antiretroviral therapy (ART) increased over time from 67% in 2004-2009 to 96% in 2019-2022. Among PLHIV initiated on ART and retained in care, 95% were virally suppressed by September 2022. However, in the longitudinal assessment, at 12 months, 24% were lost to follow-up (LTFU). After being LTFU, 34% returned to care within 12 months. Furthermore, being on ART at baseline was associated with a reduced hazard of LTFU (HR=0.71; 95% CI: 0.67-0.75) and an increased hazard of return to care after being LTFU (HR=1.38; 95% CI: 1.31-1.45). Analyses focused on the test-and-treat period showed that in the first 12 months, 41% of the PLHIV achieved suppressed VL. However, after achieving suppressed VL, the proportion of PLHIV who remained in care with suppressed VL and without other events decreased over time from 73% at 6 months to 2% at 60 months.

Cross-sectional analyses showed a high proportion of VL suppression among PLHIV retained in care, with the UNAIDS VL suppression target being achieved. However, longitudinal

models revealed that many PLHIV transitioned in-and-out of care, and the first 12 months after enrolment and LTFU are important time windows for maximizing retention. The use of longitudinal design methods is growing. Longitudinal HIV continuum of care methodological guidelines will increase the uptake of the advanced methods in different assessments.

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and they made me smile even when the situation was difficult to find a reason to smile. It wouldn't be possible without their support and presence. Sadly, during this Ph.D., we lost two family members, my grandmother, Ma Mariapia Kazinja, and my junior Sister Edina Vedastus Kalinjuma. I pray their souls to rest in eternal peace, and I will always remember them in my prayers.

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NOMENCLATURE

AIDS: Acquired immunodeficiency syndrome

ART: Antiretroviral therapy

BMI: Body Mass Index

CARTA: Consortium for Advanced Research Training in Africa

CDCI: Chronic Diseases Clinic of Ifakara

CI: Confidence interval

Cox Ph: Cox Proportional Hazard model

DELTA Africa: Developing Excellence in Leadership, Training and Science in Africa

Eq: Equation

HIV: Human immunodeficiency virus

HR: Hazard Ratio

KIULARCO: Kilimbero and Ulanga Antiretroviral Cohort

LTFU: Loss to follow-up

NASHCoP: National AIDS, STIs, and Hepatitis Control Program

OpenMRS: Open Medical Record System

PEPFAR: President's Emergency Plan for AIDS Relief

PLHIV: People Living with HIV

SDG: Sustainable Development Goals

UNAIDS: Joint United Nations Programme on HIV/AIDS

USAID: United States Agency for International Development

VL: Viral load

WHO: World Health Organization

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CHAPTER ONE: Introduction

1.0. Overview of the HIV situation

HIV/AIDS remains a disease of public health concern. In 2023, 40 million people were living with HIV worldwide (1). The roll-out of antiretroviral therapy (ART) has contributed to a tremendous change in the HIV epidemic. Worldwide, a remarkable declining trend of annual new infections was observed from 2.1 million in 2010 to 1.3 million cases in 2023, with the highest reduction (62%) found in children (1). Furthermore, the impact is observed in a reduced number of AIDS-related deaths from 1.3 million in 2010 to 630,000 deaths in 2023 (1). In Tanzania, a similar declining trend was observed, with annual new cases reduced from 72,000 in 2016-17 (2) to 60,000 in 2022-23 (3). In 2023, the country recorded 25,000 AIDS-related deaths (4). Currently, Tanzania has a 4% prevalence of HIV among adults, and the annual incidence is 0.18% among adults aged 15 years and above (3). The prevalence varies by region, with the highest prevalence reported in Njombe (13%), Iringa (11%), and Mbeya (10%).

The achievement of a suppressed viral load (VL) is the ultimate goal of HIV treatment programs. However, recent studies have reported that people living with HIV (PLHIV) who achieved viral suppression fail to sustain suppressed VL without experiencing VL rebound or intermittent high VL during follow-up (5,6). Others estimated that less than half (46%) of the PLHIV achieved VL re-suppression after elevated VL (7). A study conducted in South Africa showed that 48% of PLHIV were re-suppressed at a median time of 8 months (8), and Ethiopian study estimated a median of 6 months among newly diagnosed (9). The proportion of viral suppression and time to viral suppression are crucial indicators because many assessments of HIV care cascades show different levels of progress, with some progressing slower than expected (10–12).

1.1. HIV cascade and continuum of care challenges

Based on the progress made, in 2020 the Joint United Nations Programme on HIV/AIDS (UNAIDS) set an interim target of 95-95-95; stating by the year 2025; 95% of PLHIV should be aware of their HIV status, 95% of the PLHIV diagnosed with HIV infection should be initiated on ART, and among those on ART, 95% should be virally suppressed (13). The achievement of this target will allow the accomplishment of Sustainable Development Goal (SDG) 3.3, which aims to end the AIDS epidemic by 2030. The progress of UNAIDS 2020 and now 2025 was monitored and evaluated using the HIV care cascade framework.

The HIV care cascade conceptual framework is a very useful tool for monitoring the uptake of HIV care services (14–16). However, several authors have expressed concerns that despite its usefulness, the cascade does not capture well other patients' behaviors, such as loss to follow-up (LTFU), transfer, re-engagement from LTFU or transfer, and deaths that could explain observed challenges (14,15). Furthermore, Powers and Miller (15) and Blitz et al. (17) argued that the framework contains the underlying assumption of unidirectional flow from HIV infection to suppressed VL. This assumption does not consider the in-and-out of care behavior as depicted in Figure 1.1, which could explain the observed low VL suppression challenges in HIV treatment programs. The in-and-out of care transitions affect treatment adherence, and later the treatment outcomes.

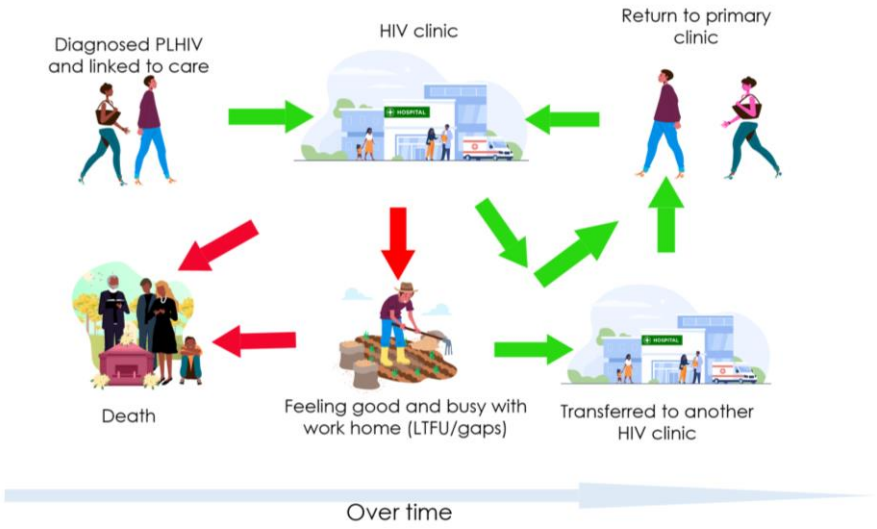

Figure 1.1: A schematic diagram that shows different transitions of PHIV over time

Regular clinic visits and good treatment adherence result in suppressed VL (that is, VL <20 or <50 copies/mL) (18) and improved health status. PLHIV enrolled in care often disengage and later re-engage in HIV care (19,20). Studies conducted in Tanzania, South Africa, and France estimated that 31-55% of PLHIV who LTFU return to care within 1-19 months (21–23). A study done at the Chronic Disease Clinic of Ifakara (CDCI) showed that a proportion of PLHIV enrolled in care experienced multiple LTFU events during follow-up (21). The consequences of transitioning out of care include morbidity, unsuppressed VL, increased risk of onward HIV transmission, and drug resistance (24–26). The achievement of the UNAIDS target of 95% viral suppression is also challenged by the existence of in-and-out of care transitions.

1.2. Research gaps

The in-and-out of care movements at various stages of HIV treatment require a specialized approach for estimating transition probabilities between states and the association between various transitions and characteristics (27). Even though the multistate Markov model was developed in the past four decades, its application in the HIV continuum of care is sparse, mostly because it's demanding in terms of data management and the analysis requires advanced skills in statistics (28,29). Few studies have used the multistate modeling approach and mainly focused on engagement and retention in care (14), testing and disengagement rates (30), engagement and state transitions (31), longitudinal care experience accounts for different transitions along the HIV care cascade (32), and mortality and ART initiation delays (33). However, assessments of engagement in care status in combination with treatment outcomes, such as suppressed VL or immune responses are scarce (34).

Information about the HIV care cascade assessments, especially for clinic-specific and transition probabilities along the continuum of care is even more limited in rural Tanzania. This information is crucial because from October 2017, the country rolled out the "treat all" strategy and routine VL testing for monitoring HIV progression and treatment outcomes. So far, no study has been conducted to investigate the state transition dynamics in the HIV cascade and continuum of care and treatment outcomes at the sub-national level in Tanzania, specifically in Ifakara. Therefore, this project aims to investigate the transition dynamics and virologic outcomes among PLHIV enrolled in care at the Chronic Diseases Clinic of Ifakara (CDCI), Morogoro, Tanzania, from 2005 to 2024.

1.3. Specific objectives

1. To conduct a systematic literature review of statistical methods used in the assessment of the HIV care cascade and continuum of care.
2. To describe the transition dynamics along the HIV cascade and continuum of care of PLHIV enrolled in CDCI, Tanzania, between 2005 and 2022.
3. To model transition probabilities along the HIV care cascade and continuum care among PLHIV enrolled in care at the CDCI, Tanzania, between 2005 and 2022.
4. To assess the treatment outcomes and engagement in care, and factors associated among PLHIV enrolled in care at the CDCI, Tanzania, between 2017 and 2024.

1.4. Research justification

The lack of program-specific cascade and continuum of care evaluation in Tanzania impedes the planning of program-specific resource allocation and interventions to address the in-and-out of care problem. On the other hand, relying on cascade estimates generated using cross-sectional design methods only is misleading due to the exclusion of PLHIV who are LTFU, dead, or transferred to other HIV clinics. This is because the excluded PLHIV are more likely to experience poor treatment outcomes, drug resistance, and continued HIV transmission due to HIV risk behaviors (35). Recent studies have shown that the achievement of suppressed VL is very likely in PLHIV with treatment compliance. However, sustaining suppressed VL throughout their lifetime is challenging, as a proportion of the PLHIV experienced VL rebound (36–38). Therefore, cross-sectional cascades complemented with longitudinal assessment provide a comprehensive evaluation of the cascade for a focused population for intervention and time to intervene. Furthermore, the information generated is useful for monitoring the new UNAIDS 95-95-95 targets for 2025, and it will guide the decision-makers and HIV program managers for specific areas to intervene and resource allocation.

1.5. Project outline

This thesis is organized as follows: Chapter Two is about the literature review and project conceptual framework. Thereafter, Chapter Three deals with general methods for the project, which includes methods of both a systematic scoping review and empirical analyses. Chapter Four focuses on the results of the systematic scoping review, and its published paper is attached in Appendix 9.3. Chapter Five focuses on the description of the progress of the HIV cascade and transition dynamics along the HIV continuum of care, as well as factors associated with various transitions. The submitted manuscript, which is under review in the BMC Infectious Diseases journal, has the submission's current status attached in Appendix 9.4. Chapter Six is mainly about the assessment of the treatment outcomes and engagement in care, and factors associated with different transitions during “test and treat”. Additionally, in Chapter Seven, there is a general discussion of the key findings and conclusions. Finally, Ph.D. contributions and recommendations for future studies and interventions are listed.

CHAPTER TWO: Literature Review

2.0. Introduction to the chapter

The purpose of this literature review is to discuss the existing studies that describe and quantify the HIV cascade and continuum of care, the study designs used, and the statistical analysis methods used for evaluating the cascade while identifying remaining research gaps. Several studies have shown that PLHIV often move in and out of care at various stages of the HIV cascade (cascade churn). The review explored the opportunity of extending the cascade assessment from a cross-sectional to a longitudinal design method. Furthermore, the review also discussed the clinical implications of cascade churn and methodological aspects to be considered during the HIV cascade assessments.

This Chapter is organized as follows: the literature review was divided into three main topics. The topics discussed included: the assessment of the HIV care cascade progress; cross-sectional versus longitudinal care cascade; and existing methods for assessing the HIV continuum of care. Afterwards, the major concepts were defined, and the formulated conceptual framework was described.

2.1. Assessment of HIV care cascade progress

Ever since the invention of the HIV care cascade framework, countries have used the framework to assess and evaluate the progress of HIV treatment programs. Worldwide, by 2023, reports showed that 86% of PLHIV knew their HIV status, 89% of those who knew their status accessed treatment, and 93% of those on treatment are virally suppressed (with only 72% of all PLHIV being suppressed) (1). However, the country-specific assessments show varying levels of progress, with higher proportions of VL suppression (>70%) being reported in the USA (39), Canada (40–42), and Europe (10). Further, recent information from assessments conducted in Eastern and Southern Africa also showed that many countries have made good progress in terms of VL suppression among PLHIV on treatment (43). However, viral suppression <70% was reported in Eritrea (65%) and South Africa (69%).

In Tanzania, a population-based survey conducted in adults PLHIV aged ≥15 years in 2022-2023 showed good progress in terms of treatment initiation (98%) and VL suppression among those on ART (90%), but not for the diagnosis, even though it has improved from 61% in 2016-2017 (44) to 83% in 2022-2023 (2). Furthermore, a few reports done at the sub-national level

in Tanzania show the proportion of HIV diagnoses ranged between 47% in Bukoba (45) and 80% in Mwanza (46). The proportion of linkage to care among the diagnosed was between 69% in Mwanza (46) and 94% in Moshi (47). The proportion of ART initiation was 50% in Mwanza (46), 68% in Bukoba(45), and 70% in Moshi (47). In studies that assessed VL, the proportion of suppressed VL was 78% in Moshi (47) and 89% in Bukoba (45). It is clear that the cascade progress varies by HIV programs, region, district, and residence (rural or urban). Hence, there was a need to further assess the cascade progress at the sub-national level to inform the design of program-specific interventions.

Available assessments show different staging methods for estimating HIV cascade and continuum of care progress from diagnosis to VL suppression level. The differences are more pronounced in estimating the proportion of PLHIV who are virally suppressed. Several authors have approached the cascade differently for this stage. Currently, there are two broad staging methods. The first method used was the dependent staging method, whereby a participant is eligible for a successive HIV care stage if he/she meet the criteria of the current care stage (48,11). The second was the independent staging method, in which cascade stages were derived independently and regardless of the previous stage attained (48). The denominator for the independent approach in all stages is always the number of PLHIV (11,48), and in the dependent staging method, the denominator is the PLHIV that achieved a previous stage, and it decreases in each successive cascade stage.

Several studies assessed the cascade using dependent and independent staging methods. For instance, a large study conducted in South Africa showed that among PLHIV on ART, 74% were suppressed, while among all PLHIV, only 24% were virally suppressed (11). Another global report also showed that 81% of those on treatment are virally suppressed, while in the independent staging method, only 48% were suppressed (49). The UNAIDS 2018 report on global, regional, and country-specific estimates has also adopted both the dependent and independent methods (50). Therefore, the HIV cascade findings of different reports should be interpreted based on the staging methods used to evaluate the HIV cascade and continuum of care.

2.2. Cross-sectional versus Longitudinal HIV care cascade

The World Health Organization (WHO) recognizes the cross-sectional and longitudinal approaches for monitoring the progress of HIV treatment programs (28). The cross-sectional

HIV care cascade was defined as an approach that presents the number of PLHIV, the number (with percentage) of PLHIV diagnosed with HIV, the number (with percentage) of PLHIV initiated on ART, and the number (with percentage) of PLHIV on ART and virally suppressed. Often, it is presented using bar graphs. The approach was identified as the easiest way of providing a snapshot of progress at a one-time point (24). This approach is commonly used to assess the HIV care cascade even in the presence of longitudinal individual-level data. Some examples include studies done in Switzerland (51), Ontario, Canada (42), the USA (39), Europe, and Central Asia (10), Tanzania (2), and sub-Saharan Africa (52).

The availability of patient-level longitudinal data from PLHIV attending HIV clinics provides a unique opportunity for a detailed evaluation of the entire HIV continuum of care. The longitudinal HIV continuum of care was defined to assess HIV care stages "for a specific time frame, with a specified beginning and a specified end" (28). The approach appeared to be very useful for detailed assessment but demanding in terms of analysis (28,53). The longitudinal analysis framework can be presented either by using vertical bar graphs with out-of-care transition arrows (15) or by using state boxes and the state represents the HIV care stages with state transition arrows (14,30,54). Several authors have advocated for the use of a longitudinal approach for assessing the continuum of care (55,56). One major advantage of the approach is that it incorporates the in-and-out of care movement of participants (14,54), which is not possible when using the cross-sectional design methods.

2.3. Existing methods for assessing the HIV continuum of care

The existence of in-and-out transitions in HIV treatment programs calls for an alternative modeling framework for HIV treatment program assessment. Methods suggested include the estimation of time spent on each care cascade stage (57), competing risk analysis (58), and multistate modeling (14,31). Although alternative modeling approaches exist, these methods are not often used. Instead, methods that focus on a single transition or aggregated data are utilized. Popular methods used include: macro-level analysis using aggregated data and mathematical modeling using data from different sources (14,56). The WHO and researchers recommend the use of a longitudinal care cascade approach whenever individual-level data is available (28,55,59).

One of the alternative approaches is multistate modelling, which provides a useful tool for analysis that cannot be done using classical analysis (60). Traditionally, time to event is modeled using a two-state transition. However, depending on the nature of the primary event,

states can further be divided into two or more states before the absorbing state (a state from which no transition is possible) (61,62). Over time, participants may experience multiple other events before the event of interest. These events are known as competing risk events, which either prevent or modify the chances of observing the primary event (63,64). In such a scenario, the multistate modeling framework is the most appropriate method for both transition dynamics and competing risk events. This modeling framework is used to estimate transition probabilities, expected length spent in transient states, and test the association between patient characteristics and state-specific transitions through regression modeling (61,65). Few studies have applied multistate models in longitudinal assessments of the HIV continuum of care; the studies were conducted in Kenya (14), the USA (54), Zambia (32), and Indonesia (66). Currently, in Tanzania, there are limited studies assessing the HIV cascade and continuum of care using multistate models.

2.4. Major concepts definitions and conceptual framework

2.4.1. HIV care cascade and HIV continuum of care

In literature, the terms "HIV care cascade" and "HIV continuum of care" are used interchangeably. However, Kay et al (67) distinguish the two. The continuum of care is defined as a dynamic and bidirectional engagement in HIV care, while the care cascade is defined as a static and cross-sectional representation of HIV care stages at the population level. The cascade framework was adopted and used in assessing the progress of the UNAIDS 90-90-90 target for HIV for 2020 (68) and the 95-95-95 target for 2025 (13). The earlier HIV care cascade conceptual framework involved 5-7 HIV stages (24,39). Recently, Gourlay et al (69) suggested the use of four stages, which included PLHIV, diagnosis, ART, and VL suppression. Therefore, both concepts are used in Chapter Five, which aims to describe the HIV cascade and continuum of care using both the cross-sectional and longitudinal design methods.

2.4.2. Cross-sectional and longitudinal designs

The study designs used in assessing the HIV cascade and continuum of care are mainly cross-sectional and longitudinal designs. A cross-sectional study design is a design in which the outcome is measured at a single time point (70). In this design, quantities such as proportions and odds ratios are estimated. On the other hand, a longitudinal study design is a design in which the outcome or response is measured at the start of the study and is measured repeatedly

over time (71). There are three major forms of longitudinal study designs: repeated cross-sectional design, prospective design, and retrospective design (72). The repeated cross-sectional design is the design that collects data of the same indicator or variable from different subjects repeatedly over time. The individual rounds of the data collection at each time are cross-sectional by nature. In the prospective design, data is collected for the same variable and from the same subjects repeatedly over time, starting from baseline (time zero). In this design, one can monitor the changes of the outcome, or one may follow subjects over time for an event to occur. Lastly, in the retrospective design, the follow-up starts from the time when the event of interest has occurred and looks backward for the possible risk behaviour or characteristics. In this design, data is also collected for the same variable and the same subjects.

The longitudinal design methods have been used in assessing the HIV continuum of care to capture the dynamic nature of the individual pathways of PLHIV through the cascade stages (15). In this design, several additional quantities are estimated, for example, transition probabilities between cascade stages (14,32), time to reach the next stage (73,74), and cumulative probabilities of ART initiation and viral suppression accounting for competing risk events (29). In this project, both cross-sectional and longitudinal designs were considered to provide a comprehensive assessment of the HIV cascade and continuum of care in Chapter Five, and the longitudinal design only was used in Chapter Six.

2.4.3. Loss to follow-up

To achieve the best expected treatment outcomes, PLHIV should adhere to regularly scheduled visits with good treatment compliance. LTFU in HIV programs has been observed in all stages of the HIV care cascade (40,41,52,75,76). This problem has been identified as a challenge to successful ART treatment, and it has been identified as among the indicators for measuring HIV program effectiveness (77). The LTFU being an important indicator, HIV researchers have defined LTFU for both program-specific and universal definitions. In 2010, Chi et al. (78) provided the program-specific definition of LTFU as being late for the last scheduled appointment for ≥ 60 days. In the next year, Chi et al. (79) recommended the universal definition of the LTFU to be defined as PLHIV not seen in the clinic for ≥ 180 days since the last HIV clinic visit. Since this project was implemented in a single HIV clinic, a program-specific definition of LTFU is used throughout.

2.4.4. Multistate models

A multistate model is a model for a stochastic process allowing individuals to move between a finite number of states (62,80). In general, there are two broad types of multistate models: discrete-time multistate models for equally spaced longitudinal data and continuous-time multistate models for unequally spaced longitudinal data (81). The multistate model is a special case of a competing risk model, and it allows subjects to transition between different states multiple times during follow-up. In the HIV cascade and continuum of care, states correspond to the HIV cascade stages (14,15,32). These include HIV infection, HIV diagnosis, linkage to care, ART initiation, retention in care, LTFU, VL suppression, and death.

A multistate modeling framework is a framework that contains distinct and ordered finite states, which is used to describe how participants transition between states. The framework can be progressive (no backward transitions) and reversible (back-and-forth transitions are allowed between states) (80). In multistate modeling frameworks, states can either be transient, of which participants can move in-and-out of the state (for example, LTFU state), or absorbing, of which no out-of-the-state transition is possible (for example, death state) (82). Based on routine data collection at CDCI, in Chapters Five and Six, the reversible continuous-time multistate models were used to address the in-and-out of care transition dynamics among PLHIV enrolled in care at the CDCI.

2.4.5. Project conceptual framework

Background of HIV cascade frameworks

The HIV care cascade is a framework that describes stages of HIV care and treatment programs from HIV infection, HIV diagnosis and awareness, linkage to care, retention, initiation of ART treatment, and achievement of suppressed VL (24,39,83). The framework characterizes and quantifies the proportions of PLHIV at each stage of the cascade (17,31). The framework was first introduced in 2011 by the CDC (39). In 2014 and 2020, the UNAIDS adapted the framework for 2020 and 2025 targets (90-90-90 and 95-95-95, respectively). This framework is referred to as the standard HIV care cascade (55) or traditional HIV care cascade (15).

The standard HIV care cascade framework often uses a cross-sectional design whereby estimates of each cascade stage are assessed at one time point and report the progress of the HIV care and treatment program at a defined time point. However, the standard HIV care cascade framework has limitations; first, the framework has an underlying assumption of

unidirectional flow of PLHIV from infection to suppressed VL (15). This assumption ignores the reality that PLHIV may have different transition experiences over time. For example, PLHIV may refuse HIV care, disengage from care, transfer to other HIV clinics, or even die. Second, the framework is cross-sectional by nature, and this limits the assessment of the underlying process behind the presented progress (15).

To address the limitations of the standard HIV care cascade, several HIV cascade researchers have proposed alternative formulations. These formulations extended the standard HIV care cascades in two ways. The first modified the cascade by introducing out-of-care transitions using the standard cascade framework (84). This type of framework maintained the cross-sectional nature of the framework with additional information about out-of-care transitions in each cascade stage (including LTFU and death). Others proposed the 'HIV states and Transition' framework (15), 'comprehensive HIV care cascade' (85), and 'Queueing model' (74). This group of frameworks addresses the dynamics of HIV care engagement while preserving the original structure of the standard HIV care cascade. Based on the suggestion of these frameworks, cascades that used multistate modeling frameworks were developed in a longitudinal design (14,31,32,66). Since this project used both the standard HIV care cascade and HIV state and transition frameworks in the assessment of the clinic, both frameworks were included to formulate the project's conceptual framework.

Project conceptual framework description

The conceptual framework of this project is designed so that both the cross-sectional and longitudinal design methods used in different studies in this project are integrated. Figure 2.1 below shows how both cross-sectional and longitudinal design methods were used in different stages of the project and the linkage of the concepts in addressing project-specific objectives. The first part mainly focuses on objective one, which is about conducting a systematic scoping review of methods used in assessing the HIV cascade and continuum of care. After this stage, both cross-sectional and longitudinal design methods were used in the empirical analyses, which evaluated the progress of the HIV cascade and continuum of care (objective two). In this case, analyses were mainly descriptive. After the description, the next step was to model the association between different transitions and baseline characteristics (objective three). Lastly, the project narrowed down to assessing treatment outcomes and engagement in care, with the focus now being the combination of the follow-up status and VL suppression status (objective four).

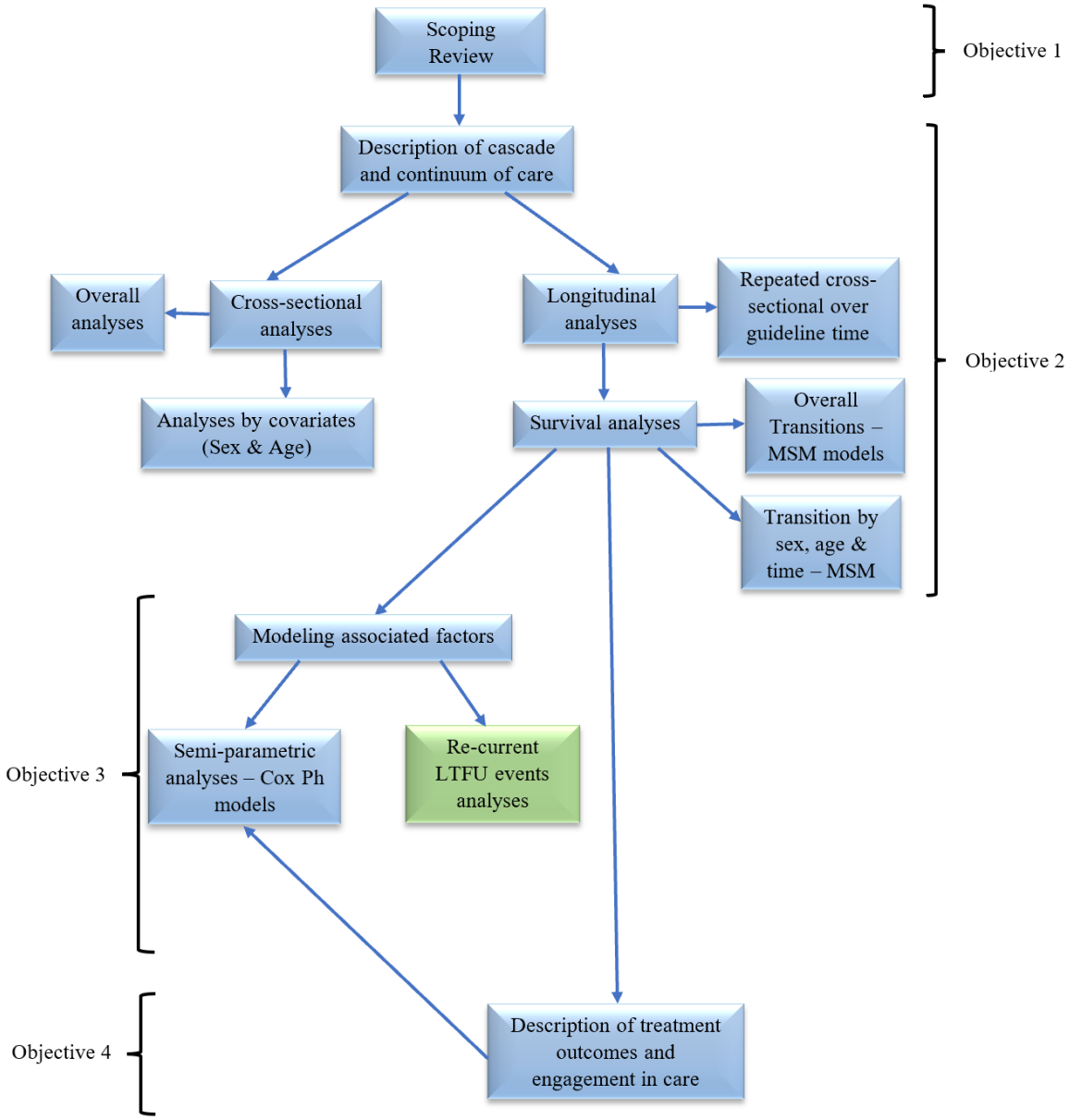

Figure 2.1: The overall project conceptual framework. The project focused on ocean blue boxes. The green box shows that the study was done separately from this project. MSM: Multistate model; LTFU: Lost to follow-up; Cox Ph: Cox proportional hazard model

CHAPTER THREE: General Materials and Methods

3.0. Introduction to the chapter

This project is a combination of a systematic scoping review of statistical methods used to assess the progress of the HIV cascade and continuum of care and the application of the methods identified to describe the HIV cascade, treatment outcomes, and engagement in care at the CDCI. The project used different materials and methods to address project objectives; however, there were common methods used across different objectives. These materials and methods are all described in this chapter, and study-specific methods are later described in the next chapters that focus on results.

The chapter is organized as follows: first, methods and justification of using a scoping review for the statistical methods used in the assessment of the progress of HIV cascade and continuum of care. Next was the description of the design and setting of the empirical analyses. Later, the description of participants and data source, inclusion and exclusion criteria, exploratory variables, data management, and statistical analyses were summarised.

3.1. Scoping review of methods for HIV cascade and continuum of care

The first objective of this project was to conduct a systematic review of the literature on methods used to assess the HIV cascade and continuum of care. The review aimed to identify and synthesize existing statistical methods used to assess the progress of HIV treatment programs in terms of the HIV cascade and continuum of care among PLHIV. The type of review appropriate for this study was a systematic scoping review. The scoping review is an exploratory type of evidence synthesis that is used to determine the scope and coverage of literature on a given topic and quantify the volume of literature existing, in addition to an overview of its focus (86,87). There are several reasons for conducting a scoping review, to mention a few: first, when the focus is to identify types of available evidence (87), second, when researchers are interested in examining how research is conducted (87), and lastly, when the interest lies in identifying research gaps (87,88). Then, the scoping review is suitable, and the review aim of this project was in line with the scoping review purposes. The details of the methods of this review are provided in Chapter Four, which focuses on the review findings.

3.2. Empirical analyses: KIUALRCO database

3.2.1. Project design and setting

The design of the empirical analysis part of the project was a secondary analysis of an ongoing prospective longitudinal cohort design. The project was conducted in the HIV clinic located at St. Francis Referral Hospital, known as the CDCI. The clinic was established in 2004 (soon after the roll-out of ART in Tanzania), and it was among the first and largest HIV clinics to be established in rural Tanzania (89). CDCI is a public-private partnership clinic that provides HIV services following the Tanzanian HIV and AIDS Management Guidelines. The CDCI is supported by the government of Tanzania through USAID Afya Yangu, Swiss Tropical and Public Health Institute (Swiss TPH), University Hospital of Basel, Ifakara Health Institute (IHI), and St. Francis Referral Hospital.

The clinic is located in Ifakara town, Kilombero district (South Eastern Tanzania), and it serves PLHIV mainly from Kilombero district and nearby districts, which include Ulanga and Malinyi districts in the Morogoro region, Tanzania. The population size of the three districts is approximately 680,000 people (90), and the districts have approximately 40,000 PLHIV. The major economic activities of residents are agriculture, livestock, and fisheries (91).

3.2.2. Participants and data sources

The project used routine data collected from PLHIV enrolled in care at the CDCI from April 2005 to December 2024 and consented to the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO). The clinic offers a research platform for HIV and related co-morbidities through the KIULARCO, which was established in 2005. KIULARCO data is generated through the electronic system known as the Open Medical Record System (Open MRS), which is connected in all units of the CDCI, including registration, triage, laboratory, clinics, and pharmacy. The cohort has data on demographic, clinical, and laboratory assessments of all consenting participants (89,92).

The collected information is later extracted from IHI servers, minimally processed, and stored in a web-based platform known as Alfresco, managed by Swiss TPH. Database extraction is done quarterly, and the database is queried and reviewed using patients' paper files managed by the Government. The queries are processed before the next data export to allow the integration of the corrections made in the database. The database is only accessed by the project principal investigator, the statistician working at CDCI, and researchers with approved research ideas by the KIULARCO scientific board. The dataset used for research is de-identified using

unique patient numbers provided by the National AIDS, STIs, and Hepatitis Control Program (NASHCoP) of Tanzania to ensure the privacy of participants.

On average, the KIULARCO clinic's yearly enrolment ranges between 300 and 500 PLHIV (including newly diagnosed and transfer-in PLHIV). The highest enrolment was observed in 2008 (n=1331 PLHIV) and 2009 (n=1277 PLHIV), and the lowest enrolment was in 2022 (n=328 PLHIV). In December 2023, the cohort had a total of 12,985 PLHIV, and among these, 3,805 (29%) PLHIV were on active follow-up, 1547 (12%) died, 5150 (40%) were LTFU, and 2483 (19%) were transferred to other HIV clinics. In total, there are 291,334 visits, with monthly total visits ranging between 300 and 1,400 visits.

3.2.3. Inclusion and exclusion criteria

The project included all PLHIV children and adults who consented to the KIULARCO research cohort. The project excluded PLHIV who visited the clinic only for consultation and/or drug refill, while they intend to continue attending their clinics elsewhere (transient PLHIV). PLHIV with missing sex, date of birth, and enrolled before April 2005 (when the second edition HIV and AIDS management guideline was not yet issued in Tanzania) were excluded. Details of the specific study inclusion and exclusion criteria are described in each results Chapter from Chapters Four to Six.

3.2.4. Explanatory variables and data management

Exploratory variables included were sex (male and female); marital status (grouped as married/cohabiting, never married, separated/divorced/widowed); age (baseline and age at last visit) grouped as children (age <10 years), adolescents (10-19 years), adults (20-49 years), and elderly (≥ 50 years); education level (none, primary school, and secondary school and above; occupation (farmers and non-farmers); and distance from the clinic (< 1km, 2-80 km, and ≥ 81 km). Other variables included were partner HIV status (positive, negative, unknown, and not applicable) and disclosure status (disclosed or not disclosed).

In children aged 0-4 years, WHO BMI-for-age was used, and z-scores were classified as Z-score < -2 was considered wasted; -2≤ Z-score ≤ 2 was normal, and Z-scores >2 were overweight or obese (93). In PLHIV aged 5-18 years, WHO BMI-for-age was classified as Z-score <-2 as wasted, -2≤ Z-score ≤1 as normal, and Z-score > 1 as overweight or obese (94). Implausible BMI-for-age z scores were excluded (in children aged 0-4 years, values < -10 and

> 10 were excluded, and in PLHIV aged 5-18 years, values < -6 and > 6 were excluded), and BMI was treated as missing. In adults aged ≥19 years, WHO BMI was estimated using the adult formula and classified as underweight (BMI <18.5kg/m^2), normal BMI (18.5-24.9kg/m^2), or overweight/obese (BMI ≥25.0kg/m^2) (95). When weight or height was missing, BMI was treated as missing.

CD4 percentage of PLHIV aged <5 years was grouped as low if aged <1 year and CD4 percentage <30%; aged 1-2 years if CD4 percentage <25%; and aged 3-4 years if CD4 percentage <20%. High CD4 percentage if PLHIV aged <1 year with CD4 percentage ≥30%; aged 1-2 years with CD4 percentage ≥25%; and 3-4 years with CD4 percentage ≥20%. CD4 cell count in PLHIV aged ≥5 years was grouped as <100, 100-199, 200-349, 350-499, and ≥500 cells/mm^3, and the WHO clinical stage was used as Stage 1, 2, 3, and 4.

Tuberculosis at ART initiation was defined as the detection of acid-fast bacilli or positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) from sputum or an extra-pulmonary sample, or prescription of anti-tuberculosis medication in the presence of an International Classification of Diseases (ICD)-10 code indicating tuberculosis (A15-A19) or clinical signs suggestive of tuberculosis and the start of anti-tuberculosis drugs within 3 months before and after ART initiation. Tuberculosis was considered unlikely if no prescription of anti-tuberculosis drugs and no clinical diagnosis was provided. In all other cases, tuberculosis was indeterminate and treated as missing data in the analyses.

The enrolment time was categorized into 6 groups following Tanzanian national guidelines for the management of HIV and AIDS changes over time. Since the ART was rolled out in Tanzania in 2005, the first guideline considered in this study was the second edition of the HIV and AIDS management guideline. Thus, the PLHIV enrolment time was categorized as follows: April 2005 - January 2009; February 2009 - March 2012; April 2012 – April 2015; May 2015 – September 2017; October 2017 – March 2019; and April 2019 – September 2022.

Baseline variables were managed as follows: the available measurement of CD4, WHO HIV stage, and BMI before 24 weeks and after 4 weeks from the enrolment date was considered as the baseline (with prioritization of measurements before) in case of missed measurements at enrolment. Tuberculosis diagnosis was considered as a baseline when the diagnosis was done within 3 months before and after the ART initiation date. Beyond 3 months processing window, TB status remained undetermined.

3.2.5. General statistical analyses

Systematic scoping review

Descriptive statistics such as summary measures and proportions were used to describe the characteristics of the articles included in the systematic scoping review. Data were presented using figures, maps, and tables. The details of all methods applied are explained in Chapter Four.

Baseline characteristics and cross-sectional cascade assessment

Empirical analyses began with exploratory data analysis, whereby descriptive statistics were used to understand the distribution of baseline characteristics of PLHIV included in different studies. This analysis also identified PLHIV with missing data, and the proportion of missing data was described in variables with missing data. Tables were used to summarise the results. Furthermore, counts with their corresponding percentages were used in the cross-sectional cascade analyses to describe the progress of the standard HIV cascade. Results were presented using tables and bar graphs, and the details of the methods for cascade analyses are elaborated in Chapter Five.

Longitudinal assessment of engagement in HIV care

Based on the findings of the systematic scoping review of methods, in this project, the longitudinal assessment of engagement in HIV care and treatment was done in two stages. First, the repeated cross-sectional assessment of the HIV cascade was done over the years (following changes in HIV and AIDS management guidelines in Tanzania). The characteristics of PLHIV included were summarised following guideline changes in Tanzania to understand the pattern of the distribution of PLHIV in different variables over time. Results were summarized in tabular format, and the details of the methods are found in Chapter Five.

Second, was the application of a continuous-time non-parametric multistate Markov model. In this method, the multistate modeling frameworks (state space) were formulated based on the research question of each Chapter. The state space of each model had a range of 5-10 states, with the corresponding transitions ranging from 10 to 24 transitions. The transition matrix was formulated for each model, and analyses began with the summary of the transition frequencies

between states in a multistate modeling framework. These transitions indicated the frequency and the corresponding proportion out of all transitions of the specified model. In this exploratory data analysis, the unexpected transitions or transitions with very low frequencies (<8 counts) were identified and restricted by including additional assumptions to allow models to provide reliable estimates. Even though experts in multistate modeling have suggested the use of ≥6 transitions in analysis (96), models in this project were stable when transition frequencies started from 8 onwards, and I decided to use ≥8 transitions in all multistate modeling.

The estimation of the transition probabilities between HIV states before including baseline covariates is done in three stages. In the non-parametric multistate model, the quantity of interest is the transition probabilities between states estimated over time. To estimate this, the modeling starts with the transition intensities or hazard rates, which indicate the instantaneous risk of transition between states over a time interval (97,98). Assuming the state space comprises ordered states from state 1 to state n (where n is the last in the state space and in this project n = 5 or 10 depending on the research question). Examples of states used in this project included in care, LTFU, re-engaging with suppressed VL, transfer out before achieving suppressed VL, and death. The transition hazard rates are expressed using the following formula;

$$\alpha_{gh}(t) = lim_{\Delta t \to 0} \frac{P(X(t+\Delta t)=h \mid X(t)=g)}{\Delta t} \qquad \text{Eq.1}$$

Where: $\alpha_{gh}(t)$ is the transition intensity or hazard rate from state g to state h, etc. $X(t)$ is the state occupied by the PLHIV at the time t, and Δt is the change in time during the transitions between engagement in HIV care states. Under this transition hazard rates definition, it implies the multistate model is Markovian, and the Markov assumption states that the probability of future transition only depends on the current state (97,98). Through the transition hazard rates, the baseline cumulative hazard of transition between engagement in care states was estimated through the Nelson-Aalen estimator, expressed as follows, with the assumption of independent censoring;

$$\hat{A}_{gh}(t) = \sum_{t_i \le t} dN_{gh}(t_i) \,/\, Y_g(t_i) \qquad \text{Eq.2}$$

Where: $\hat{A}_{gh}(t)$ is the Nelson-Aalen estimator of cumulative baseline hazard rates between state g and state h. t_i Indicates event times, the $i = 0, 2, \ldots, n$ (where n is the last event time or administrative censoring time due to database closure for analysis). In all analyses, time was measured in months. $dN_{gh}(t_i)$ is the observed number of transitions from state g to state h at the time t_i. $Y_g(t_i)$ is the number of PLHIV at risk of transitioning from state g to state h at the time t_i.

Non-parametric predicted transition probabilities between states were estimated using the Aalen-Johansen estimator through the fitted cumulative transition hazard model. The estimator of the transition probability matrix was presented as follows;

$$\widehat{\boldsymbol{P}}_{gh}(s,t) = \prod_{\mu \epsilon (s,t]} (\boldsymbol{I} + \Delta \widehat{\boldsymbol{A}}(\mu)) \qquad \text{Eq.3}$$

Where: $\widehat{\boldsymbol{P}}_{gh}(s,t)$ denote the transition probability matrix at the time interval $(s,t]$. $\boldsymbol{I}$ is the identity matrix, $\widehat{\boldsymbol{A}}(\mu)$ is the matrix containing Nelson-Aalen estimates estimated in Eq.2 above. In both the Nelson-Aalen estimator and Aalen-Johansen estimators, the variance was estimated using the Greenwood estimator (98). The estimated transition probabilities were summarised using stacked shaded line graphs when all states involved in the models were included, and line graphs whenever fewer states were selected for plotting. Furthermore, the transition probabilities were estimated by sex, age, and time (grouped following the changes in HIV and AIDS guidelines over time). The expected length of stay in each transient state was estimated with the predicted probabilities (obtained in Eq.3) being the input in the estimation using the following formula proposed by Beyersmann and Putter in 2014 (99);

$$\hat{E}_k = \int_0^{\tau} \hat{P}\left(X_\mu = k\right) d\mu \qquad \text{Eq.4}$$

Where $\hat{P}(X_\mu = k)$ is obtained from initial estimates of the distribution of ($\hat{P}(X_0 = 1)$, $\hat{P}(X_0 = 2)$, …, $\hat{P}(X_0 = n)$) in a state space of $1, 2, 3, \ldots, n$ (where n is the last state) and $\hat{P}(s,t)$ through estimates of cumulative baseline hazards of $\hat{A}_{gh}(t)$. τ is the end of follow-up time.

The effect of covariates in different transitions of multistate models was assessed using the Cox proportional hazard (Cox Ph) model in selected transitions where the research question had the highest interest. The Cox Ph model used for a selected transition, say from state g to state h, was expressed as follows (98);

$$\hat{\lambda}_{gh}(t|\boldsymbol{Z}) = \lambda_{gh,0}(t)\exp(\beta'_{gh}\boldsymbol{Z}) \qquad \text{Eq.5}$$

Where: $\hat{\lambda}_{gh,0}(t)$ is the baseline hazard of the transition from state $g \rightarrow h$; $\boldsymbol{Z}$ is the vector of baseline covariates such as sex, age, and CD4 cell counts; and β'_{gh} is the vector of the regression coefficients of the baseline covariates.

3.2.6. Ethical considerations

The KIULARCO was approved by the Ifakara Health Institute Review Board (IHI/IRB/No:16-2006) and the National Health Research Committee of the National Institute of Medical Research of Tanzania (NIMR/HQ/R.8a/Vol. IX/620) with yearly approval extensions. Upon registration at CDCI, all PLHIV individuals were informed about KIULARCO, and written informed consent was obtained for recruitment into the KIULARCO. PLHIV aged <18 years, consent was provided by parents or a responsible guardian/caregiver on their behalf. PLHIV who did not consent to participate in KIULARCO, their decision did not affect HIV care and treatment services provision, because these services are provided to all PLHIV enrolled in care following Tanzanian HIV and AIDS management guidelines. The study adhered to the Declaration of Helsinki, and there were no potential risks to participants recruited in KIULARCO and those included in this project. Additionally, this Ph.D. project is embedded within the KIULARCO. The Ph.D. was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) with the reference number R14/49.

CHAPTER FOUR: A Systematic Scoping Review

4.0. Introduction to the chapter

The systematic scoping review of statistical methods used to assess the HIV cascade and continuum of care was done to synthesize the existing literature and the remaining gaps in the application of advanced methods for assessing the HIV cascade and continuum of care. The major findings of the review showed that the majority of the cascade was conducted using cross-sectional design methods (93%). The application of longitudinal design methods was scarce (7%), and for those who applied the methods, the application varied across studies. This makes it difficult to compare the findings of different studies. Therefore, there is a need for a methodological guideline for the application of different types of longitudinal design methods in assessing the HIV continuum of care. This chapter is organized based on a journal article manuscript for scoping review. It started with the study title page, abstract, introduction, methods, results, discussion, conclusions, and statements. The published research article is included in Appendix 9.3.

Statistical Methods Applied for the Assessment of the HIV Cascade and Continuum of Care: A Systematic Scoping Review

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4.1. Abstract

Objectives: This scoping review aims to identify and synthesise existing statistical methods used to assess the progress of human immunodeficiency virus (HIV) treatment programs in terms of the HIV cascade and continuum of care among people living with HIV (PLHIV).

Design: Systematic scoping review.

Data sources: Published articles were retrieved from PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete, and Excerpta Medica dataBASE (EMBASE) databases between April and July 2022. We strategically search using the Google Scholar search engine and reference lists of published articles.

Eligibility criteria: This scoping review included original English articles that estimated and described the HIV cascade and continuum of care progress in PLHIV. The review considered quantitative articles that evaluated either HIV care cascade progress in terms of the Joint United Nations Programme on HIV and AIDS (UNAIDS) targets or the dynamics of engagement in HIV care.

Data extraction and synthesis: The first author and the librarian developed database search queries and screened the retrieved titles and abstracts. Two independent reviewers and the first author extracted data using a standardized data extraction tool. The data analysis was descriptive, and the findings are presented in tables and visuals.

Results: This review included 300 articles. Cross-sectional study design methods were the most commonly used to assess the HIV care cascade (n=279, 93%). In cross-sectional and longitudinal studies, the majority used proportions to describe individuals at each cascade stage (276/279 (99%) and 20/21 (95%), respectively). In longitudinal studies, the time spent in cascade stages, transition probabilities, and cumulative incidence functions were estimated. The logistic regression model was common in both cross-sectional (101/279, 36%) and longitudinal studies (7/21, 33%). Of the 21 articles that used a longitudinal design, six articles used multistate models, which included non-parametric, parametric, continuous-time, time-homogeneous, and discrete-time multistate Markov models.

Conclusions: Most literature on the HIV cascade and continuum of care arises from cross-sectional studies. The use of longitudinal study design methods in the HIV cascade is growing because such methods can provide additional information about transition dynamics along the

cascade. Therefore, a methodological guide for applying different types of longitudinal design methods to the HIV continuum of care assessments is warranted.

Keywords: Cross-sectional design; Longitudinal design; Multistate Modelling; HIV care and treatment programs

4.2. Introduction

The HIV care cascade is a framework that describes the stages of people living with HIV (PLHIV) transitioning through HIV infection, diagnosis, linkage to care, initiation of antiretroviral therapy (ART), retention in care, and VL suppression (24,39). This framework characterizes and quantifies the proportion of PLHIV in each stage of the cascade (17,31). It is a useful tool for monitoring the uptake of HIV services and the progress of HIV treatment programs (14–16).

In the literature, the terms 'HIV care cascade' and 'HIV continuum of care' are used interchangeably (14,17,54,100), but Kay et al. (67) distinguished the two concepts. They defined the 'HIV continuum of care' as a dynamic and bidirectional engagement in HIV care, whereas the 'HIV care cascade' was defined as a static and cross-sectional representation of HIV care stages at the population level. In recent years, many researchers have embraced these concepts, and the distinction between them has been recognised in literature, particularly after the Joint United Nations Programme on HIV and AIDS (UNAIDS) announced the 90-90-90 targets for HIV for 2020 (68) and 95-95-95 targets for 2025 (13). The 95-95-95 target states that 95% of PLHIV know their HIV status, 95% of those diagnosed are initiated on ART, and 95% of those on ART are virally suppressed.

Currently, most HIV treatment program assessments and evaluations are performed following the HIV care cascade approach, which aims to report progress toward UNAIDS targets for 2020 or 2025 (12,41,73,101–107). These assessments often apply descriptive statistics and show progress at a particular time point, referred to as a cross-sectional design. In recent years, assessments of the HIV cascade and continuum of care that use a longitudinal design have been increasingly featured in the published literature. In these applications, methods such as multistate models (14,31), competing risk methods (58), and the distribution time spent in each cascade stage (57) were used. The existence of various methods and their applications in the HIV cascade and continuum of care evaluation calls for a review that identifies the statistical methods used in these assessments.

Different types of reviews exist on this topic, the majority of which focus on synthesising estimates for each HIV care cascade stage. These reviews mainly focused on HIV testing, engagement in care and treatment (108,109), cascades among alcohol users (110), longitudinal methods for assessing retention in care (111), and cascades among people who inject methadone drug (112). Others reviewed cascade stage definitions (113), measures of patient engagement in HIV care (114), cascade experiences among indigenous people (115), cascades

among adolescents and young adults (116), and cascades among children and adolescents (117).

Currently, few systematic reviews have synthesised methods used to assess the HIV cascade and continuum of care progress. The first systematic review was conducted by Medland et al. (118) and published in 2015. At that time, few cascade articles were published, and most studies used descriptive statistics in a cross-sectional study design. Granich et al. (119) conducted a review of methods and the status of progress towards the UNAIDS 90-90-90 from 2010–2016, and they showed that different methods were used. However, they focused mainly on articles that used a cross-sectional study design and methods used to determine indicators and data sources. In 2021, Vourli et al. (120) published a systematic review that highlighted the importance of expanding the scope of cascade assessment to include time to the next cascade stage. In these reviews, the components of the statistical methods applied to the HIV cascade and continuum of care assessments were limited. Therefore, this systematic scoping review aimed to identify and summarise the statistical methods used to assess HIV treatment program progress in terms of the HIV cascade and continuum of care among PLHIV using both cross-sectional and longitudinal study designs.

4.3. Methods

4.3.1. Review protocol

The scoping review protocol was developed from November to December 2021, following the Joanna Briggs Institute System for the Unified Management, Assessment, and Review of Information (JBI SUMARI) Manual for Evidence Synthesis (Scoping Review Chapter) (121).

4.3.2. Eligibility criteria

This scoping review included original articles written in English that focused on estimating and describing the HIV cascade and continuum of care among PLHIV. Specifically, the review considered quantitative articles that either evaluated or assessed the HIV care cascade in terms of UNAIDS targets or the dynamics of engagement in HIV care and treatment clinics for the HIV continuum of care. Mixed-method articles were included if the quantitative component was well described (i.e., the method used to assess the cascade and results of the cascade were presented in the article). The review excluded articles comparing the HIV care cascade with other cascades, such as the TB care cascade, hepatitis cascade, and prevention of mother-to-

child transmission of HIV. The review further excluded review and meta-analysis articles, opinions, editorials, commentary articles, and non-peer-reviewed articles (because the methods sections were not well-described). Finally, the review did not include published conference abstracts or proceedings, because the methods were typically not provided in sufficient detail.

4.3.3. Search strategy

The development of an electronic bibliographical database search strategy began with a pilot phase, whereby review concepts were searched independently in PubMed and Google Scholar. The retrieved relevant titles and abstracts were screened to identify keywords to include in the development of electronic database search queries. The database search query was first developed in English using the PubMed database and adapted to the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete and Excerpta Medica dataBASE (EMBASE) databases as needed (Table S4.1). The database search dates were from April to July 2022.

4.3.4. Source of the evidence selection process

Titles and abstracts were retrieved from all three databases, and duplicates were removed based on the digital object identifier and article content. Titles and abstracts were screened for eligibility by the lead author, and irrelevant articles were excluded. All potentially relevant full-text articles were downloaded for review. The first author and two independent reviewers each conducted a full-text review of all articles, during which the review criteria were applied. The article search and assessment of inclusion and exclusion criteria were summarised and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram (122).

4.3.5. Data extraction and data entry process

The extracted information included the first author's name and publication year, type of participants, age, country, sample size, study design, study level of representation, and data source. Other extracted information included cascade stages, cascade size, cascade staging methods, and statistical methods used to assess the HIV cascade and continuum of care (Table S4.2). All extracted information was first entered into an Excel spreadsheet. The data extraction

tool was modified and revised whenever necessary, depending on new information available in the articles and their relevance to this review. The first author reviewed all the extracted data. Disagreements between reviewers were resolved by consensus. After finalising the data collection template, an electronic data capture system was developed using Open Data Kit (ODK), and data entry was performed by the reviewers. The information entered into ODK was pooled in Excel with a comma-separated value file format using the ODK briefcase.

4.3.6. Data items

The variables used in this review included publication year, which included three groups: 2011–2014, referring to the time between the first cascade report and before the announcement of the UNAIDS 90-90-90 targets; 2015–2019, following the UNAIDS 90-90-90 targets announcement and the implementation time; 2020–2022 (by July), representing the reporting time for the UNAIDS 90-90-90 targets and the implementation of the new UNAIDS 95-95-95 targets. The study site was country-specific if a study was conducted in one country and regionally if a study was conducted in at least two countries. The study regions included Asia and Europe, North and South America, sub-Saharan Africa, and global (a single report that included multiple regions).

A cross-sectional study design included articles that presented cascade results at a single time point. A longitudinal design included articles that presented cascade outcomes either repeatedly over time (i.e., repeated cross-sectional study design), or prospective or retrospective study designs (including cohort data) (72). In this review, studies that included cascade assessments using both cross-sectional and longitudinal designs were included in the longitudinal study design group, because cross-sectional analyses can be considered a subset of longitudinal analyses.

Other variables included data sources (cohort, laboratory test records, hospital records, surveys, surveillance, and clinical trial data) and study level of representation, which was grouped into facility, sub-district/town/municipal/city, state/province, population (when a study estimated the number of PLHIV, diagnosed, and linkage to care), community/district/county, regional, country, and global studies. Another variable was the sample size (the number of diagnosed HIV-positive participants assessed). The sample size was grouped into four categories: <1000, 1000–5000, 6000–10000, and >10000. The types of participants were grouped into all PLHIV, children only, adolescents, adults, HIV key populations, prisoners, veterans, refugees, and the

military. The HIV key populations included men who had sex with men, female sex workers, people who inject drugs, and transgender men and women. Finally, the statistical methods applied in different articles were grouped into two categories: descriptive statistics and regression models. Variables such as study design, data sources, types of participants, and statistical methods were allowed for multiple responses; the obtained responses were converted into multiple individual variables with binary responses.

Stage names with similar meanings were reorganised to formulate simple cascade stage names, such as HIV infection (PLHIV), diagnosis, linkage to care, loss to follow-up (LTFU), retention in care, transfer to other HIV clinics, ART eligibility, on ART, VL suppression, and death. Articles that used a longitudinal design and multistate models had slightly different names for their cascade stages. In this case, stage names were used as they were written by the authors. The size of the cascade and continuum of care frameworks was categorised into four groups based on the number of stages assessed. The four categories were extra-large cascades (> 6 stages), large cascades (5–6 stages), medium cascades (4 stages), and small cascades (≤ 3 stages).

Types of cascade framework used were grouped into six: the CDC 2011 cascade framework (including PLHIV, diagnosis, linkage to care, retention in care, ART status, and VL suppression status stages (39)). CDC with five stages (starting from the diagnosis stage), and CDC with four stages (starting from linkage to care). Gourlay and others in 2017 (here abbreviated as Gourlay 2017) included PLHIV, diagnosis, ART status, and VL suppression stages (69). Gourlay 2017 with three stages, started from the diagnosis stage. Other cascade formulations included stages such as ART eligibility, clinical staging, ART adherence, LTFU/disengagement, engagement in care, death, transfer out, CD4 testing, current use of ART, and history of ART. The cascade staging method used was grouped into three categories: dependent (also known as conditional), independent, and a combination of the two. In the dependent method, PLHIV are eligible for the next cascade stage if they are in the previous cascade stage, whereas in the independent method, each cascade stage was derived independently of the prior cascade stage (123).

4.3.7. Data analysis and presentation

The review data were analysed and summarised using summary statistics, such as counts with percentages, medians with interquartile ranges (IQR), and data ranges. Results were presented

using tables. The geographical distribution of articles by country was summarised using world maps. Maps were plotted for country-specific articles (excluding 28 regional articles). The constructed cascade and continuum of care frameworks were summarised in terms of the size and cascade stages used. Types of cascade framework used were summarised using counts with percentages. The frameworks of a subset of articles that used a longitudinal study design and multistate models were compiled to document similarities, differences, and existing gaps. All data management and statistical analyses were performed using Stata software version 14 (StataCorp LP, College Station, Texas, USA).

4.3.8. Patient and Public Involvement

No patient involved

4.4. Results

4.4.1. Description of the article selection process

The search query retrieved 5,805 titles and abstracts from all three databases, and 5,505 titles were excluded in the title and abstract screening stages (Figure 4.1). The 310 abstracts were identified as meriting full-text reviews, of which 300 articles were included (Table S4.2).

4.4.2. Characteristics of articles

The majority of the 300 articles were published between 2015 and 2019 (n=177, 63%) (Table 4.1). Various PLHIV groups were assessed, including children, adolescents, adults, migrants, prisoners, veterans, the military, and HIV key populations. Key HIV populations were reported in 74 articles, which included men having sex with men (n=35, 47%), female sex workers (n=19, 26%), people who inject drugs (n=20, 27%), transgender men (n=8, 11%), and women (n=19, 26%).

Assessments of the HIV cascade and continuum of care were performed using cross-sectional (279/300, 93%) and longitudinal (21/300, 7%) designs (Table 4.1). The review included 28 studies conducted in regions or globally. Many of these studies were conducted in Asia and Europe (n=11, 39%) and in Sub-Saharan Africa (n=11, 39%). Focusing on country-specific studies, most of the articles that used a cross-sectional study design were from the USA,

Canada, Zimbabwe, and South Africa (these countries each contributed between 9 and 83 of 252 studies) (Figure 4.2). Articles that used a longitudinal study design were mainly from the USA (6/20 studies).

Various data sources have been used to describe the HIV cascade and continuum of care. In the 279 articles that used a cross-sectional study design, the survey data source was common (n=110, 39%), whereas in the 21 articles that used a longitudinal design, the cohort data source was often used (n=10, 48%) (Table 4.1). The sample size varied across articles, with the smallest study including 22 hard-to-reach individuals and the largest study including 37.9 million PLHIV (UNAIDS report of 170 countries). In articles that used a cross-sectional study design, the median sample size was 1,721 PLHIV (IQR: 524–8,744), whereas in articles that used a longitudinal design, the median was 3,311 PLHIV (IQR: 1,080–11,510). Articles that used a cross-sectional study design had various levels of representation, with many being sub-district/town/municipal/city-based studies (68/278, 25%), while for articles that used a longitudinal design, the majority were facility-based studies (6/18, 33%).

4.4.3. HIV cascade and continuum of care stages

In general, a median of four cascade stages (IQR: 3–5) was used (Table 4.2). The smallest cascade had two stages, and the largest cascade had nine stages. Approximately 34% (95/279) of the cross-sectional studies used large cascades (5-6 stages), while articles that used a longitudinal study design mostly used large (5-6 stages) and small cascades (≤3 stages) (7/21, 33%). In articles that used a longitudinal design, the larger the cascade size, the larger the median sample size. However, there was no clear pattern between sample size and the number of stages used in articles that used cross-sectional study design methods (Figure S4.1).

In articles that used a cross-sectional study design, 12% (34/279) used Gourlay 2017 cascade framework (Table 4.2). The CDC 2011 cascade framework was used in various forms: 15/279 (5%) studies used all six stages, and others used the shorter form with either five stages (9/279, 3%) or four stages (11/279, 4%). In 21 articles that used a longitudinal study design, few used the CDC 2011 framework (n=1, 5%) and Gourlay 2017 (n=1, 5%). In all articles reviewed, 71% (190/267) used dependent staging methods. In articles that used a cross-sectional study design, only 7% (17/255) used both dependent and independent methods (Table 4.2).

In both study designs, common stages were PLHIV, diagnosis, linkage to care, ART status, VL suppression, death, and LTFU (Table S4.3). In articles that used a longitudinal design, some

used other stages such as optimal care, sub-optimal care, disengaged, and no ART. Lastly, two articles used a longitudinal design with formulated stages in combination with either ART status or CD4 cell count (Figure S4.2).

4.4.4. Statistical methods applied

In the descriptive analyses, the majority of articles used proportions to describe participants at each cascade stage (cross-sectional design (276/279, 99%) and longitudinal design (20/21, 95%)) (Table 4.3). Articles that used a longitudinal study design often estimated transition probabilities between cascade stages (5/21, 24%), which was rare among studies that used a cross-sectional design (1/279, 0.4%). Furthermore, the time spent in each cascade stage (5/21, 24%) and the Kaplan–Meier or cumulative incidence function (5/21, 24%) were often estimated in the longitudinal studies. Approximately 28% (78/300) of the articles in both designs used simple test statistics, such as the Chi-square test, Fisher's exact test, t-test, Wilcoxon rank-sum test, and Kruskal–Wallis test.

To assess the association between cascade stages or transitions and participant characteristics, 176/300 (59%) of the included articles performed regression analysis. The regression models used in the reviewed articles primarily considered discrete and survival outcomes (Table 4.3). In the articles that used a cross-sectional study design, the logistic regression model was common (101/279, 36%). Logistic and Cox proportional hazard models were commonly used in studies that used a longitudinal design (7/21, 33%) and (4/21, 19%), respectively.

4.4.5. Longitudinal design with multistate models

Among the 21 articles that used a longitudinal study design, different analysis methods were used. Articles that used longitudinal analysis methods were mainly in five groups (Table S4.4): classic survival analyses (n=2), survival analysis with competing risk methods (n=5), repeated cross-sectional and time spent in each cascade method (n=2), survival analysis with multistate models (n=6), and repeated measure analysis methods (n=1).

In articles that used a longitudinal study design and multistate models (n=6), five types of multistate models were used. These included non-parametric multistate, parametric, continuous-time multistate, time-homogeneous Markov models, discrete-time multistate Markov, and general multistate models (Table 4.4). Three articles adopted the Markov process,

and one study considered the Markov process with first-order dependence. In almost all reviewed articles (n=5), the assessment of the care cascade started at enrolment in HIV care, and one article considered ART initiation as the baseline. Regardless of the type of multistate model used, death was considered an absorbing state in all the reviewed articles. Other absorbing states included LTFU and transfer to other HIV clinics. Three studies used a model that allowed for back-and-forth movement for LTFU and disengagement states (Figure S4.2).

4.5. Discussion

The findings of this scoping review showed that cross-sectional study design methods were most commonly used to assess the progress of HIV service uptake and treatment responses (93%). The reviewed articles were mainly available at the subnational level. The articles used a cross-sectional study design covering a wide range of PLHIV, including children, adolescents, adults, migrants, prisoners, and key populations. In general, the cascade size had a median of four stages (IQR: 3–5). The dependent staging method was often used in articles with a cross-sectional study design. Various longitudinal design methods were used, including repeated cross-sectional, repeated measures, and survival analyses. In articles that used a longitudinal study design and multistate methods (n=6 out of 21 articles), only three articles used analytical frameworks that integrated the in- and out-of-care movements of PLHIV enrolled in care. Although cascade researchers pointed out the challenges of using a cross-sectional design in 2015 (15,17), articles using a longitudinal design and addressing the in- and out-of-care pathways in cascade assessments are scarce. The major reason is that these methods require advanced data management and analysis skills (29,53).

Several authors have proposed different types of frameworks that include various pathways through the HIV cascade and continuum of care. The ‘HIV states and Transition’ framework was formulated to capture the interaction of PLHIV with HIV testing, care, and treatment services at a given time (15). It has two key features: mutually exclusive states (cascade stages) and transitions between states. This framework was adapted by the articles that expanded the cascade assessment using longitudinal design with multistate methods (Figure S4.2) (14,32,34,54,66). Others proposed the ‘comprehensive HIV care cascade’, which is a framework formulated by combining stages used in the standard HIV care cascade with the additional consideration of poor outcomes (LTFU or death before or after ART initiation) (85). The ‘Cyclical cascade of HIV care’ was proposed to capture the nonlinearity of PLHIV

engagement in HIV treatment clinics (124). The framework also maintained stages of the standard HIV care cascade (diagnosis, linkage, and ART initiation) with additional stages of early retention (<6 months) and long retention (>6 months). Disengagement was incorporated with the possibility of re-engaging in care.

In this review, less than half (n=83, 28%) used either the CDC 2011 or Gourlay 2017 cascade frameworks to quantify and describe the HIV cascade and continuum of care. Other researchers modified the cascade for various reasons. First, data availability, which affects mostly stages included; for example, some studies started with PLHIV linked in care (19,125,126), while others did not have VL data (127). In articles that used longitudinal design and multistate methods, the lack of transfer-out information (54) and failure to capture re-engagement in care after LTFU (66) affected the inclusion of these stages as transient states. Second, the HIV management guidelines used during the cascade assessments changed over time. This resulted in the inclusion of cascade stages such as ART eligibility (128) and CD4 testing (129). Third, additional information on the cascade. This was the case when ART status was further divided into two stages: ever on ART or history of ART use and current use of ART (130–132). Others added the ART adherence stage (130,133,134) or used the retention stage in both pre-ART and post-ART initiation (135). Lastly, addressing the in-and-out of care transitions. In assessments that used a longitudinal design with multistate methods, engagement in care was expanded to capture PLHIV who were LTFU or disengaged from care and later returned to care (14,32).

Almost all articles quantified the cascade using the proportion of PLHIV achieving each cascade stage. Quantification was done either by using a dependent or independent staging method (73). The independent staging method is often used in combination with the dependent method, but it is used mainly to assess the proportion of PLHIV with suppressed VL (136). This is because the independent staging method reflects the actual uptake of health services (48), while dependent staging methods mainly focus on PLHIV retained in care (103,137). Furthermore, approximately 60% of the articles performed regression analyses to examine the relationship between patient characteristics and either each of the cascade stages (128,138–141) or a few selected cascade stages (142–146). In these assessments, modifiable characteristics were identified to plan for interventions that will improve cascade progress in stages with poor progress.

This review revealed different longitudinal design methods. Assessments were mostly conducted using survival methods. These were mainly in three groups: classic survival

analysis, competing risk methods, and multistate models. Competing risk methods were primarily used to estimate the cumulative probability function of each stage (58,73), whereas, in multistate methods, the aim was to capture all possible transitions between stages (14,34).

The multistate methods used included parametric and non-parametric multistate, continuous-time and discrete-time multistate, and general multistate models. A multistate model is a continuous-time stochastic process that allows individuals to move between a finite number of states (62). In the HIV cascade and continuum of care, states correspond to the HIV cascade stages (14,15,32). In multistate modelling frameworks, states can be either transient (participants can move in-and-out of the state) or absorbing (no transition is possible out of the state) (82). In this review, articles that used multistate models considered death and transfer to other HIV clinics as absorbing states. Depending on the availability of data, LTFU and disengagement from care were allowed to be transient or absorbing states (Figure S4.2).

This review is among the largest and most recent systematic scoping reviews conducted on the methods used to assess the HIV cascade and continuum of care, with extensive coverage and diversity. Furthermore, because of its coverage, the review identifies areas with limited research in terms of methods and their applications to the HIV cascade and continuum of care and provides recommendations for future studies. However, there were some limitations. First, this review was restricted to English articles. The impact of including other languages in this review is unknown, but areas with a high burden of HIV are mostly Anglophone countries. Therefore, the pattern of review findings is not expected to change. Second, the review included peer-reviewed articles. The impact of omitting grey literature is also unknown, but because cross-sectional design methods are widely used, the conclusion of this review is unlikely to be affected by the missed grey literature.

4.6. Conclusion

Most studies on the HIV cascade and continuum of care applied cross-sectional study design methods. The use of longitudinal study design methods in the assessment of the HIV cascade is increasing. These methods provide additional information about the transition dynamics along the cascade, establish detailed progress, and identify additional areas for interventions. Multistate modelling frameworks can be viewed as extensions of established cross-sectional design frameworks regarding engagement in HIV care, but further work is needed to integrate ART status and VL suppression status into these frameworks. Therefore, a methodological

guide on the application of different types of longitudinal design methods in the HIV cascade and continuum care and their corresponding frameworks is needed to guide future studies.

4.7. Statements

4.7.1. Author contributions

AVK designed the study, obtained funding, conducted the review, and prepared the manuscript. KO and FV contributed to the study design and supervised the implementation. TRG, MW, ASM, and HM participated in the study design and reviewed the manuscript. All authors have reviewed and approved the final manuscript.

4.7.2. Conflict of interest

Maja Weiser was sponsored by different sponsors to attend the ECCMID conferences during the last 10 years, and she was a member of the Menari Advisory Board in 2022. All other authors declared no conflict of interest.

4.7.3. Funding

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4.7.4. Role of the funder

The funder of this systematic scoping review had no role in the review design, data extraction, synthesis of results and interpretation, preparation of the review manuscript, and the choice of journal for submission of the manuscript for publication.

4.7.5. Data availability

All review data extracted and processed is available upon request through the corresponding author.

4.7.6. Acknowledgments

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Dr. Yeromin Mlacha, who is a Medical Entomologist and Senior Researcher at the Ifakara Health Institute, Tanzania. Dr. Mlacha assisted in the data preparation for maps of the included articles.

4.8. Figures and Tables

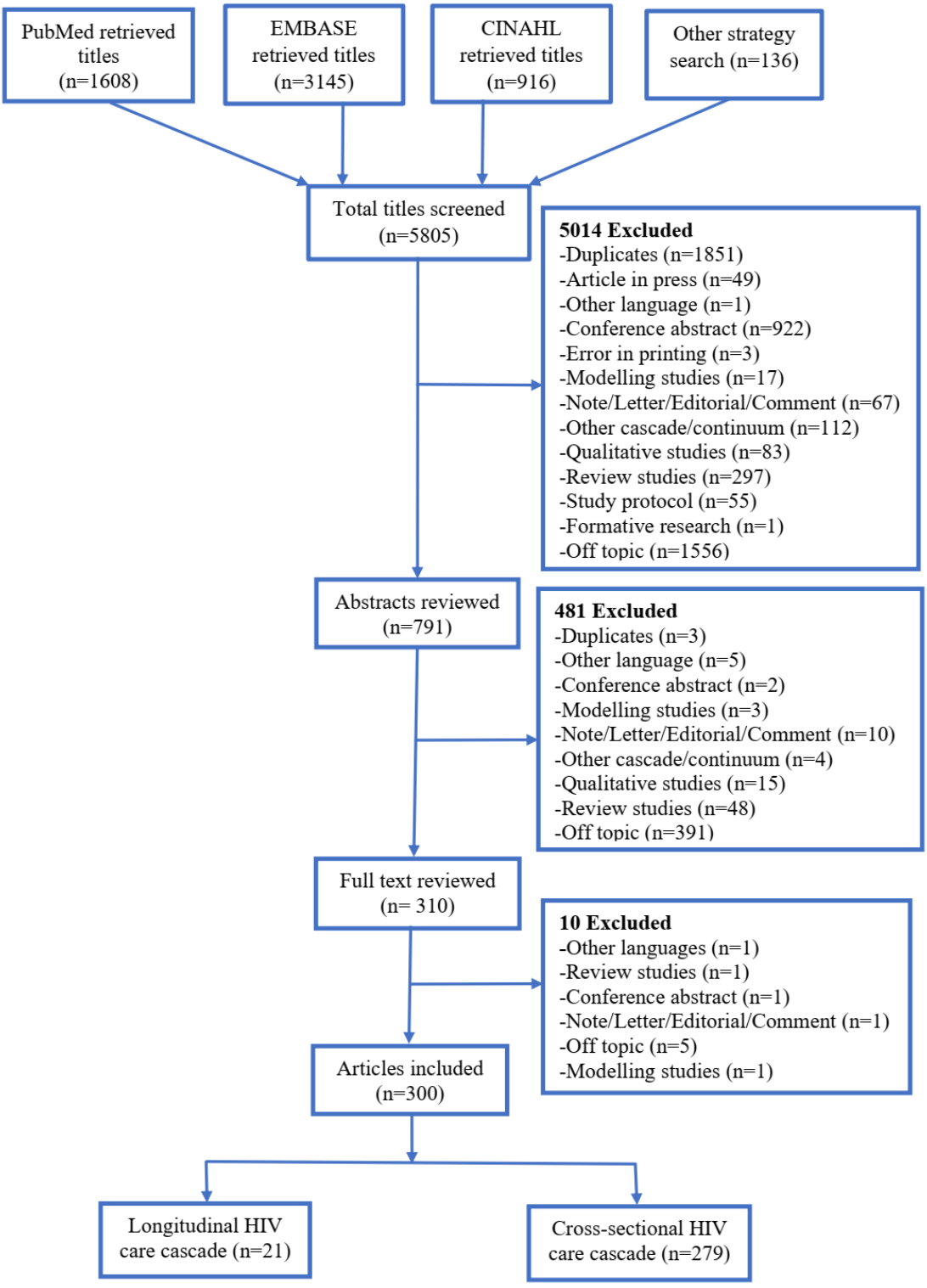


Figure 4.1: Flow chart of the inclusion and exclusion of research articles

Table 4.1: Characteristics of articles included in the scoping review (n=300)

Characteristics of articles	Cross-Sectional	Longitudinal[1]	Overall
Papers included[2]	279/300 (93.0%)	21/300 (7.0%)	300/300 (100%)
Publication year[3]			
2011 - 2014 (Before 90-90-90)	18/279 (6.5%)	0/21 (0%)	18/300 (6.0%)
2015 - 2019 (Post 90-90-90)	177/279 (63.4%)	14/21 (66.7%)	191/300 (63.7%)
2020 - 2022 (90-90-90 reporting)	84/279 (30.1%)	7/21 (33.3%)	91/300 (30.3%)
Regional studies (involved ≥2 countries)			
Asia and Europe	10/27 (37.4%)	1/1 (100%)	11/28 (39.3%)
North and South America	5/27 (18.5%)	0/1 (0%)	5/28 (17.9%)
Sub-Saharan Africa	11/27 (40.7%)	0/1 (0%)	11/28 (39.3 %)
Global[4]	1/27 (3.7%)	0/1 (0%)	1/28 (3.6%)
Type of participants[5]			
Mixture (All PLHIV)	47/279 (16.9%)	3/21 (14.3%)	50/300 (16.7%)
Children only	10/279 (3.6%)	1/21 (4.8%)	11/300 (3.7%)
Adolescents	29/279 (10.4%)	5/21 (23.8%)	34/300 (11.3%)
Adult	127/279 (45.5%)	14/21 (66.7%)	141/300 (47.0%)
Key population	72/279 (25.8%)	2/21 (9.5%)	74/300 (24.7%)
Migrants	5/279 (1.8%)	0/21 (0%)	5/300 (1.7%)
Prisoners	2/279 (0.7%)	0/21 (0%)	2/300 (0.7%)
Veterans	2/279 (0.7%)	0/21 (0%)	2/300 (0.7%)
Refugees	0/279 (0%)	1/21 (4.8%)	1/300 (0.3%)
Military	0/279 (0%)	1/21 (4.8%)	1/300 (0.3%)
Types of HIV key population[5,6], n (%)			
Men having sex with men	33/72 (45.8)	2/2 (100%)	35/74 (47.3)
Female sex workers	19/72 (26.4)	0/2 (0%)	19/74(25.7)
People who inject drugs	20/72 (27.8)	0/2 (0%)	20/74 (27.0)
Transgender women	19/72 (26.4)	0/2 (0%)	19/74 (25.7)
Transgender men	7/72 (9.7)	1/2 (50.0)	8/74 (10.8)
Data sources[5]			
Cohort data	65/279 (23.3%)	10/21 (47.6%)	75/300 (25.0%)
Laboratory test records	11/279 (3.9%)	0/21 (0%)	11/300 (3.7%)
Hospital medical records	55/279 (19.7%)	5/21 (23.8%)	60/300 (20.0%)
Survey data	110/279 (39.4%)	3/21 (14.3%)	113/300 (37.7%)
Surveillance data	70/279 (25.1%)	3/21 (14.3%)	73/300 (24.3%)
Clinical trials data	4/279 (1.4%)	1/21 (4.8%)	5/300 (1.7%)
Others[7]	19/279 (6.8%)	3/21 (14.3%)	22/300 (7.3%)
Sample size, median (IQR)	1721 (524-8744)	3311 (1080-11510)	1862 (545-8859)
Sample size range (minimum, maximum)	22 – 39000000	100 – 92215	22 – 39000000
Sample size (number of participants)			
<1000	103/279 (37.3%)	5/21 (21.8%)	108/297 (36.4%)
1000 – 5000	85/279 (30.8%)	7/21 (33.3%)	92/297 (31.0%)
6000 – 10000	24/279 (8.7%)	3/21 (14.3%)	27/297 (9.1%)
>10000	64/279 (23.2)	6/21 (28.6%)	70/297 (23.6%)
Level of representation			
Facility[8]	51/278 (18.4%)	6/18 (33.3%)	57/296 (19.3%)
Sub-district/Town/Municipal/City	68/278 (24.5%)	2/18 (11.1%)	70/296 (23.7%)
State/Provide	36/278 (13.0%)	0/18 (0%)	36/296 (12.2%)
Population[9]	52/278 (18.7%)	2/18 (11.1%)	54/296 (18.2%)
Community/District/County	31/278 (11.2%)	3/18 (16.7%)	34/296 (11.5%)
Regional	17/278 (6.1%)	2/18 (11.1%)	19/296 (6.4%)
Country	22/278 (7.9%)	3/18 (16.7%)	25/296 (8.5%)
Global[4]	1/278 (0.4%)	0/18 (0%)	1/296 (0.3%)

[1]Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses

[2]Row percentage
[3]The UNAIDS 90-90-90 target of the year 2020 stated that 90% of PLHIV know their HIV status, 90% of those diagnosed positive are initiated on ART, and 90% of those on ART are virally suppressed.
[4]Global studies are studies that included multiple regions such as Europe, Asia, America, and sub-Saharan Africa
[5]Percentage was estimated for each type of response, and the report in this table is for 'yes' for all binary variables processed from multiple response variables
[6]Analysis was restricted to the articles that reported the key population participants (n=74)
[7]Other data sources largely included clinic and program registries, databases, different types of medical records, consortia, population estimates reports, social insurance schemes, and AIDS program databases. IQR is the interquartile range
[8]Ficility level studies at a health facility or clinic or hospital-based studies
[9]Population studies are the studies that included population-level cascade stages, which include PLHIV, diagnosis, and linkage to care

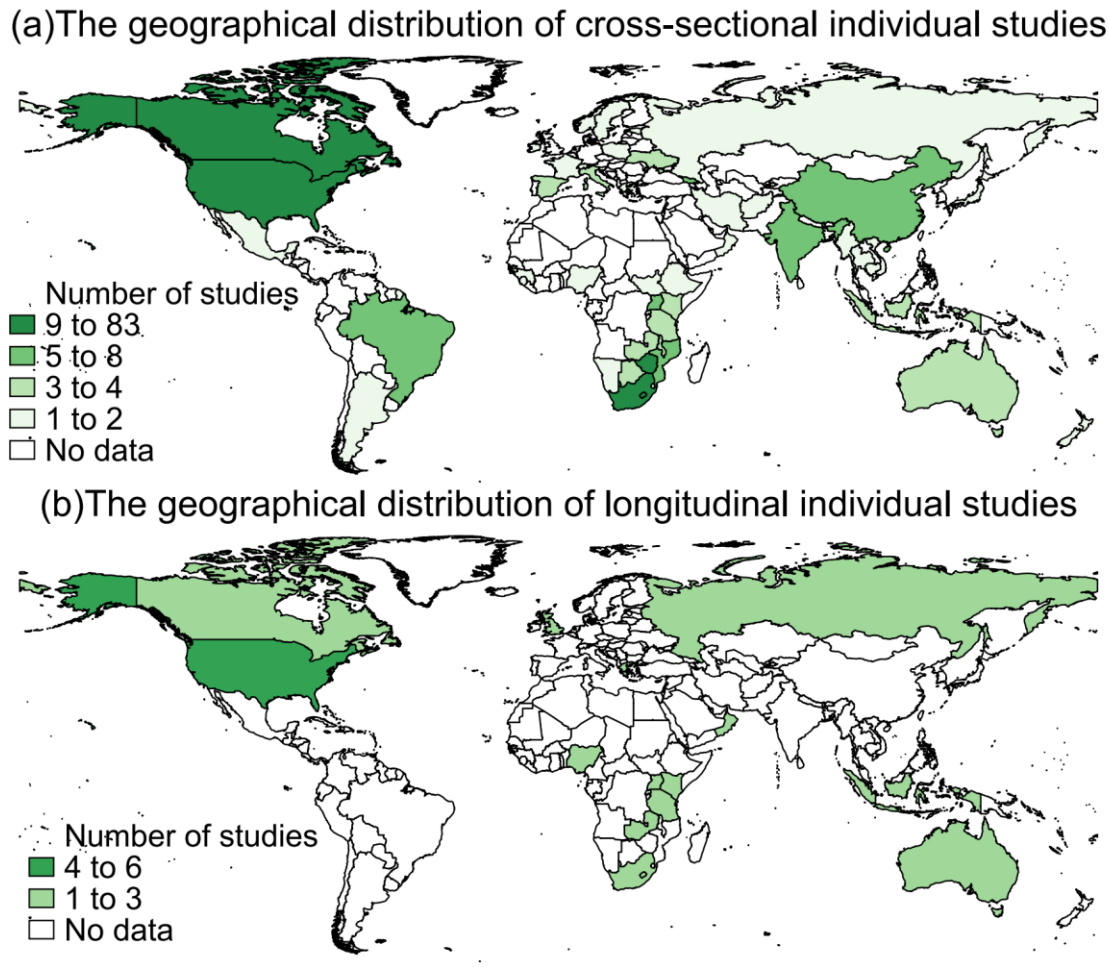


Figure 4.2: The geographical location distribution of country-specific studies of cross-sectional (n=252) and longitudinal studies (n=20) (regional studies, such as sub-Saharan Africa or Asia and Europe, were excluded)

Table 4.2: Summary of various forms of outcomes used in the articles included in the scoping review (n=300)

Outcome	Cross-sectional	Longitudinal[1]	Overall
Number of cascade stages, median (IQR)	4 (3-5)	4 (3-5)	4 (3-5)
Size of the HIV care cascade, n (%)			
Extra-large cascade (> 6 stages)	15/279 (5.4%)	1/21 (4.8%)	16/300 (5.3%)
Large cascade (5-6 stages)	95/279 (34.1%)	7/21 (33.3%)	102/300 (34.0%)
Medium cascade (4 stages)	75/279(26.8%)	6/21 (28.6%)	81/300 (27.0%)
Small cascade (≤3 stages)	94/279 (33.7%)	7/21 (33.3%)	101/300 (33.7%)
Sample size by size of the HIV care cascade, Median (IQR)			
Extra-large cascade (> 6 stages)	3295 (595-7489)	NA	3674 (645-10315)
Large cascade (5-6 stages)	1418 (500-7843)	7810 (1532-32242)	1532 (592-8382)
Medium cascade (4 stages)	2355 (440-10076)	3287 (2196-6850)	2617 (463-9829)
Small cascade (≤3 stages)	1999 (579-9150)	476 (175-11510)	1931 (528-9150)
Types of cascade framework used			
CDC 2011[2]	15/279 (5.4%)	1/21 (4.8%)	16/300 (5.3%)
Gourlay 2017[3]	34/279 (12.2%)	1/21 (4.8%)	35/300 (11.7%)
CDC 2011 with 5 stages[4]	9/279 (3.2%)	0/21 (0%)	9/300 (3.0%)
CDC 2011 with 4 stages[5]	11/279 (3.9%)	0/21 (0%)	11/300 (3.8%)
Gourlay 2017 with 3 stages[6]	12/279 (4.3%)	0/21 (0%)	12/300 (4.0%)
Other[7]	198/279 (71.0%)	19/21 (90.5%)	217/300 (72.3%)
Cascade staging approaches[8], n (%)			
Dependent[9]	183/255 (71.8%)	7/12 (58.3%)	190/267 (71.2%)
Independent[10]	55/255 (21.6%)	4/12 (33.3%)	59/267 (22.1%)
Both dependent and independent	17/255 (6.9%)	1/12 (8.3%)	18/267 (6.7%)

[1]Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses

IQR is the interquartile range

[2]Six cascade stages were used as follows: PLHIV, diagnosis, linkage in care, retention in care, on ART, and viral load suppression

NA is not applicable because there was one study under this group with a sample size of 23,227

[3]Four stages were used as follows: PLHIV, diagnosis, on ART, and viral load suppression

[4]The cascade adopted stages like CDC 2011, but the assessment started from the diagnosis stage

[5]The cascade adopted stages like CDC 2011, but the assessment started from linkage in the care stage

[6]The cascade adopted stages like Gourlay and others in 2017, but the assessments started from the diagnosis

[7]Other cascade formulations that included other stages and longitudinal frameworks

[8]Studies used longitudinal and multistate models or survival analyses; staging methods for each cascade stage are not applicable

[9]The dependent method, PLHIV are eligible for the next cascade stage if they have achieved the prior cascade stage

[10]Independent method, each cascade stage is derived independently of the prior cascade stage

Table 4.3: Statistical methods used in articles included in the scoping review (n=300)

Methods	Cross-sectional	Longitudinal[1]	Overall
Descriptive statistics[2], n (%)			
Proportion for each stage of the HIV care cascade	276/279 (98.9%)	20/21 (95.2%)	296/300 (98.7%)
Simple test statistics[3]	78/279 (28.0%)	6/21 (28.6%)	84/300 (28.0%)
Time spent in each stage of the HIV care cascade	7/279 (2.5%)	5/21 (23.8%)	12/300 (4.0%)
Transition probabilities[4]	1/279 (0.4%)	5/21 (23.8%)	6/300 (2.0%)
Kaplan-Meier or cumulative incidence function	0/279 (0%)	5/21 (23.8%)	5/300 (1.7%)
Regression models[1], n (%)			
Logistic model	101/279 (36.2%)	7/21 (33.3%)	108/300 (36.0%)
Cox Ph model	15/279 (5.4%)	4/21 (19.1%)	19/300 (6.3%)
Poisson model	32/279 (11.5%)	0/21 (0%)	32/300 (10.7%)
Competing risk model	3/279 (1.1%)	0/21 (0%)	3/300 (1.0%)
Generalized linear model	10/279 (3.5%)	0/21 (0%)	10/300 (3.3%)
Weighted and unweighted linear model	4/279 (1.4%)	0/21 (0%)	4/300 (1.3%)
Log-Binomial regression model	5/279 (1.8%)	0/21 (0%)	5/300 (1.7%)
Multinomial regression model	0/279 (0%)	3/21 (14.3%)	3/300 (1.0%)
Generalized estimating equation model	1/279(0.4%)	0/21 (0%)	1/300 (0.3%)
Other models[5]	19/279 (6.8%)	2/21 (9.5%)	21/300 (7.0%)

[1]Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses
[2]Percentage was estimated for each type of response, and the report in this table is for yes for all binary variables processed from multiple response variables

[3]Simple test statistics used included the Chi-Square test, Fisher-Exact test, t-test, Wilcoxon rank sum test, and Kruskal–Wallis test

[4]Transition probability is a predicted probability of moving between two consecutive states in a given time
[5]Other models applied were ARIMA and SIRIMA, Bayesian hierarchical models, bivariable and multivariable regression, generalized additive model, negative binomial model, generalized linear mixed model, spectrum model, and generalized linear mixed models

Table 4.4: Articles that used longitudinal study design and multistate model (n=6)

Methods	Number of articles
Baseline[1]	
Enrolment/recruitment	5
ART initiation	1
Reason for censoring[2]	
End of follow-up	2
Transfer, death, and follow-up	1
Transfer out, death, or status less than 12 months	1
Absorbing[3] state	
Death	2
Death and LTFU	2
Death and transfer out	2
Types of multistate models	
Non-Parametric[4] multistate model	1
Parametric[5], continuous-time[6] multistate	1
Time-homogeneous[7] Markov model	1
Discrete-time[8] multistate Markov model	2
General multistate model	1
Multistate model assumptions	
First-order dependence	1
Markov process[9]	2
Markov, first-order dependence	1
Missing data techniques	
Multiple imputations	2
Missing data indicator	3

[1]Baseline is the time at which the assessment of the cascade started

[2]Censoring occurs when the exact survival time is unknown from the start until the end of the study

[3]Absorbing state is a state in which, once visited, no out-of-state transition is possible

[4]Non-parametric model is a model that does not take any distribution assumptions

[5]Parametric model is the model that follows a certain distribution, for example, Exponential and Weibull

[6]Continuous-time model is the model used in a dataset collected in unequal-spaced time

[7]Time-homogenous model is the model that assumes transition intensity rates are constant over time

[8]Descrite-time model is the model used in a dataset collected in an equally spaced time interval

[9]Markov assumption is the assumption used in multistate models that assumes the future transition is only dependent on the current state

4.9. Supplementary figures and tables

Table S4.1: Database search queries

Database	Query number	Query	Number of articles
PubMed (Searched on 05-04-2022)	1	((HIV) AND ((Care cascade) OR (cascade of care) OR (UNAIDS 90-90-90) OR (continuum of care[Title/Abstract]))) **OR** (((HIV) AND ((Care cascade) OR (UNAIDS 90-90-90) OR (cascade of care) OR (continuum of care[Title/Abstract]))) AND ((Multistate models[Title/Abstract]) OR (longitudinal[Title/Abstract]) OR (Markov models[Title/Abstract]) OR (Multi-state models[Title/Abstract])))	1,608
CINAHL Complete (04-07-2022)	S1	MH human immunodeficiency virus or hiv	32,691
	S2	MH hiv infection	945
	S3	TI (HIV infection or Human immunodeficiency virus or HIV) OR AB (HIV infection or Human immunodeficiency virus or HIV)	104,219
	S4	S1 OR S2 OR S3	106,982
	S5	MH care cascade	1,284
	S6	MH continuum of care	7,104
	S7	MH 90-90-90	17,568
	S8	TI (care cascade or cascade of care or continuum of care or "care cascade progress" or UNAIDS 90-90-90 progress" or UNAIDS 90-90-90 or "cross-sectional care cascade") OR AB (care cascade or cascade of care or continuum of care or "care cascade progress" or UNAIDS 90-90-90 progress" or UNAIDS 90-90-90 or "cross-sectional care cascade")	5,497
	S9	S5 OR S6 OR S7 OR S8	6,288
	S10	S4 AND S9	916
	S11	MH Multistate models	293
	S12	MH Multi-state models	1,763
	S13	MH Markov models	2,000
	S14	TI (Multistate models or Multi-state models or Markov models or "longitudinal care cascade") OR AB (Multistate models or Multi-state models or Markov models or "longitudinal care cascade")	3,925
	S15	S11 OR S12 OR S13 OR S14	3,992
	S16	S10 AND S15	5
	S17	S10 OR S16	916
EMBASE (Search date 15-07-2022)	#1	'human immunodeficiency virus'/exp OR 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus':ti,ab,kw OR 'human immunodeficiency virus infection':ti,ab,kw OR hiv:ti,ab,kw OR 'hiv infection':ti,ab,kw	601495
	#2	'cascade of care'/exp OR 'continuum of care'/exp OR 'care continuum':ti,ab,kw OR '90 90 90':ti,ab,kw OR 'care cascade':ti,ab,kw OR 'cascade of care':ti,ab,kw OR 'continuum of care':ti,ab,kw OR 'care cascade progress':ti,ab,kw OR 'unaids 90-90-90 progress':ti,ab,kw	9220

		OR 'unaids 90-90-90':ti,ab,kw OR 'cross-sectional care cascade':ti,ab,kw	
	#3	#1 AND #2	3145
	#4	'multistate model'/exp OR 'multistate model' OR 'multi state model'/exp OR 'multi state model' OR 'markov chain'/exp OR 'markov chain' OR 'multistate models':ti,ab,kw OR 'multi state models':ti,ab,kw OR 'markov models':ti,ab,kw OR 'longitudinal':ti,ab,kw	429711
	#5	#3 AND #4	171
	#6	#3 OR #5	3145
Other strategic searches	PubMed and Google scholar search using individual key works such as “HIV care cascade” or “HIV care cascade and multistate models” or “HIV care cascade and multi-state models” or “HIV care cascade and Markov models”. Bibliographic list of the articles.		136

Table S4.2: Data extraction tool for the scoping review

Information extracted from articles	Possible responses
Paper ID number	
Authors	
Study site in terms of the country	
The specific study site of the research article	
The level of study representation	
The study design	Cross-sectional, Case-Control, Longitudinal, Cohort, Prospective cohort, Retrospective cohort, Clinical trial, Not stated in the article, Other
Other study designs not listed above.	
Data sources for the studies reviewed	Cohort data, Laboratory test data (including CD4 and viral load tests), Medical records from the hospital, Survey data, Simulated data (mathematical modeling), Surveillances, Others
Specify other data sources not listed in the list above.	
Number of patients/participants included in the final analysis of the study	
The actual age of participants included in the study	
Categories of the age of participants included in the study	All (children and adults) PLHIV, Adults (≥18 years), Adults (≥15 years), Adults (≥16 years), Adolescents and adults (>=13 years), Adolescents and adults (>=12 years), Adolescents (10-19 years), Neonates
Type of participants included in a research article	All (mixture) PLHIV, Children only, Adolescents, Adults, Key populations, Migrants, Prisoners, Veterans, Refugees, Military
Key population, please specify	Men having sex with men, Female sex workers, injected drug users, Transgender women, Transgender men
Cascade size	Full cascade stages, More than full cascade (> 6 stages), Medium cascade stages, Small to very small cascade stages, Other
Specify other study outcomes.	
Number of the cascade stages	
Actual stage name	
stage 1	
stage 2	
stage 3	
stage 4	
stage 5	
stage 6	
stage 7	
stage 8	
stage 9	
Absorbing state	Death, LTFU, Transfer, Other
Specify other absorbing states.	

Information extracted from articles	Possible responses
The type of multistate model used	Non-Parametric multistate model, Parametric, continuous-time multistate Markov model, Time-homogeneous Markov models, Discrete-time multistate Markov model, General multistate model, Other
Specify other types of multistate models used	
Multistate model assumptions	
Assessment starting point (baseline)	Enrolment/recruitment date, ART start date
Reason for censoring	
Descriptions of statistics used	Prevalence, Incidence rates, Proportion for each stage of HIV care cascade, Chi-square test of independence, Fisher Exact test (small sample size), t-test, Wilcoxon rank test, Time spent in each cascade stage, Transition probabilities, Mean, Standard deviation, Median, Interquartile range
Type of regression models used	Logistics regression, Cox Ph regression, Poisson regression, competing risk regression, Generalized linear regression model (GLM), Weighted linear regression, Mathematical back-calculation, Log-Binomial regression, Generalized linear mixed models (GLMM), Multinomial regression model, Other
Other regression models specify	
The method used for handling missing data.	Weighted analysis, Multiple imputations, Missing data indicator, Not addressed
Methods used for assessing the goodness of fit of the model	Pearson-type Chi-Square test, Visual comparison of observed and fitted value plots, Not assessed, Other
Other methods for assessing the goodness of fit of the model	
Broad categories of approaches used in research articles	Cross-sectional, Longitudinal
Specification of the cascade staging method	Yes, no
Cascade staging method	Dependent, independent, and both dependent and independent

Table S4.3: Cascades stages used in HIV cascade and continuum of care assessments in articles included in this review

Cross-sectional	**Longitudinal**
ALL (HIV negative)	PLHIV
PLHIV (incidence and prevalence)	Diagnosis
Diagnosis	Linkage to care or in HIV care
Linkage to care	Optimal care
ART eligibility	On ART (in care or transferred out or LTFU or re-engaged or death)
Clinical staging	No ART or off-ART (in care or transferred out or LTFU or death)
On ART (history of ART or ever on ART and current use of ART)	ART eligibility
ART adherence	Retention in care
Retention in care	LTFU or disengaged
Viral load suppression	Sub-optimal care
LTFU	Engagement in care
In care	Transferred out
Death	Death
CD4 testing	Viral load suppression or high CD4

Table S4.4: The reported study design and data analysis methods used to assess the HIV cascade and continuum of care among longitudinal studies (n=21)

Reported study design	Data analysis methods used	Number of articles
Longitudinal	Survival analysis: Competing risk methods	5
Longitudinal	Repeated cross-sectional	1
Longitudinal	Survival analysis	2
Longitudinal	Survival analysis and multistate models	6
Longitudinal	Cross-sectional analysis	5
Longitudinal	Repeated cross-sectional and the time spent in the cascade stage	1
Longitudinal	Repeated measure analysis	1

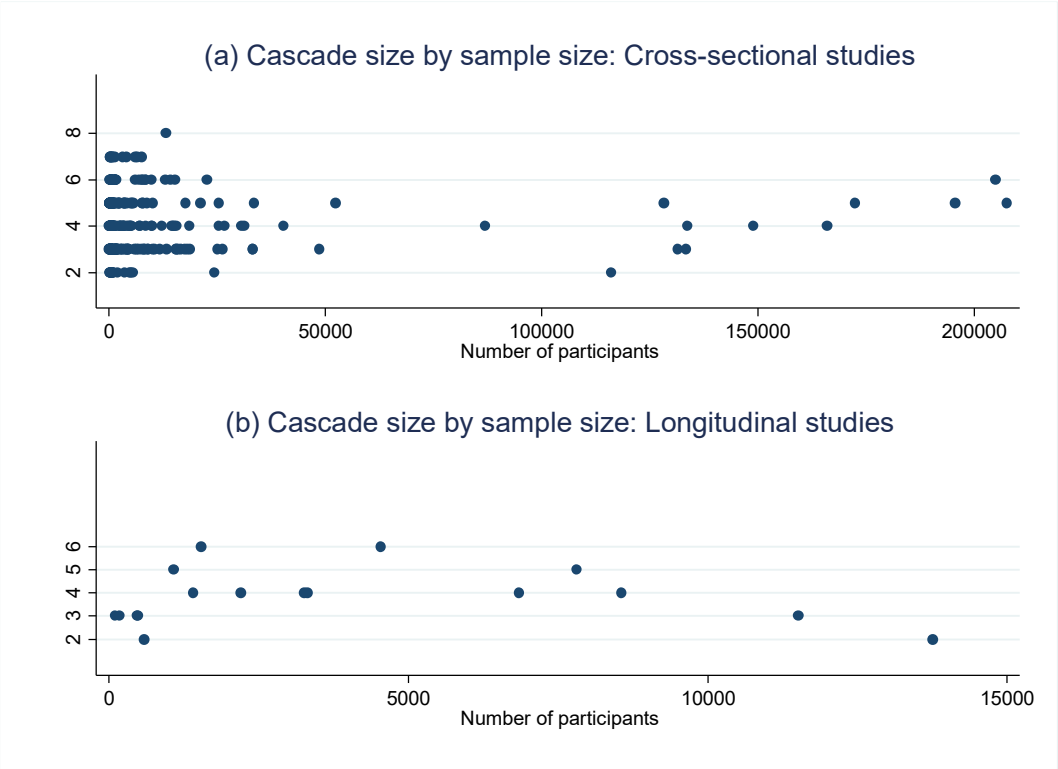
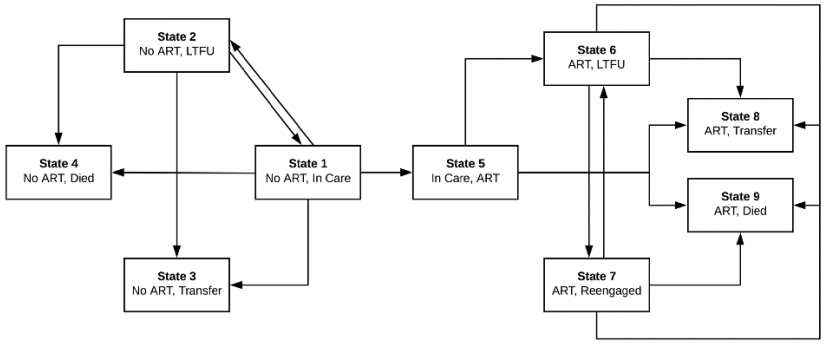
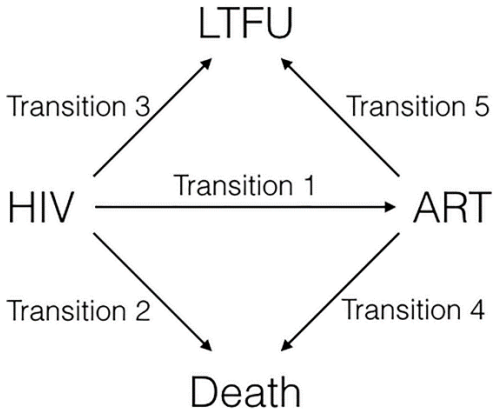


Figure S4.1: The distribution of cascade size by study number of participants included, in panel (a), sample size was truncated at 300,000 (excluded 12 studies), and in panel (b), sample size was truncated at 20,000 (excluded 4 studies) to allow better visualization of the distribution.

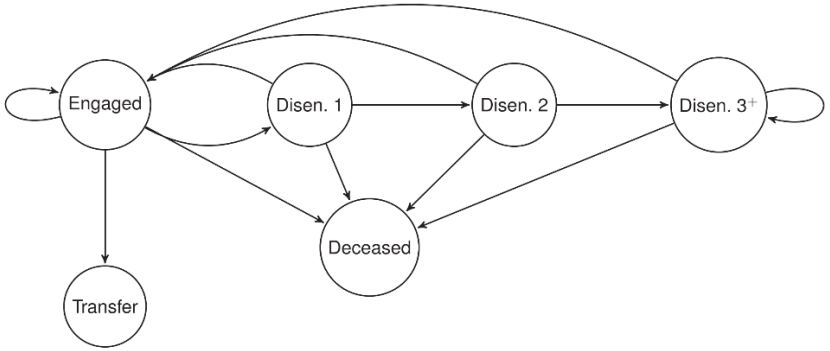
(a) Mody et al 2020



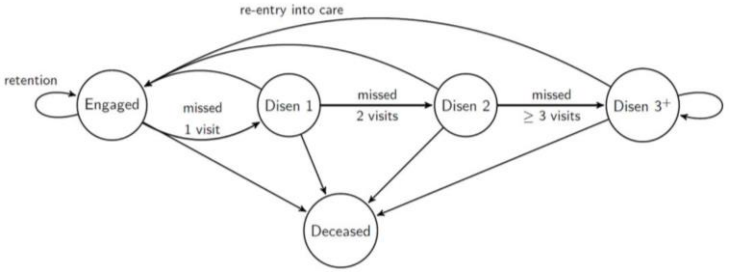
(b) Rahmalia et al 2019



(c) Lee et al 2017



(d) Lee et al 2018



(e) Wang et al 2019

(f) Gillis et al 2016

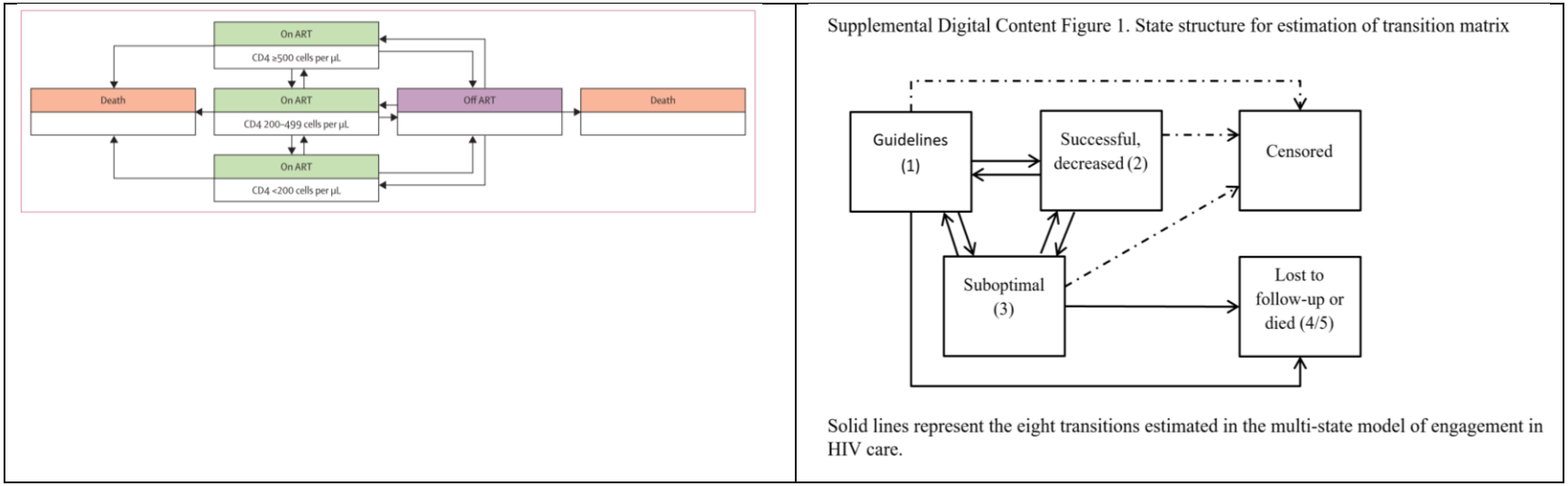


Figure S4.2: Multistate frameworks of included articles

CHAPTER FIVE: HIV Cascade and Transition Dynamics

5.0. Introduction to the chapter

The scoping review Chapter showed that few studies applied longitudinal design methods to assess the HIV cascade and continuum of care. Among those, very few applied both the cross-sectional and longitudinal methods in the assessment of the cascade. In these, the classical survival models were used in longitudinal cascade assessments. In this chapter, the cross-sectional and longitudinal design methods (with the application of multistate models) were used in the assessment of the advancement of the HIV cascade and engagement in care among PLHIV enrolled in care at the CDCI, in Ifakara, Morogoro, Tanzania. This chapter covered two objectives of the predefined thesis objectives. The second objective was about the description of the transition dynamics along the HIV cascade and continuum of care of PLHIV enrolled at the CDCI, Tanzania, between 2005 and 2022. The third objective was about the modelling of transition probabilities along the HIV care cascade and continuum of care among PLHIV enrolled in care at the CDCI, Tanzania, between 2005 and 2022.

In cross-sectional analyses, a high proportion of VL suppression was found in PLHIV on ART and retained in care (95%), with the UNAIDS target of 2025 being achieved as of September 2022. However, the longitudinal assessment of the same PLHIV showed in-and-out of care transitions were common. The 12 months after enrollment and LTFU were an important window for maximizing retention in care. Furthermore, PLHIV on ART at enrolment were less likely to be LTFU, while those on ART and LTFU were more likely to return to care compared to those not on ART at enrolment. The details of the assessment are summarized in this Chapter, and the Chapter is organized in the journal manuscript format for observational cohort studies, starting with the title page, abstract, introduction, methods, results, discussion, conclusion, and statements.

Progress of HIV care cascade and transition dynamics along the continuum of care among persons living with HIV in Ifakara, Tanzania: A prospective study

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5.1. Abstract

Introduction: While cross-sectional assessments offer snapshots of care cascade progress, longitudinal analyses are essential to capture the dynamic engagement in care of people living with HIV (PLHIV). Therefore, we assessed the advancement of the HIV care cascade and engagement in care among PLHIV at the CDCI, Ifakara, Tanzania, using both cross-sectional and longitudinal analyses.

Methods: In this prospective study, we included PLHIV enrolled in care from April 2005 to September 2022 and consented to the Kilombero and Ulanga Antiretroviral Cohort. A cross-sectional care cascade was assessed descriptively. In the longitudinal analysis, we used continuous-time, non-parametric multistate, and Cox proportional hazards models to assess engagement in care.

Results: Of the 11,591 PLHIV enrolled, 7353 (63%) were female and 8637 (75%) were adults aged 20-49 years. Cross-sectionally, 9599 (83%) of the enrolled PLHIV were initiated on antiretroviral therapy (ART), and 3647 (38%) participants of those on ART were retained in care, and of these, 3450 (95%) had a viral load (VL) <1000 copies/mL as of September 2022. The repeated cross-sectional cascade results showed that the proportion of ART initiation increased over time (from 67% in April 2005-January 2009 to 96% in April 2019-September 2022). In the longitudinal assessment, at 12 months, 45% were in care, and 24% were lost to follow-up (LTFU). After being LTFU, 34% returned to care within 12 months. Being on ART at baseline was associated with a reduced risk of LTFU (adjusted Hazard ratio (aHR)=0.71; 95% Confidence interval (CI): 0.67-0.75) and an increased hazard of return to care after being LTFU (aHR=1.38; 95% CI: 1.31-1.45). Being PLHIV aged ≥15 years and in WHO HIV stage 3 (aHR=1.09; 95% CI: 1.03-1.16) and stage 4 (aHR=1.31; 95% CI: 1.21-1.42) were associated with an elevated hazard of LTFU, while those in WHO HIV stage 4 (aHR=0.76; 95% CI: 0.69-0.83) had a reduced hazard of returning to care after being LTFU.

Conclusions: Cross-sectional analyses showed a high proportion of VL suppression, achieving the UNAIDS target among PLHIV retained in care. However, longitudinal models revealed that many PLHIV transitioned in-and-out of care, and the first 12 months after enrolment and LTFU are important time windows for maximizing retention.

5.2. Introduction

Quantification of the HIV care cascade from diagnosis to viral load (VL) suppression is crucial for monitoring the progress of national and sub-national HIV treatment programs. Additionally, care cascade assessments are used to track the progress of the 2025 Joint United Nations Programme on HIV/AIDS (UNAIDS) target (95-95-95) (13). That is by 2025, 95% of people living with HIV (PLHIV) will be aware of their HIV status, 95% of those diagnosed positive will be initiated on antiretroviral therapy (ART), and 95% of those on ART will be virally suppressed. However, the reports of 95-95-95 are cross-sectional and do not capture the longitudinal HIV care journeys of PLHIV over time, which often include repeated cycles of disengagement and return to care, as well as deaths (21,22). As HIV treatment programs have advanced and are closer to reaching epidemic control, it has become increasingly necessary to understand how these complex care transitions unfold over time to identify where the relevant gaps in care lie.

The majority of global (136), national (10,11,147), and sub-national (45,148) assessments of the care cascade use cross-sectional design methods (149). However, these methods only provide a snapshot of time, depicting engagement in care as a linear process. The methods fail to capture critical events that unfold over time, including repeated cycles of disengagement and reengagement in care, or death (15,111). For example, cross-sectional HIV care cascade metrics can be improved from one year to the next simply by removing individuals who are doing poorly and have died from the denominator in the following year's assessment, even though these are undesirable outcomes. However, for the case of longitudinal cascade analyses, these methods can capture the dynamic nature of PLHIV engagement in care over time, which includes poor engagement in care (55).

Cascade researchers proposed the application of multistate models to address the in-and-out of care behavior of PLHIV (14,32,66). Previous studies have compared cross-sectional and longitudinal continuum of care using standard survival analysis and competing risk methods (29,73,104,137). Furthermore, in Tanzania, the cascade of care is often evaluated using cross-sectional design methods (130,147), and cascade progress differs between studies. Few studies applied longitudinal study design methods or both cross-sectional and longitudinal design methods (46). Therefore, the study assessed the advancement of the HIV care cascade and engagement in care among people living with HIV (PLHIV) at the Chronic Disease Clinic of Ifakara (CDCI) and

consented to the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) in Ifakara, Tanzania, using both cross-sectional and longitudinal methods with the application of multistate models.

5.3. Methods

5.3.1. Study setting and participants

The study was conducted at the CDCI, the HIV care and treatment center of the St. Francis Regional Referral Hospital in Ifakara, Morogoro, Tanzania. The CDCI serves PLHIV from the Kilombero, Ulanga, and Mlimba districts. The clinic is a public-private partnership that provides HIV services following the Tanzanian HIV and AIDS Management Guidelines. It offers a research platform for HIV and related co-morbidities through the KIULARCO, established in 2005. The cohort routinely collects data on demographic, clinical, pharmacological, and laboratory assessments of the KIULARCO-consenting PLHIV using standardized tools in an integrated Open Medical Record System (OpenMRS) in the clinic (89).

5.3.2. Inclusion and exclusion criteria

This study included all PLHIV enrolled at the CDCI from 04/2005 to 09/2022 and consented to KIULARCO. We excluded transient PLHIV (those who visited the clinic only for medical consultation or drug refills and had no intention of continuing with HIV care and treatment at the CDCI) and PLHIV with missing date of birth or sex variables.

5.3.3. Explanatory variables

We included socio-demographic baseline variables, such as sex, age, marital status, education level, occupation, and distance from the clinic to the ward center of the PLHIV residence. Clinical variables included pregnancy status of female PLHIV, partner HIV status, HIV disclosure status, body mass index (BMI), WHO HIV stage, CD4 cell count, and CD4 percentage of children below 5 years. Education level, occupation, partner HIV status, and disclosure status variables were assessed only among PLHIV aged ≥15 years. Furthermore, the enrolment time was categorized into six groups corresponding to Tanzanian National Guidelines for the Management of HIV and

AIDS changes as follows: April 2005-January 2009, February 2009-March 2012, April 2012-April 2015, May 2015-September 2017, October 2017-March 2019, and April 2019-September 2022.

5.3.4. Analyses

Cross-sectional HIV care cascade framework

In a cross-sectional design, individuals' current care status as of September 7th, 2022 was assessed based on four stages: first, recruitment at CDCI. The second was ART initiation (PLHIV with ART initiation date (69)). The third was retention in care at CDCI (PLHIV with no records of transfer, loss to follow-up (LTFU), or death). The fourth was treatment response (latest within one year from the date of database closure for analysis). The treatment response was either an immunological response or VL suppression. The immunological response was defined as having a CD4 percentage ≥30% for PLHIV aged <1 year or CD4 percentage ≥25% for PLHIV aged 1-2 years or CD4 percentage ≥20% for PLHIV aged 3-4 years, or CD4 cell count ≥350 cells/mm^3 for PLHIV aged ≥5 years (150,151). Suppressed VL was defined as VL <1000 copies/mL (152) and VL <50 copies/mL (153). PLHIV who did not meet the CD4 or VL criteria and those missing these tests were categorized as poor treatment response (69,150).

Cross-sectional assessment of HIV care cascade

The cross-sectional care cascade progress was estimated descriptively overall and stratified by sex and age (at baseline and last recorded visit). The cascade was further stratified by enrolment time following the Tanzanian guideline implementation period using repeated cross-sectional analyses with analyses done at the end of each implementation time (73,150). We assessed the cross-sectional care cascade using both a dependent staging approach, whereby PLHIV were required to complete all prior stages, and an independent approach, whereby each care cascade stage was derived independently of the prior stages (the denominator was all PLHIV enrolled) (123). The independent staging findings were only presented for treatment response.

Longitudinal engagement in care framework

After being enrolled in an HIV clinic, individual engagement in care may change over time, and a longitudinal design was used to assess the different patterns of engagement in care. We adopted the "HIV state and transition" framework proposed previously (15,66). PLHIV individuals were grouped into five mutually exclusive and exhaustive states as depicted in Figure 5.1; an individual was either in active care (state 1), LTFU (state 2; defined as late for a scheduled appointment for >60 days (78)), re-engaged in care after LTFU or transfer (state 3; used to distinguish those who remained in care throughout from those with at least one event due to varying probabilities of future transitions and to better capture the experiences (32,111)), transferred to another HIV clinic (state 4), or all cause-death (state 5; considered as absorbing state i.e., no out of state transitions). In this framework, in care state, time zero was the enrolment date; in the LTFU state, time zero was the LTFU date; and in the transfer-out state, time zero was the date of transfer-out. PLHIV was censored at either death or the end of follow-up (i.e., September 7th, 2022).

Longitudinal assessment of engagement in HIV care and treatment

A continuous-time non-parametric multistate Markov model was used to assess engagement in care in two stages. First, the Nelson-Aalen estimator was used to estimate baseline cumulative hazards as explained in Eq.2 in Chapter Three (65,97). Thereafter, transition probabilities over time were estimated using the Aalen-Johansen estimator as described in Eq.3 in Chapter Three (98). Transition probabilities were estimated overall, stratified by age and enrolment years, focusing on care and LTFU states. Finally, separate Cox proportional hazards models described in Eq.5 in Chapter Three were used to identify baseline factors associated with different transitions, with time zero being the entry into a particular state. A complete case analysis was performed after excluding variables that had missing data due to improvements in data collection tools. Data management and analysis were performed using Stata software version 14 (StataCorp LP, College Station, Texas, USA) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

5.4. Results

5.4.1. Patient characteristics at enrolment

As of September 7th, 2022, a total of 12,411 PLHIV were enrolled and consented to KIULARCO. Among these, 820 PLHIV were excluded (772 were transient PLHIV, 13 had missing birth dates, 21 had missing sex information, and 14 were enrolled before April 2005). Among the 11,591 PLHIV included, 7353/11591 (63%) were female and 8637/11591 (75%) were adults aged 20-49 years. The proportion of PLHIV with HIV-negative partners was above 10% from May 2015 onward (Table 5.1). Over the years, the proportion of PLHIV with known HIV positive partner increased from 282/3061 (9%) in April 2005-January 2009 to 163/845 (19%) in October 2017-March 2019, while PLHIV with partners of unknown HIV status reduced from 2578/3061 (84%) in April 2005-January 2009 to 330/1218 (27%) in April 2017-September 2022. Lastly, the proportion of PLHIV in WHO HIV stage 1 gradually increased over time, with 647/1316 (49%) being in stage 1 in April 2019-September 2022.

5.4.2. Progress of the cross-sectional HIV care cascade

Among PLHIV enrolled since April 2005, 9599 (83%) were initiated on ART, of which 3647 (38%) were retained in care as of September 2022 (Figure 5.2). Ninety-five percent of PLHIV initiated on ART and retained in care had VL <1000 copies/mL and 90% had VL <50 copies/mL. Among all PLHIV enrolled in care from 2005 (independent approach), only 37% had VL <1000 copies/mL and 35% had VL<50 copies/mL by September 2022. The assessment by age at enrolment shows a similar proportion of ART initiation across different age groups, and a high proportion of VL <1000 copies/mL (>93%) was among PLHIV on ART and retained in care, except for adolescents (89%) (Table 5.2). However, the assessment by age at the last recorded visit showed the highest proportion of ART initiation (91%) and VL <1000 copies/mL (96%) among the elderly (Table S5.1).

The repeated cross-sectional cascade results showed the proportion of ART initiation increased over time (from 67% in April 2005-January 2009 to 96% in April 2019-September 2022) (Table 5.2). The proportions of retention in care across years were between 57% and 80%. Among PLHIV on ART and retained in care, the proportion of achieving immune response was only 32% in

PLHIV enrolled in April 2005-January 2009, and 48% of the PLHIV enrolled in May 2015-September 2017 on ART and retained in care had achieved immune response or suppressed VL. We further observed that the majority of PLHIV had CD4 tests for April 2012 to March 2019, hence the composite outcome that combined immune response or suppressed VL was largely from CD4. Of the 2796 PLHIV with CD4 or VL tests between April 2012 and March 2019, 2,777 (99%) PLHIV had CD4 tests, and of those, 1447 (52%) PLHIV had CD4 ≥ 350 cells/mm^3. The CD4 tests decreased from 1275 PLHIV with tests in April 2012-April 2015 to 625 tests in October 2017-March 2019. While in the same period, 739 (26%) PLHIV had VL tests done, and of those, 619 (84%) PLHIV had VL < 1000 copies/mL. In this case, VL tests increased from 265 tests in April 2012-April 2015 to 301 tests in October 2017-March 2019. In recent years (April 2019-September 2022), 82% of PLHIV on ART and retained in care had VL<1000 copies/mL.

5.4.3. Status of the longitudinal engagement in HIV care and treatment

The proportion of PLHIV remaining in care (without any event) decreased over time, with 45% (95% confidence interval (CI): 44-46%) remaining in care in the first 12 months and 12% (95% CI: 11-12%) at 60 months (Figure 5.3a and Table S5.2). In 12 months after enrolment, 24% (95% CI: 23-25%) were in the LTFU state. After LTFU, at 12 months, 60% (95% CI: 59-61%) of the PLHIV LTFU remained in the LTFU state, while the probability of being in the re-engage state was 34% (95% CI: 33-35%) (Figure 5.3b and Table S5.2). Lastly, 75% (95% CI: 73-77%) of the transferred PLHIV remained transferred at 60 months (Figure 5.3c and Table S5.2).

The transition probabilities between states by age were similar in PLHIV aged <15 years and those aged ≥15 years. However, PLHIV aged <15 years were slightly more likely to be transferred over time (Figure 5.4). Over time, the proportion of PLHIV in the death state was higher in PLHIV enrolled when eligibility for treatment was determined by CD4 and WHO clinical stage (April 2005-September 2017) than in PLHIV enrolled during "treat all" (October 2017-September 2022) (Figure S5.1a and b). Retention in care among PLHIV enrolled in earlier years decreased over time (Figure S2a and b), and the increasing trend of re-engagement in care over time was similar across the years (Figure S5.2-S5.4).

5.4.4. Factors associated with LTFU and return to care from LTFU and transfer

We identified several factors associated with the hazard of transition from care to LTFU in PLHIV aged ≥15 years (Table 5.3). Compared to male PLHIV, being female was associated with a reduced hazard of LTFU (Hazard ratio (HR)=0.86; 95% CI: 0.82-0.91). PLHIV aged 31-49 years (HR=0.90; 95% CI: 0.85-0.95) or age ≥50 years (HR=0.89; 95% CI: 0.82-0.96) were also related to a reduced hazard of being LTFU compared to PLHIV aged 15-30 years. Furthermore, being on ART at baseline was associated with a reduced hazard of LTFU compared to PLHIV enrolled while they were ART naïve (HR=0.71; 95% CI: 0.67-0.75). Compared to PLHIV married or cohabiting, those who were never married were more likely to become LTFU (HR=1.26; 95% CI: 1.16-1.36). Living far from the clinic (≥81 Km) was associated with an increased hazard of being LTFU compared to PLHIV who lived in ≤1 Km (HR=1.26; 95% CI: 1.17-1.35). PLHIV with HIV negative partner (HR=1.11; 95% CI: 1.01-1.23), unknown HIV status (HR=1.17; 95% CI: 1.09-1.26), and those without a partner (HR=1.13; 95% CI: 1.02-1.24) had an increased hazard of being LTFU compared to PLHIV with HIV positive partner. Lastly, being in WHO HIV stage 3 (HR=1.09; 95% CI: 1.03-1.16) and stage 4 (HR=1.31; 95% CI: 1.21-1.42) were associated with an elevated hazard of LTFU compared to PLHIV in WHO HIV stage 1. These findings were broadly similar to the analyses focused on PLHIV aged <15 years (Table S5.3).

We also identified several characteristics associated with return to care after being LTFU among PLHIV ≥15 years (Table 5.3). For example, compared to PLHIV aged 15-30 years, PLHIV aged 31-49 years were more likely to return to care (HR=1.18; 95% CI: 1.12-1.25). PLHIV who lived in ≥81Km had an increased hazard of returning to care compared to PLHIV living in ≤ 1Km (HR=1.27; 95% CI: 1.19-1.36). PLHIV on ART at baseline had an increased hazard of returning to care compared to those who were ART naïve (HR=1.38; 95% CI: 1.31-1.45). Additionally, PLHIV never married (HR=0.91; 95% CI: 0.84-0.99 compared to those who were married or cohabiting) and those in WHO HIV stage 4 (HR=0.76; 95% CI: 0.69-0.83 compared to those in WHO HIV stage 1) had a reduced hazard of returning to care. However, in analyses that used PLHIV <15 years, PLHIV in WHO HIV stage 2 were more likely to return to care compared to those in WHO HIV stage 1 (HR=1.37; 95% CI: 1.12-1.67) (Table S5.3).

The analysis of return to care after transfer of PLHIV aged ≥15 years (Table 5.3) shows that those separated/divorced/widowed had an increased hazard of return to care compared to those who were married or cohabiting (HR=1.23; 95% CI: 1.01-1.51). The characteristics associated with a reduced hazard of return after transfer included being female (HR=0.79; 95% CI: 0.66-0.95, compared to male), PLHIV aged 31-49 years (HR=0.81; 95% CI: 0.66-0.98, compared to PLHIV aged 15-30 years), PLHIV aged ≥50 years (HR=0.61; 95% CI: 0.47-0.80, compared to PLHIV aged 15-30 years), those living ≥81 Km (HR=0.72; 95% CI: 0.58-0.89, compared to those who lived ≤ 1Km), and PLHIV with unknown HIV status partner (HR=0.70; 95% CI: 0.55-0.89, compared to PLHIV with HIV positive partner). However, in the analyses of PLHIV aged <15 years, these relationships were absent, and we noted a small sample size for this transition (Table S5.3).

5.5. Discussion

This study comprehensively evaluated the care cascade using cross-sectional and longitudinal design methods. It covered approximately 17 years, spanning several HIV and AIDS Management Guidelines in Tanzania, for a better understanding of the clinic. In the cross-sectional cascade, over the years, the proportion of ART initiation increased from 66% in April 2005-September 2009 to 96% in April 2019-September 2022. Among PLHIV on ART and retained in care, 95% had VL <1000 copies/mL, with only 37% of all PLHIV enrolled having VL <1000 copies/mL. Furthermore, across the years, the proportion of PLHIV on treatment and retained in care was between 56 and 80%. However, in longitudinal analyses, in the first 12 months, only 45% of the enrolled PLHIV remained in care, and 24% were LTFU. Among those LTFU, 34% returned to care within 12 months. Being on ART at enrolment reduced the hazard of LTFU (HR=0.71; 95% CI: 0.67-0.75) and increased the hazard of return to care after being LTFU (HR=1.38; 95% CI: 1.31-1.45).

In cross-sectional analyses, the increased proportion of ART initiation was mostly related to the changes in the HIV and AIDS Management Guidelines from treatment by eligibility to “treat all”. We further found that 95% of PLHIV in care and on ART were suppressed, and the result was similar to that of the national estimate (2). This indicates good progress towards attaining the UNAIDS 2025 third target. However, in longitudinal analyses, frequent in-and-out-of-care

transitions highlight ongoing challenges and the need for interventions aiming to retain PLHIV in care, especially in the first 12 months. Even though our model formulation did not distinguish pre- and post-ART initiation, our transition probability estimates assessed after being LTFU were similar to those of Zambia for the assessment of LTFU before initiating ART. At one year, the study found 32% returned to care after being LTFU, and 52% remained LTFU (32). This information is not captured by cascade analyses applying only cross-sectional design methods. PLHIV out-of-care are likely to have detectable VL because of poor treatment adherence (18).

The in-and-out of care threatens the benefits of the "treat all" strategy. In this study, being on ART at baseline was associated with a reduced risk of LTFU and an increased likelihood of returning to care, which was similar to studies conducted in Kenya and the USA (14,54). PLHIV on ART and temporarily out of care are at increased risk of detectable VL (18), which increases the risk of onward HIV transmission, drug resistance, and HIV-related deaths (154). Furthermore, PLHIV LTFU who return to care often present with advanced HIV that was not previously diagnosed (155). This complicates the management of HIV because of the complex management of opportunistic infections such as tuberculosis and cryptococcal meningitis. Currently, the clinic offers enhanced adherence counseling for PLHIV with unsuppressed VL as per national guidelines and video interventions to reduce stigma and improve retention (156).

This study has several limitations. First, retention in care was based on retention at CDCI. PLHIV transferred could be retained in other HIV clinics, but this information is not accessible to CDCI because the HIV clinics are not interconnected in terms of data capture. Furthermore, there is a chance that PLHIV who are LTFU are also self-transferred to other clinics (157) and retained in care elsewhere, hence underestimating retention. Second, the return to care assessed was a return to the CDCI, and there is a possibility of underestimating the proportion of patients returning to care, especially when LTFUs self-transfer to other HIV clinics without notifying the CDCI. Finally, the estimate may not be representative of PLHIV enrolled at the CDCI and did not consent to KIULARCO.

5.6. Conclusions

In the cross-sectional analyses, the proportion of VL suppression was high, with the UNAIDS 3rd 95% target being achieved among PLHIV on ART and retained in care. However, the longitudinal analysis results showed varied risks of transitioning in-and-out of care, and this information was sparsely reported in cross-sectional cascade analyses. Furthermore, many PLHIV who were LTFU returned to care within 12 months, and baseline characteristics were associated differently with different state transitions. To improve retention in care, interventions should focus on the first 12 months after enrolment with enhanced tracing of PLHIV who are LTFU to ascertain their outcomes.

5.7. Statements

5.7.1. Authors' contributions

A.V.K designed the study, conducted all analyses, and drafted the manuscript; F.V., A.M., and K.O. contributed to designing the study, supervised analyses, and reviewed the manuscript; T.R.G., M.W., E.L., and H.M. contributed to designing the study and reviewing the manuscript. All authors have read and approved the final manuscript.

5.7.2. Conflict of interest statement

Other authors have declared no conflict of interest, except A.V.K., who received funds from the Consortium for Advanced Research Training in Africa (CARTA) for the Ph.D. studies, and this article is part of the Ph.D. outcome and received payment from the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) through Ifakara Health Institute. A.M. had grants from the National Institute of Health, the Bill and Melinda Gates Foundation, and Gilead. F.V. and T.R.G. received payment from KIUALRCO through the Swiss Tropical and Public Health Institute.

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Public Health Institute, Switzerland; the University Hospital Basel, Switzerland; the Ifakara Health Institute, Tanzania; and the United States Agency for International Development (USAID) Afya Yangu through USAID from the President's Emergency Plan for AIDS Relief (PEPFAR) program.

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5.7.4. Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5.7.5. Acknowledgments

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5.8. Figures and Tables

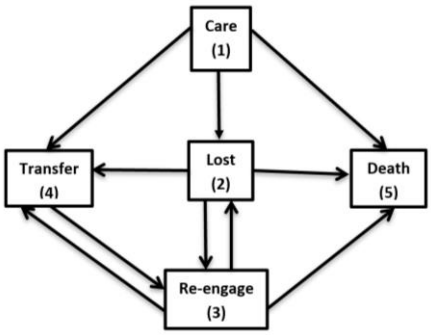

Figure 5.1: The state-transition framework for engagement in care at the CDCI. PLHIV were transitioning from LTFU to death or LTFU to transfer out via the information obtained during LTFU tracing in the community. The information is updated in the OpenMRS system. CDCI: Chronic Disease Clinic of Ifakara; PLHIV: People living with HIV; LTFU: Loss to follow-up; OpenMRS: Open Medical Records System

Table 5.1: Percentage distribution of baseline characteristics of people living with HIV enrolled in care from 2005 to 2022 (n=11,591)

Characteristics	Overall (n=11591)	Apr2005-Jan2009 (n=3356)	Febr2009-Mar2012 (n=2417)	Apr2012-Apr2015 (n=1848)	May2015-Sept2017 (n=1697)	Oct2017-Mar2019 (n=957)	Apr2019-Sept2022 (n=1316)
Sex							
Male	4238 (36.6)	1226 (36.5)	903 (37.4)	647 (35.0)	644 (38.0)	361 (37.7)	457 (34.7)
Female	7353 (63.4)	2130 (63.5)	1514 (62.6)	1201 (65.0)	1053 (62.1)	596 (62.3)	859 (65.3)
Age							
Children (< 10 years)	877 (7.6)	241 (7.2)	198 (8.2)	138 (7.5)	128 (7.5)	100 (10.5)	72 (5.5)
Adolescent (10-19 years)	423 (3.7)	102 (3.0)	77 (3.2)	69 (3.7)	64 (3.8)	36 (3.8)	75 (5.7)
Adults (20-49 years)	8637 (74.5)	2619 (78.0)	1827 (75.6)	1339 (72.5)	1238 (73.0)	667 (69.7)	947 (72.0)
Elderly (≥50 years)	1654 (14.3)	394 (11.7)	315 (13.0)	302 (16.3)	267 (15.7)	154 (16.1)	222 (16.9)
Marital status[†]							
Married or cohabiting	5853 (55.6)	1474 (48.2)	1170 (53.5)	1016 (60.5)	911 (59.1)	512 (60.6)	770 (63.2)
Never married	1423 (13.5)	541 (17.7)	349 (16.0)	156 (9.3)	158 (10.3)	90 (10.7)	129 (10.6)
Separated/divorced/widowed	3105 (29.5)	910 (29.7)	657 (30.0)	503 (30.0)	473 (30.7)	243 (28.8)	319 (26.2)
Missing	152 (1.4)	136 (4.4)	12 (0.6)	4 (0.2)	0 (0)	0 (0)	0 (0)
Education level[†#]							
None	676 (6.4)	59 (1.9)	74 (3.4)	131 (7.8)	190 (12.3)	87 (10.3)	135 (11.1)
Primary school	5901 (56.0)	849 (27.7)	911 ((41.6)	1313 (78.2)	1231 (79.8)	674 (79.8)	923 (75.8)
Secondary school and above/other	588 (5.6)	55 (1.8)	66 (3.0)	102 (6.1)	121 (7.9)	84 (9.9)	160 (13.1)
Missing	3368 (32.0)	2098 (68.5)	1137 (52.0)	133 (7.9)	0 (0)	0 (0)	0 (0)
Occupation[†]							
Farmers	5983 (56.8)	830 (27.1)	921 (42.1)	1299 (77.4)	1312 (85.1)	676 (80.0)	945 (77.6)
Non-Farmers	1182 (11.2)	133 (4.3)	130 (5.9)	247 (14.7)	230 (14.9)	169 (20.0)	273 (22.4)
Missing	3368 (32.0)	2098 (68.5)	1137 (52.0)	133 (7.9)	0 (0)	0 (0)	0 (0)
Pregnant or not, among females							
Not pregnant	5264 (71.6)	1076 (50.5)	993 (65.6)	1011 (84.2)	953 (90.5)	532 (89.3)	699 (81.4)
Pregnant	529 (7.2)	65 (3.1)	96 (6.3)	91 (7.6)	86 (8.2)	60 (10.1)	131 (15.3)
Missing	1560 (21.2)	989 (46.4)	425 (28.1)	99 (8.2)	14 (1.3)	4 (0.7)	29 (3.4)
Distance to the clinic							
≤ 1 Km	4507 (38.9)	1075 (32.0)	963 (39.8)	774 (41.9)	588 (34.7)	387 (40.4)	720 (54.7)
2- 80 Km	4695 (40.5)	1359 (40.5)	1085 (44.9)	725 (39.2)	733 (43.2)	372 (38.9)	421 (32.0)
≥ 81 Km	1748 (15.1)	583 (17.4)	296 (12.3)	303 (16.4)	301 (17.7)	158 (16.5)	107 (8.1)
Missing	641 (5.5)	339 (10.1)	73 (3.0)	46 (2.5)	75 (4.4)	40 (4.2)	68 (5.2)
Partner HIV status[†]							
Positive	1601 (15.2)	282 (9.2)	321 (14.7)	332 (19.8)	287 (18.6)	163 (19.3)	216 (17.7)
Negative	914 (8.7)	141 (4.6)	159 (7.3)	159 (9.5)	176 (11.4)	119 (14.1)	160 (13.1)

Unknown	5832 (55.4)	2578 (84.2)	1614 (73.8)	627 (37.3)	452 (29.3)	231 (27.3)	330 (27.1)
Not applicable‡‡	1846 (17.5)	2 (0.1)	2 (0.1)	448 (26.7)	605 (39.2)	327 (38.7)	462 (37.9)
Missing	340 (3.2)	92 (4.2)	92 (4.2)	113 (6.7)	22 (1.4)	5 (0.6)	50 (4.1)
Any HIV disclosure[†]							
Not disclosed	2724 (25.9)	920 (30.1)	541 (24.7)	351 (20.9)	365 (23.7)	205 (24.3)	342 (28.1)
Disclosed	6439 (61.1)	1231 (40.2)	1389 (63.5)	1203 (71.7)	1155 (74.9)	635 (75.2)	826 (67.8)
Missing	1370 (13.0)	910 (29.7)	258 (11.8)	125 (7.4)	22 (1.4)	5 (0.6)	50 (4.1)
ART status[‡]							
ART Naïve	4926 (42.5)	2610 (77.8)	1172 (48.5)	653 (35.3)	332 (19.6)	74 (7.7)	85 (6.5)
on ART	6665 (57.5)	746 (22.2)	1245 (51.5)	1195 (64.7)	1365 (80.4)	883 (92.3)	1231 (93.5)
Body mass index[†]							
Wasted[¥] or Underweight[§]	2165 (18.7)	740 (22.1)	493 (20.4)	358 (19.4)	293 (17.3)	133 (13.9)	148 (11.3)
Normal BMI	5877 (50.7)	1242 (37.0)	1254 (51.9)	1079 (58.4)	1063 (62.6)	572 (59.8)	667 (50.7)
Overweight/obese	1729 (14.9)	251 (7.5)	346 (14.3)	286 (15.5)	285 (16.8)	1895 (20.4)	366 (27.8)
Missing	1820 (15.7)	1123 (33.5)	324 (13.4)	125 (6.8)	56 (3.3)	57 (6.0)	135 (10.3)
CD4 percentage[¶]							
Low CD4 percentage	266 (46.7)	58 (42.3)	53 (37.1)	53 (60.2)	37 (46.3)	46 (61.3)	19 (40.4)
High CD4 percentage	136 (23.9)	12 (8.8)	45 (31.5)	17 (19.3)	20 (25.0)	21 (28.0)	21 (44.7)
Missing	168 (29.5)	67 (48.9)	45 (31.5)	18 (20.5)	23 (28.8)	8 (10.7)	7 (14.9)
CD4 cells count in cells/mm$^{3\Psi}$							
<100	1828 (16.6)	400 (12.4)	368 (16.2)	300 (17.1)	364 (22.5)	171 (19.4)	225 (17.7)
100-199	1338 (12.1)	281 (8.7)	284 (12.5)	209 (11.9)	267 (16.5)	125 (14.2)	172 (13.6)
200-349	1634 (14.8)	299 (9.3)	324 (14.3)	239 (13.6)	322 (19.9)	187 (21.2)	263 (20.7)
350-499	1047 (9.5)	165 (5.1)	229 (10.1)	167 (9.5)	181 (11.2)	135 (15.3)	170 (13.4)
≥ 500	1436 (13.0)	232 (7.2)	284 (12.5)	218 (12.4)	234 (14.5)	197 (22.3)	271 (21.4)
Missing	3738 (33.9)	1842 (57.2)	785 (34.5)	627 (35.6)	249 (15.4)	67 (7.6)	168 (13.2)
WHO HIV stage							
Stage 1	4517 (39.0)	1192 (35.5)	942 (39.0)	690 (37.3)	625 (36.8)	421 (44.0)	647 (49.2)
Stage 2	2256 (19.5)	696 (20.7)	648 (26.8)	293 (15.9)	223 (13.1)	151 (15.8)	245 (18.6)
Stage 3	2974 (25.7)	818 (24.4)	627 (25.9)	523 (28.3)	533 (31.4)	261 (27.3)	212 (16.1)
Stage 4	1533 (13.2)	472 (14.1)	182 (7.5)	274 (14.8)	314 (18.5)	120 (12.5)	171 (13.0)
Missing	311 (2.7)	178 (5.3)	18 (0.7)	68 (3.7)	2 (0.1)	4 (0.4)	41 (3.1)

The percentage may be slightly above or below 100 due to rounding decimals.

[†]Data applicable only in PLHIV aged 15 years and above (n=10,533)

[#]Education level data captured the highest education level attained by PLHIV at enrolment time

‡‡Not applicable group included children, adolescents, and adults who did not have a partner at enrolment time

[‡]ART Status at baseline was estimated based on ART status at enrolment, including those initiated on ART within 30 days after enrolment

[†]PLHIV aged 0 -18 years, the body mass index (BMI) for age was estimated, and for PLHIV aged ≥19 years, the BMI formula for adults was used
[¥]Wasting classification was used in children, school children, and adolescents
[§]Underweight BMI classification for adults was used
[¶]CD4 percentage of PLHIV aged below 5 years (n=570)
[ψ]CD4 categories of PLHIV aged 5 years and above (n=11,021)

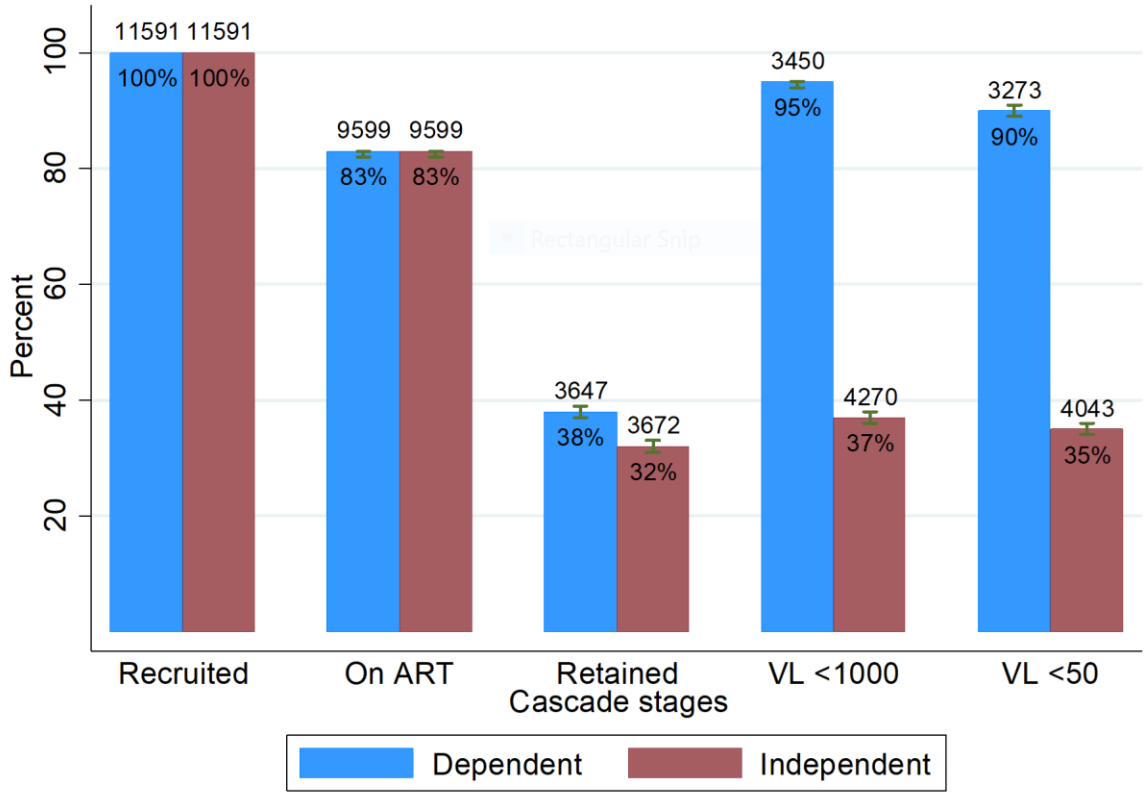

Figure 5.2: The overall percentage distribution of the HIV care cascade of PLHIV enrolled at the CDCI and consented to KIULARCO as of September 7th, 2022, using both dependent (the denominator is PLHIV who achieved previous cascade stage) and independent (the denominator is all PLHIV enrolled in care) staging methods (n=11,591). The green lines on top of the bar graphs represent the confidence intervals of the percentages. PLHIV: people living with HIV; CDCI: Chronic Disease Clinic of Ifakara; KIULARCO: Kilombero and Ulanga Antiretroviral Cohort; ART: Antiretroviral therapy; VL: Viral load

Table 5.2: The HIV care cascade of the PLHIV enrolled at the CDCI and consented to KIULARCO by sex, age, and time (n=11,591)

Characteristics	Recruited[†]	On ART	Retained in care[¥§]	Treatment response (Dependent)[†]		Treatment response (Independent)[‡]	
				CD4 count ≥ 350 cell/mm^3 or Viral load < 1000 copies/mL	CD4 count ≥ 350 cells/mm^3 or Viral load < 50 copies/mL	CD4 count ≥ 350 cell/mm^3 or Viral load < 1000 copies/mL	CD4 count ≥ 350 cells/mm^3 or Viral load < 50 copies/mL
Sex[¶]							
Male	4238 (36.6)	3406 (80.4)	1153 (33.9)	1076 (93.3)	1006 (87.3)	1347 (31.8)	1258 (29.7)
Female	7353 (63.4)	6194 (84.2)	2495 (40.3)	2375 (95.2)	2268 (90.9)	2923 (39.8)	2785 (37.9)
Age[¶ψ]							
Children (< 10 years)	877 (7.6)	733 (83.6)	270 (36.8)	252 (93.3)	225 (83.3)	307 (35.0)	274 (31.2)
Adolescent (10-19 years)	423 (3.7)	363 (85.8)	126 (34.7)	112 (88.9)	104 (82.5)	150 (35.5)	136 (32.2)
Adults (20-49 years)	8637 (74.5)	7089 (82.1)	2702 (38.1)	2571 (95.2)	2454 (90.8)	3196 (37.0)	3045 (35.3)
Elderly (≥50 years)	1654 (14.3)	1415 (85.6)	550 (38.9)	516 (93.8)	491 (89.3)	617 (37.3)	588 (35.6)
Enrolment time							
April 2005-January 2009[⁑]	3356 (29.0)	2231 (66.5)	1619 (72.6)	523 (32.3)	523 (32.3)[¶¶]	824 (24.6)	824 (24.6)[¶¶]
February 2009-March 2012[⁑]	2417 (20.9)	1989 (82.3)	1156 (58.1)	398 (34.4)	398 (34.4)[¶¶]	617 (25.5)	617 (25.5)[¶¶]
April 2012-April 2015[‡‡]	1848 (15.9)	1678 (90.8)	1336 (79.6)	725 (54.3)	669 (50.1)	877 (47.5)	816 (44.2)
May 2015-September 2017[‡‡]	1697 (14.6)	1521 (89.6)	1005 (66.1)	504 (50.2)	481 (47.9)	679 (40.0)	655 (38.6)
October 2017-March 2019[‡‡]	957 (8.3)	916 (95.7)	665 (72.6)	420 (63.2)	385 (57.9)	524 (54.6)	481 (50.3)
April 2019-September 2022[¶]	1316 (11.4)	1265 (96.1)	703 (55.6)	573 (81.5)	534 (76.0)	716 (54.4)	663 (50.4)

[†]The dependent staging method was used, whereby individuals were eligible in the next cascade stage when they were in the current cascade stage. In this approach, the start is all PLHIV recruited, and the denominator changes as the number of PLHIV who have achieved a previous stage changes.

[‡]The independent staging method was used, whereby each cascade stage was derived independently regardless of the cascade stage before the current stage. In this approach, the denominator is the total number of PLHIV recruited.

[†]Sum of percentages could be slightly above or below 100 due to rounding decimals

[¥]Retention estimates by guideline time were estimated separately and at the end of each guideline implementation time; therefore, the total retained for all years will not be the same as the overall total retained before stratifying time based on guideline years

[§]Estimated based on the dependent staging method

[¶]Cascade treatment outcome was assessed based on the latest viral load test available (within 1 year from the date of database closure)

[ψ]Age was estimated at enrolment

[⁑]Cascade treatment outcomes were assessed based on the latest CD4 count because, during this guideline period in Tanzania, viral load tests were not routinely done.

[¶¶]Treatment outcomes are based on the latest CD4 only, and it is the same as the previous column because of the same CD4 cut-off

[‡‡]Cascade treatment outcomes were assessed by using the latest CD4 or viral load because, in this period, viral load tests were done as per the clinician's request or as a result of research studies or the beginning of routine viral load testing to monitor treatment outcome in Tanzania

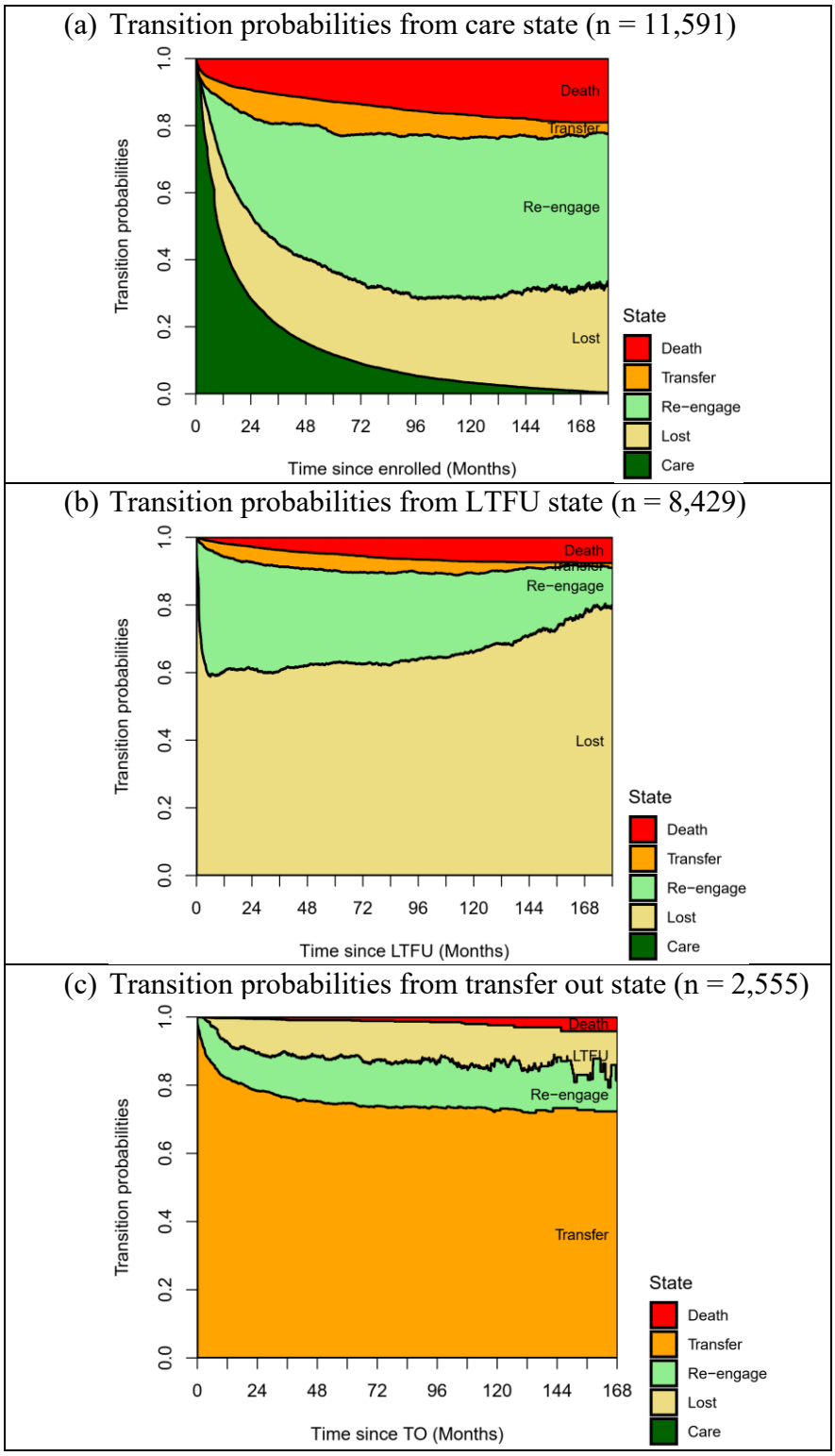

Figure 5.3: Transition probabilities from each transient state. In the transfer-out state, the transition to LTFU or death is among those who re-engaged after transfer-out; the model does not allow a direct transition from the transfer state to LTFU and death. LTFU: Loss to follow-up; TO: Transfer out

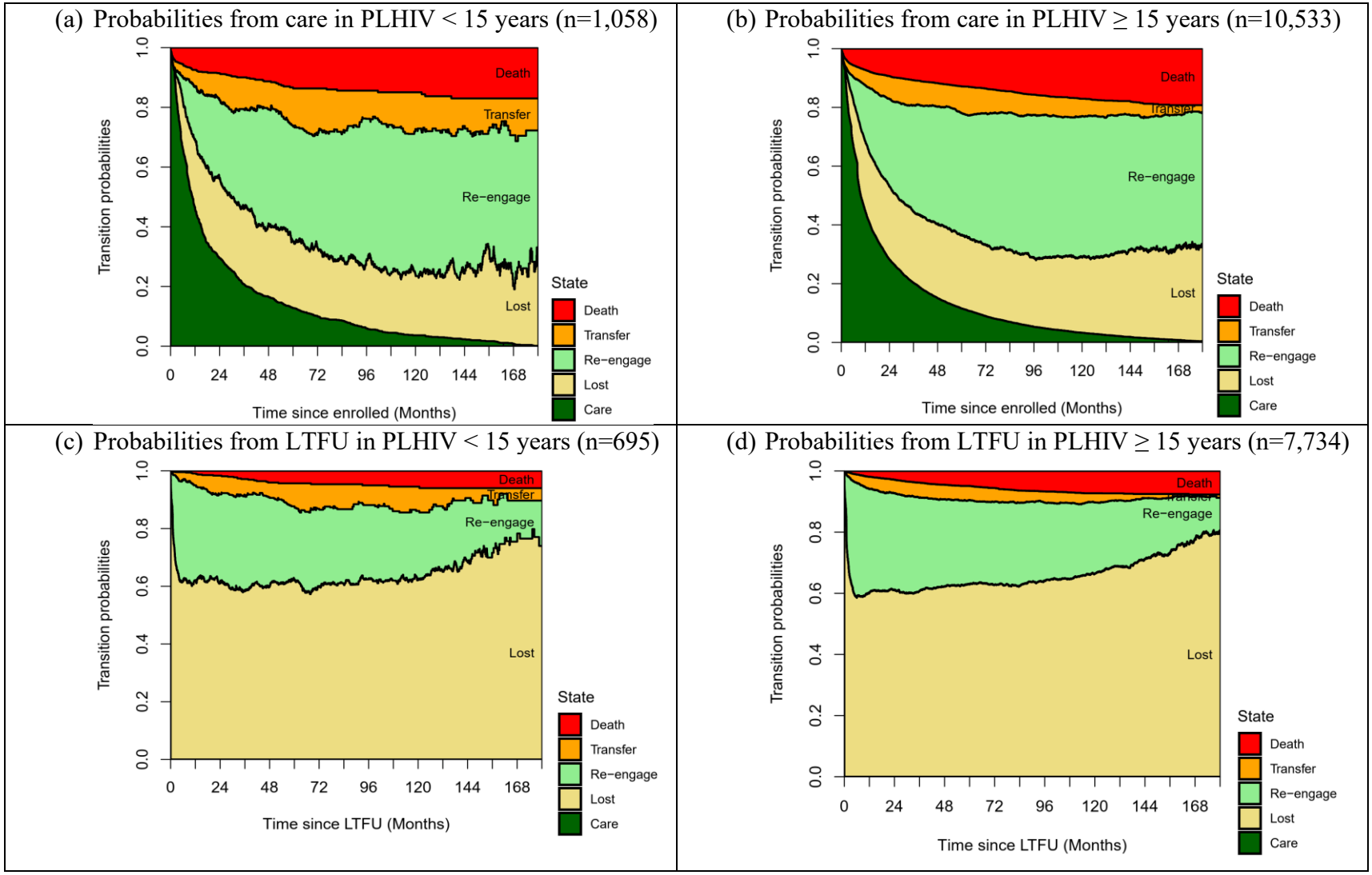

Figure 5.4: Transition probabilities stratified by age in care and LTFU states. LTFU: Loss to follow-up; PLHIV: People Living with HIV

Table 5.3: Baseline factors associated with three major transitions among PLHIV aged 15 years and above enrolled in care from 2005 to 2022

Characteristics	Care → Lost to follow-up (n=9493)		Lost to follow-up → Re-engage (n=4782)		Transfer → Re-engage (n=649)	
	aHR [95% CI]	P-value	aHR [95% CI]	P-value	aHR [95% CI]	P-value
Sex						
Male	Ref		Ref		Ref	
Female	0.86 [0.82-0.91]	<0.001	1.04 [0.99-1.09]	0.142	0.79 [0.66-0.95]	0.013
Age in years						
15-30	Ref		Ref		Ref	
31-49	0.90 [0.85-0.95]	<0.001	1.18 [1.12-1.25]	<0.001	0.81 [0.66-0.98]	0.028
≥50	0.89 [0.82-0.96]	0.003	1.07 [0.99-1.16]	0.094	0.61 [0.47-0.80]	<0.001
Marital status						
Married or cohabiting	Ref		Ref		Ref	
Never married	1.26 [1.16-1.36]	<0.001	0.91 [0.84-0.99]	0.020	1.11 [0.85-1.44]	0.455
Separated/divorced/widowed	0.97 [0.91-1.03]	0.256	0.98 [0.93-1.03]	0.433	1.23 [1.01-1.51]	0.039
Distance from the clinic						
≤ 1 Km	Ref		Ref		Ref	
2- 80 Km	1.19 [1.13-1.26]	<0.001	1.05 [1.00-1.10]	0.063	0.99 [0.82-1.19]	0.909
≥ 81 Km	1.26 [1.17-1.35]	<0.001	1.27 [1.19-1.36]	<0.001	0.72 [0.58-0.89]	0.002
Partner HIV status						
Positive	Ref		Ref		Ref	
Negative	1.11 [1.01-1.23]	0.033	1.01 [0.92-1.11]	0.858	0.79 [0.56-1.09]	0.153
Unknown	1.17 [1.09-1.26]	<0.001	1.01 [0.94-1.07]	0.858	0.70 [0.55-0.89]	0.004
Not applicable	1.13 [1.02-1.24]	0.014	0.94 [0.86-1.03]	0.183	0.76 [0.55-1.05]	0.098
ART status						
ART naïve	Ref		Ref		Ref	
On ART	0.71 [0.67-0.75]	<0.001	1.38 [1.31-1.45]	<0.001	0.96 [0.81-1.14]	0.654
WHO HIV stage						
Stage 1	Ref		Ref		Ref	
Stage 2	0.95 [0.89-1.01]	0.111	0.97 [0.92-1.03]	0.3623	1.19 [0.96-1.48]	0.109
Stage 3	1.09 [1.03-1.16]	0.004	0.96 [0.91-1.02]	0.156	0.92 [0.75-1.12]	0.408
Stage 4	1.31 [1.21-1.42]	<0.001	0.76 [0.69-0.83]	<0.001	1.10 [0.82-1.48]	0.521
Enrolment time						
April 2005-January 2009	Ref		Ref		Ref	
February 2009-March 2012	1.32 [1.24-1.42]	<0.001	1.16 [1.09-1.24]	<0.001	1.46 [1.15-1.86]	0.002
April 2012-April 2015	0.99 [0.91-1.07]	0.787	1.75 [1.62-1.89]	<0.001	1.35 [1.04-1.77]	0.026
May 2015-September 2017	1.34 [1.23-1.47]	<0.001	1.64 [1.49-1.80]	<0.001	1.66 [1.19-2.31]	0.003
October 2017-March 2019	1.69 [1.52-1.89]	<0.001	2.03 [1.81-2.28]	<0.001	2.38 [1.59-3.54]	<0.001
April 2019-September 2022	2.10 [1.87-2.35]	<0.001	2.56 [2.24-2.94]	<0.001	2.45 [1.53-3.92]	<0.001

PLHIV: People living with HIV; aHR: adjusted hazard ratio; CI: confidence interval; Ref: Reference category

5.9. Supplementary Figures and Tables

Table S5.1: The HIV care cascade of the PLHIV enrolled at the CDCI and consented to KIULARCO by age at the last visit (n=11,591)

Characteristics	Recruited[†]	On ART	Retained in care[¥§]	Treatment response (Dependent)[†]		Treatment response (Independent)[‡]	
				CD4 count ≥ 350 cell/mm^3 or Viral load < 1000 copies/mL	CD4 count ≥ 350 cells/mm^3 or Viral load < 50 copies/mL	CD4 count ≥ 350 cell/mm^3 or Viral load < 1000 copies/mL	CD4 count ≥ 350 cells/mm^3 or Viral load < 50 copies/mL
Age[¶ψ]							
Children (< 10 years)	580 (5.0)	442 (76.2)	93 (21.0)	83 (89.3)	73 (78.5)	101 (17.4)	90 (15.5)
Adolescent (10-19 years)	508 (4.4)	449 (88.4)	190 (42.3)	178 (93.7)	162 (85.3)	225 (44.3)	202 (39.8)
Adults (20-49 years)	7673 (66.2)	6130 (79.9)	2050 (33.4)	1925 (93.9)	1836 (89.6)	2428 (31.6)	2307 (30.1)
Elderly (≥50 years)	2830 (24.4)	2579 (91.1)	1315 (51.0)	1265 (96.2)	1203 (91.5)	1516 (53.6)	1444 (51.0)

[†]The dependent staging method was used, whereby individuals were eligible in the next cascade stage when they were in the current cascade stage. In this approach, the start is all PLHIV recruited, and the denominator changes as the number of PLHIV who have achieved a previous stage changes.

[‡]The independent staging method was used, whereby each cascade stage was derived independently regardless of the cascade stage before the current stage. In this approach, the denominator is the total number of PLHIV recruited.

[†]Sum of percentages could be slightly above or below 100 due to rounding decimals

[¥]Retention estimates by guideline time were estimated separately and at the end of each guideline implementation time; therefore, the total retained for all years will not be the same as the overall total retained before stratifying time based on guideline years

[§]Estimated based on the dependent staging method

[¶]Cascade treatment was assessed based on the latest viral load test available (within 1 year from the date of database closure)

[ψ]Age was estimated at the latest visit encountered at CDCI

Table S5.2: Transition probabilities with a 95% confidence interval from different states at a selected time

Time (Months)	Remained in care	From Care state			
		Care → LTFU	LTFU/TO → Re-engage[‡]	Care → TO	Care → Death
12	0.45 (0.44-0.46)	0.24 (0.23-0.25)	0.19 (0.18-0.20)	0.05 (0.05-0.06)	0.07 (0.07-0.08)
24	0.28 (0.28-0.29)	0.25 (0.24-0.26)	0.29 (0.28-0.31)	0.08 (0.07-0.09)	0.09 (0.09-0.10)
60	0.12 (0.11-0.12)	0.25 (0.23-0.26)	0.41 (0.40-0.43)	0.09 (0.08-0.11)	0.13 (0.12-0.14)
		From LTFU state			
	Remained LTFU	LTFU → Re-engage		LTFU → TO	LTFU → Death
12	0.60 (0.59-0.61)	0.34 (0.33-0.35)	-	0.04 (0.03-0.05)	0.02 (0.01-0.02)
24	0.61 (0.60-0.62)	0.32 (0.30-0.33)	-	0.05 (0.04-0.05)	0.03 (0.02-0.03)
60	0.63 (0.62-0.64)	0.27 (0.26-0.29)	-	0.05 (0.04-0.06)	0.05 (0.04-0.05)
		From TO state			
	Remained TO	TO → Re-engage		Re-engage → LTFU[¶]	Re-engage → TO[§]
12	0.82 (0.80-0.83)	0.11 (0.93-0.12)	-	0.07 (0.06-0.08)	0.08 (0.05-0.12)
24	0.78 (0.77-0.80)	0.11 (0.10-0.13)	-	0.10 (0.09-0.12)	0.14 (0.11-0.19)
60	0.75 (0.73-0.77)	0.13 (0.12-0.16)	-	0.11 (0.09-0.13)	0.24 (0.20-0.30)

[‡]There is no direct transition from care to re-engage; these transitions are either from LTFU or transfer out states

[¶]The transition to LTFU or death is among those who re-engaged after transfer out; the model does not allow direct transition from transfer state to LTFU or death

[§]The re-engage to TO transition is from a different row (row number 2 in the multistate modeling matrix); the probabilities estimated in this column should not be included to make the row probabilities sum to 1. These probabilities were included here to simplify the table

LTFU: Loss to follow-up; TO: Transfer out

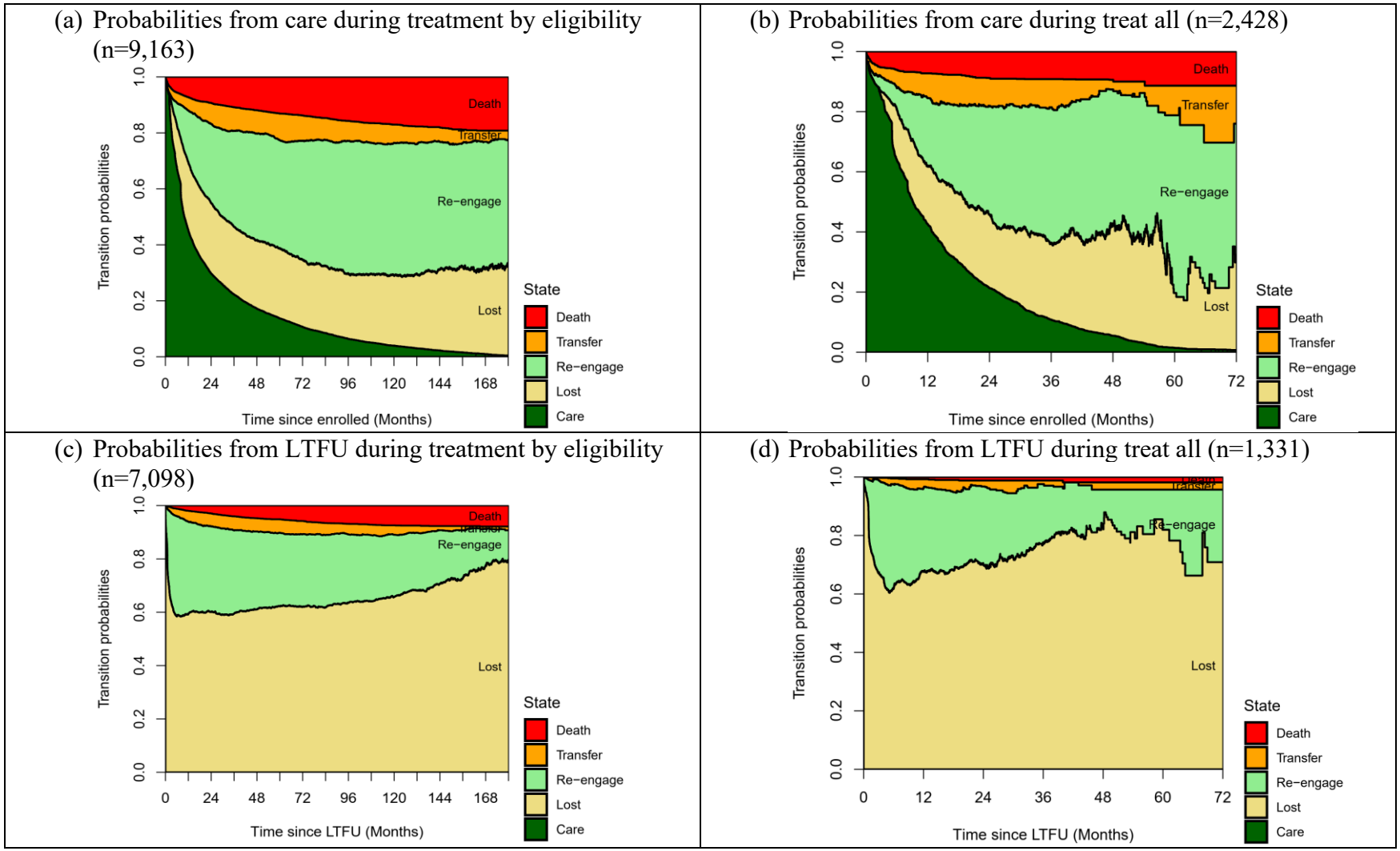

Figure S5.1: Transition probabilities care and LTFU states stratified by treatment by eligibility period (April 2005 – April 2015 in PLHIV <15 years and April 2005 - September 2017 in PLHIV ≥15 years) and treat all period (from May 2015 in PLHIV <15 years and from October 2017 in PLHIV ≥15 years to date). LTFU: Loss to follow-up; PLHIV: People living with HIV

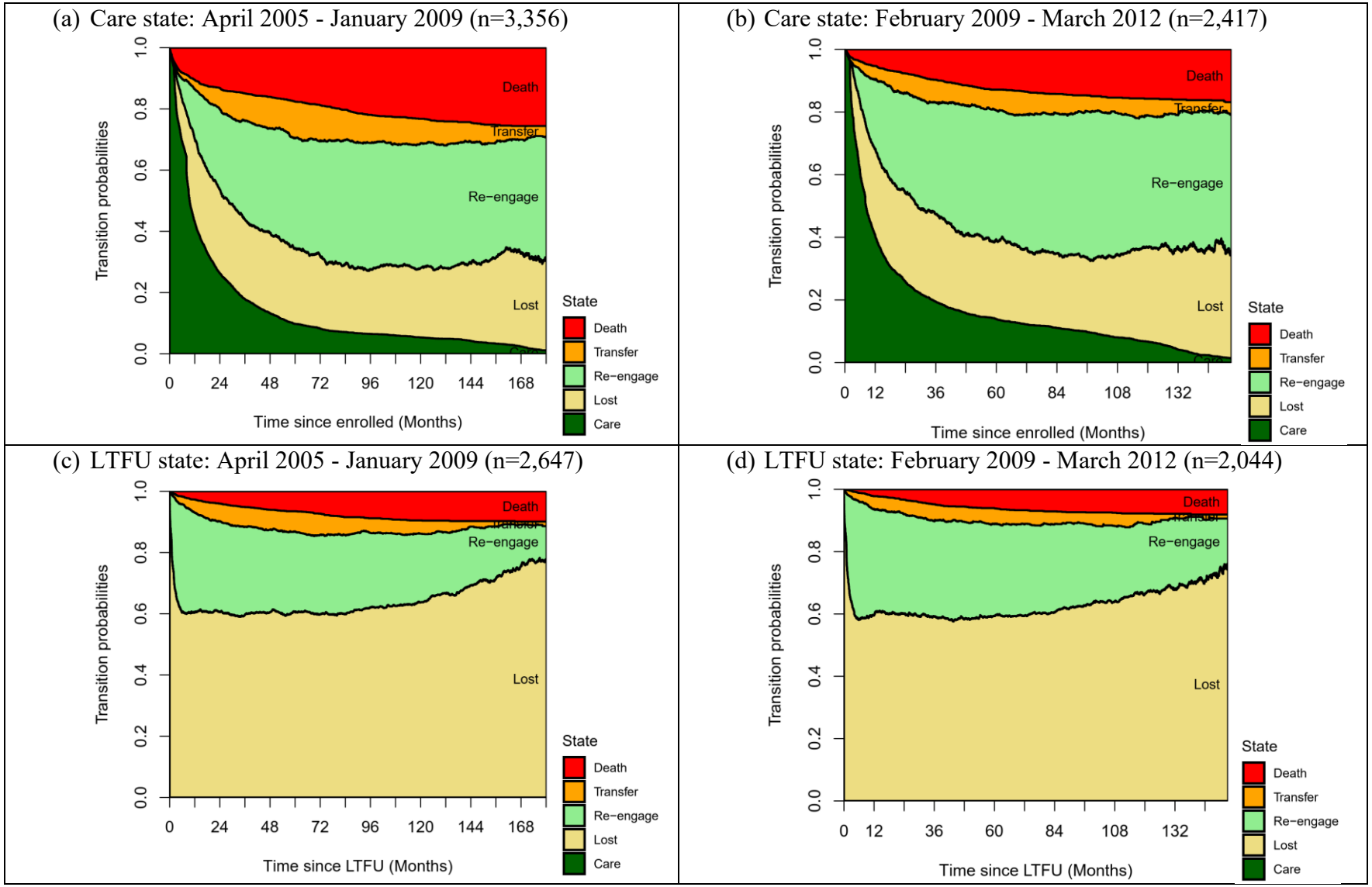

Figure S5.2: Transition probabilities from care and LTFU states stratified by enrolment time (from April 2005 – March 2012) following changes in Tanzanian HIV and AIDS management guidelines time. LTFU: Loss to follow-up

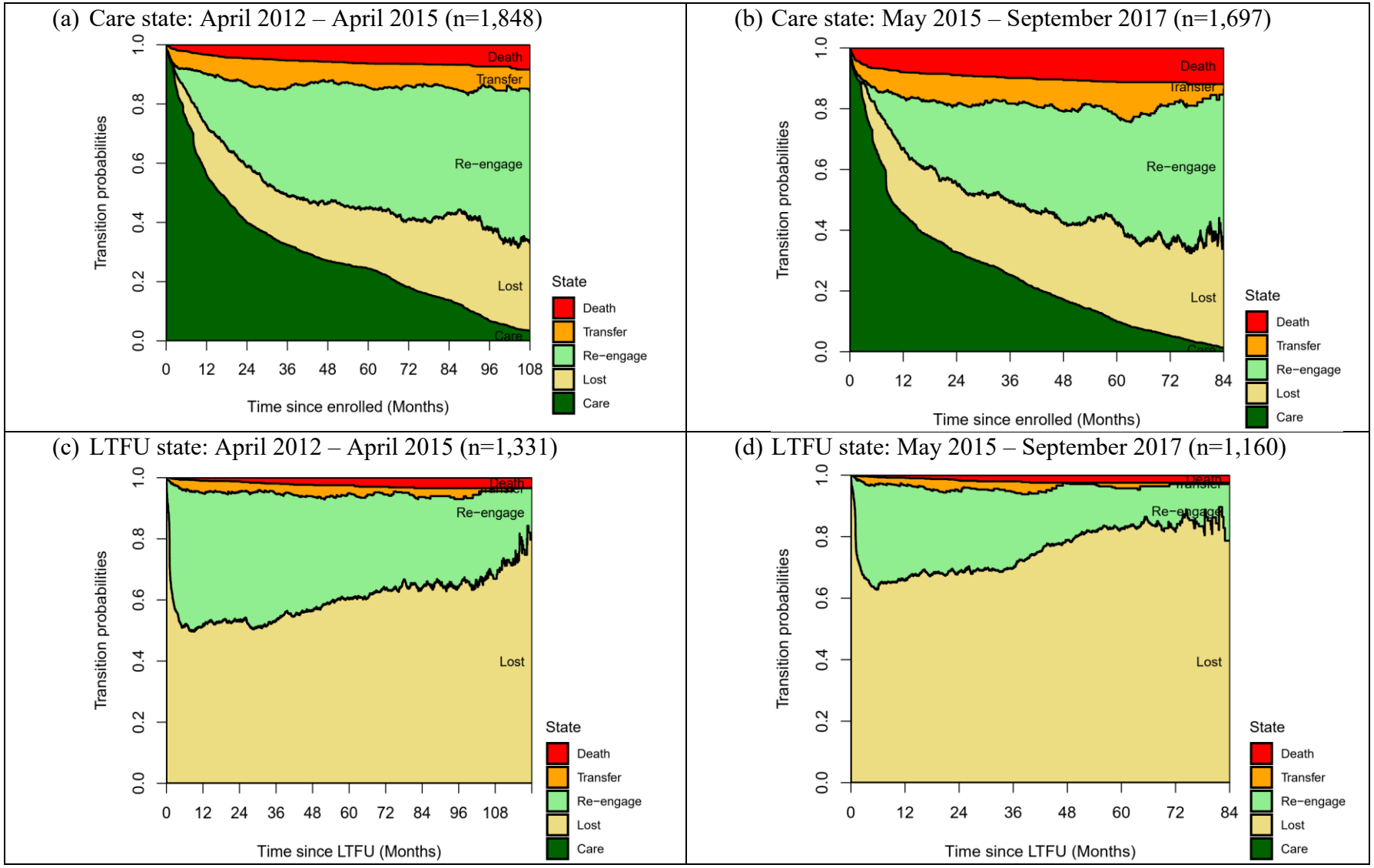

Figure S5.3: Transition probabilities from care and LTFU states stratified by enrolment time (from April 2012 – September 2017) following changes in Tanzanian HIV and AIDS management guidelines time. LTFU: Loss to follow-up.

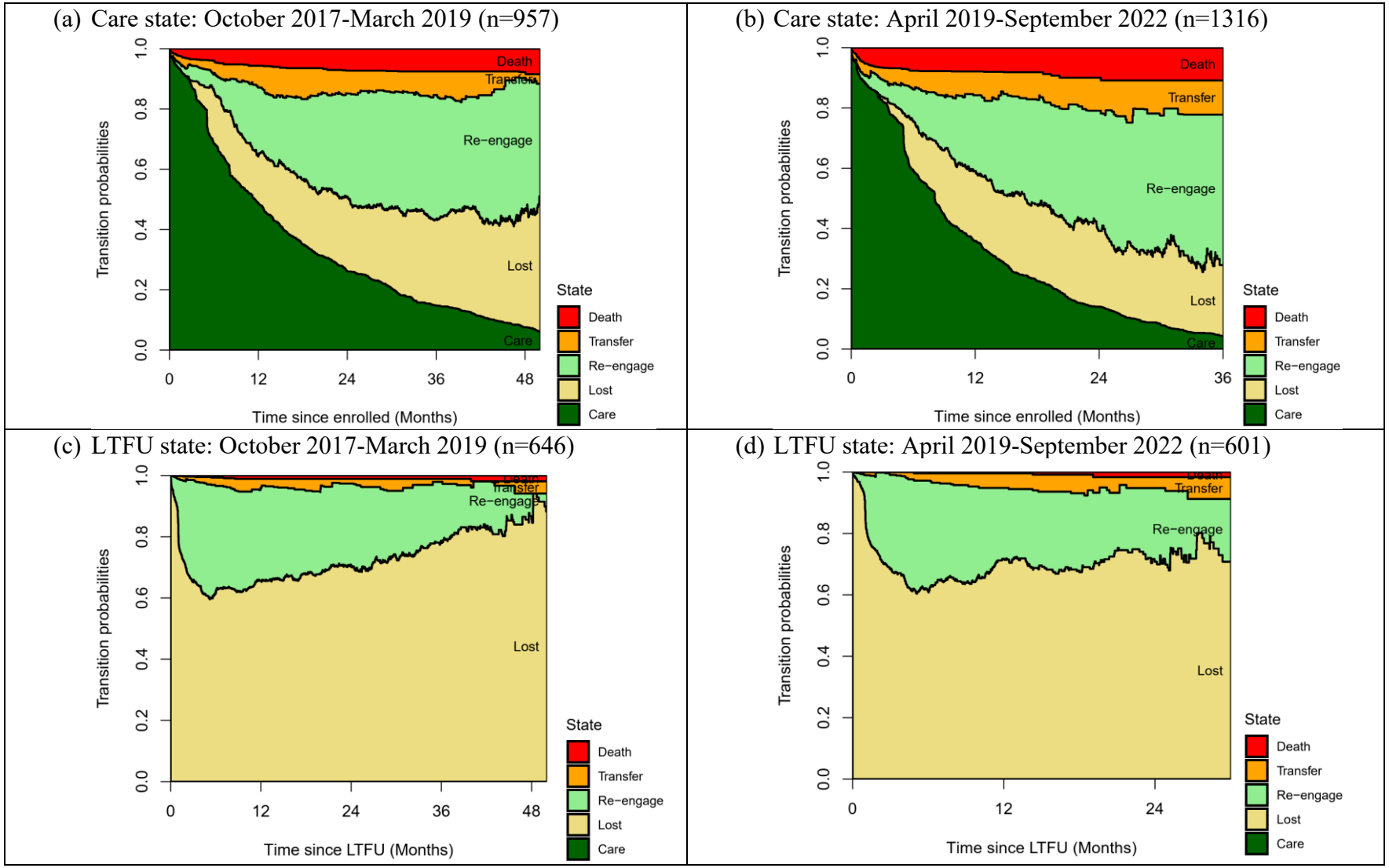

Figure S5.4: Transition probabilities from care and LTFU states stratified by enrolment time (from October 2017 – September 2022) following changes in Tanzanian HIV and AIDS management guidelines time. LTFU: Loss to follow-up

Table S5.3: Baseline factors associated with three major transitions among PLHIV aged below 15 years enrolled in care from 2005 to 2022

Characteristics	Care → Lost to follow-up (n=974)		Lost to follow-up → Re-engage (n=454)		Transfer → Re-engage (n=100)	
	aHR [95% CI]	P-value	aHR [95% CI]	P-value	aHR [95% CI]	P-value
Sex						
Male	Ref		Ref		Ref	
Female	1.16 [0.99-1.35]	0.073	1.08 [0.93-1.25]	0.317	1.24 [0.74-2.08]	0.417
Age in years						
0-4	Ref		Ref		Ref	
5-10	0.80 [0.67-0.96]	0.015	1.14 [0.97-1.34]	0.116	0.85 [0.49-1.47]	0.552
11-14	0.78 [0.62-0.99]	0.041	1.15 [0.93-1.43]	0.195	0.68 [0.33-1.40]	0.295
Distance to the clinic						
≤ 1 Km	Ref		Ref		Ref	
2- 80 Km	1.20 [1.01-1.44]	0.043	0.94 [0.79-1.11]	0.457	0.72 [0.43-1.21]	0.215
≥ 81 Km	1.04 [0.82-1.32]	0.726	1.15 [0.91-1.45]	0.252	1.04 [0.54-1.99]	0.904
ART status						
ART naïve	Ref		Ref		Ref	
On ART	0.68 [0.56-0.82]	<0.001	0.96 [0.81-1.15]	0.684	1.16 [0.60-2.27]	0.660
WHO HIV stage						
Stage 1	Ref		Ref		Ref	
Stage 2	1.05 [0.84-1.31]	0.697	1.37 [1.12-1.67]	0.002	0.63 [0.33-1.18]	0.149
Stage 3	1.26 [1.02-1.56]	0.033	1.14 [0.94-1.39]	0.184	1.12 [0.60-2.09]	0.719
Stage 4	1.51 [1.18-1.95]	0.001	0.99 [0.76-1.29]	0.931	0.54 [0.23-1.26]	0.155
Enrolment time						
April 2005-January 2009	Ref		Ref		Ref	
February 2009-March 2012	1.52 [1.23-1.89]	<0.001	1.41 [1.16-1.71]	<0.001	1.72 [0.70-4.24]	0.235
April 2012-April 2015	0.84 [0.64-1.11]	0.219	1.90 [1.47-2.46]	<0.001	2.20 [0.94-5.14]	0.070
May 2015-September 2017	1.12 [0.83-1.51]	0.444	1.75 [1.29-2.38]	<0.001	0.72 [0.21-2.47]	0.606
October 2017-March 2019	1.03 [0.72-1.46]	0.887	2.08 [1.41-3.08]	<0.001	0.82 [0.18-3.63]	0.792
April 2019-September 2022	1.74 [1.15-2.64]	0.009	2.73 [1.54-4.85]	<0.001	10.7 [0.75-153.0]	0.081

PLHIV: People living with HIV; aHR: adjusted hazard ratio; CI: confidence interval; Ref: Reference category

CHAPTER SIX: Treatment outcomes and engagement in care

6.0. Introduction to the chapter

In this Chapter, the assessment has narrowed down to the test-and-treat period in Tanzania (from October 2017 to January 2024). This is the period where all newly diagnosed PLHIV were initiated on ART immediately after being linked to HIV care and treatment clinics, regardless of clinical or immunological indication. The aim was to assess the treatment outcomes and engagement in care and factors associated among PLHIV enrolled in care at the CDCI in Ifakara, Morogoro, Tanzania, from 2017 to 2024. The assessment focused on the application of multistate models to show the implications of "test and treat" on VL suppression and engagement in care while considering the in-and-out of care transitions.

The findings show a high proportion of PLHIV initiated on ART achieved VL (0.41 with 95% CI: 0.39-0.43) in the first 12 months of ART initiation. In those who achieved VL, 0.73 (95% CI: 0.61-0.89) were retained in care in the first 6 months. On the other hand, in both before and after suppressed VL, the proportion of LTFU was very low in the beginning and steadily increased over time. Furthermore, among PLHIV who were LTFU with unsuppressed VL, 46% of these re-engaged in care with suppressed VL in the first 24 months. Compared to male PLHIV, females were more likely to achieve suppressed VL, while being overweight or obese was associated with a reduced hazard of re-engaging with unsuppressed VL. PLHIV who were initiated on ART in recent years were more likely to achieve suppressed VL, and they had an increased risk of becoming LTFU with suppressed VL compared to those initiated on ART in 2017-2019.

The details of the study are described in this Chapter, and the Chapter is organized following the journal manuscript structure for observational cohort studies. The Chapter started with the title page, abstract, introduction, methods, results, discussion, conclusion, statements, and a list of tables and figures.

Treatment outcomes and engagement in care among persons living with HIV in Ifakara, Tanzania: A multistate modeling study

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6.1. Abstract

Introduction: The achievement of suppressed viral load (VL) among people living with HIV (PLHIV) initiated on antiretroviral therapy (ART) is the ultimate goal of HIV care and treatment programs. However, sustaining suppressed VL throughout their lifetime is challenging. This study aimed to assess VL outcomes and engagement in care among PLHIV enrolled in care at the Chronic Disease Clinic of Ifakara (CDCI).

Methods: In this prospective study, we included PLHIV aged ≥10 years enrolled in care at CDCI and who consented to the Kilombero and Ulanga Antiretroviral Cohort. Included PLHIV were initiated on ART from 2017 to 2023 (during "test and treat"), with the baseline being the ART initiation date. The continuous-time non-parametric multistate Markovian model was used to assess transition probabilities between states. We used a 10-state reversible transition multistate model with 24 transitions. States were defined based on VL suppression status (suppressed if <50 copies/mL and unsuppressed if ≥50 copies/mL) and engagement in care(which included in care, loss to follow-up (LTFU), transfer, and death status). Being in care was defined as not being classified as LTFU, transfer out, or death. LTFU was defined as being late for scheduled appointments for > 60 days. Cox proportional hazard models were used to investigate the association between characteristics and different transitions.

Results: Among 1959 PLHIV included, the majority were female (65%), aged 20-35 years (41%), and had CD4 cell counts of 200-349 cells/mm3 (23%). A median follow-up time was 21 months (Interquartile range (IQR): 6-45). The proportion of PLHIV who remained in care with unsuppressed VL decreased from 0.56 (95% CI: 0.54-0.59) at 6 months to 0.15 (95% CI: 0.14-17) at 12 months. The proportion of PLHIV achieving suppressed VL while in care was 0.41 (95% CI: 0.39-0.43) at 12 months. After achieving suppressed VL, the proportion of PLHIV remaining in care with suppressed VL was high in the first 6 months (0.73 with 95% CI: 0.61-0.89). Among PLHIV who were lost to follow-up (LTFU) with unsuppressed VL, we observed an increasing probability of re-engaging with suppressed VL in the first 24 months and a decreasing probability of re-engaging with unsuppressed VL in 6-24 months. Being female (HR=1.38; 95% CI: 1.18-1.60) was associated with an increased hazard of achieving suppressed VL compared to male PLHIV. PLHIV who were in WHO HIV stage 3 had a reduced hazard of achieving suppressed VL compared to those in WHO HIV stage 1 (HR=0.80; 95% CI: 0.66-0.98). Lastly, PLHIV aged 20-

35 years (HR=0.44; 95% CI: 0.23-0.82) and being overweight or obese (HR=0.68; 95% CI: 0.49-0.95) had reduced the hazard of re-engaging with unsuppressed VL after being LTFU with unsuppressed VL.

Conclusion: In this rural cohort, the highest proportion of suppressed VL was observed in the first 12 months of ART initiation. However, re-engagement in care with suppressed VL while they were LTFU with unsuppressed VL was suggestive of undocumented temporary self-transfer. Emphasis on building a connected web-based HIV database is crucial for capturing the undocumented self-transfer to reduce the under-reporting of transfers and overestimation of the proportion of LTFU.

Keywords: HIV viral load; Longitudinal care cascade; multistate models; Sub-Saharan Africa

6.2. Introduction

Achieving suppressed viral load (VL) among people living with HIV (PLHIV) initiated on antiretroviral therapy (ART) is the ultimate goal of HIV care and treatment programs. PLHIV who achieve suppressed VL have improved well-being (158,159), reduced risk of opportunistic infections, and ultimately have a low chance of HIV transmission (160). However, sustaining suppressed VL throughout their lifetime can be challenging, and recently published articles estimated viral rebound proportion ranging between 2% and 40% (36,161). Some of the characteristics associated with VL rebound include poor adherence (162), few clinic visits (36), switching facilities (163), and gaps in care (18). This necessitates a continuous re-evaluation of engagement in care and treatment outcomes of PLHIV enrolled in care.

Due to changing engagement in care over time and the risk of VL rebound, assessments that consider these changes are important for a better understanding of the cascade. Assessments that integrated the back-and-forth transitions with various multistate modeling frameworks exist (14,31,32,34,54). The first group of assessments analyzed patterns of engagement in care over time without involving ART and VL suppression status in modeling frameworks (14,31,54). In these assessments, only engagement in care states was included, and ART was used as a covariate in models that evaluated the association between different transitions and PLHIV characteristics. The second group of assessments constructed multistate modeling frameworks that combined ART status and engagement in care (32,34). In these models, it is easy to assess how gaps in care occurred before and after ART initiation and the changes occurring over time. However, in both groups, the VL status of PLHIV studied was not captured in multistate modeling frameworks.

Routine VL monitoring for treatment outcomes is now the standard of care in many sub-Saharan African countries. Longitudinal cascade assessments that used multistate methods while integrating VL suppression status and engagement in care states are emerging in the literature (164,165). These assessments have improved our understanding of the success and remaining challenges, especially the gaps in care as a function of time and the time to intervene. However, in both previous studies, VL outcomes before and after gaps in HIV care were not considered in modeling. To better characterize the impact of 'cascade churn' in longitudinal cascades, especially progress toward undetectable viremia, treatment outcomes evaluation at the return after gaps in care is crucial. This study aimed to assess VL outcomes and engagement in care among PLHIV

enrolled in care at the Chronic Disease Clinic of Ifakara (CDCI) who were initiated on ART from 2017 to 2023 using the multistate model during the "test and treat" era.

6.3. Methods

6.3.1. Study setting and participants

This study was conducted at the CDCI located at St. Francis Regional Referral Hospital, which is in Ifakara town in Kilombero District, Morogoro, Tanzania. The clinic is a public-private partnership that provides services to PLHIV from the Kilombero, Ulanga, and Malinyi districts in Morogoro. Services are provided following Tanzanian HIV and AIDS management guidelines. The CDCI uses an electronic data collection system known as the Open Medical Record System for all services provided from registration, triage, clinical, laboratory, and pharmacy (89,92). Furthermore, upon presentation, all PLHIV are offered participation in the ongoing Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), which stores data of PLHIV who consented since 2005.

Immediately after HIV diagnosis during "test and treat", PLHIV is enrolled at the CDCI, and baseline tests, including the CD4 cell count, are done. As per national HIV and AIDS management guidelines, pre-ART counseling is done and ART is initiated within 0-3 days since diagnosis. Six months after ART initiation, the first VL test is done and repeated at 12 months. If PLHIV has a VL <1000 copies/mL, then the VL test is repeated annually. In case the VL test result is ≥1000 copies/mL, enhanced counseling is initiated, and the VL test is done after three months, then at 6 months, and thereafter repeated annually. When a VL test is not available, a CD4 test is recommended every 6 months. Other laboratory tests, such as full blood picture, kidney function (serum creatinine), and liver enzyme (which include alanine transaminase (ALT) and aspartate aminotransferase (AST)), are done at baseline and in 4 weeks or one month after ART initiation and thereafter repeated every 6 months.

After being initiated on ART, after 2 weeks, PLHIV returns for toxicity evaluation, and if tolerated, one monthly prescription will follow. When a patient is suppressed and stable on ART, ART is prescribed every 3-6 months. However, when PLHIV is not stable, unsuppressed, and has poor treatment adherence, including missing appointments during enhanced ART adherence counseling. ART is prescribed monthly until PLHIV is stable on ART. In between ART

prescriptions, PLHIV may have scheduled clinical appointments with clinicians or may have unscheduled clinical visits for other consultations.

6.3.2. Inclusion and exclusion criteria

We included PLHIV aged ≥10 years who started ART between October 1st, 2017 and December 31st, 2023, during the "test and treat" period. We excluded transient PLHIV (PLHIV who visit CDCI for either drug refills and/or clinical consultation with no intention to continue HIV care and treatment at CDCI), PLHIV who did not start ART, and those with ART exposure before enrolling at CDCI.

6.3.3. State definitions

This prospective study utilized longitudinal data collected routinely at the CDCI. The multistate model comprised 10 mutually exclusive states, which were a combination of engagement in care (defined considering all types of visits) and VL suppression status (considering all tests available per individual). Engagement in care at the CDCI included four states: the first was in care, defined as being in active care without any report of death, transfer, or loss to follow-up (LTFU). The second was LTFU, defined as missing scheduled appointments for >60 days (78). The third was transfer to other HIV clinics, and the fourth was documented all-cause deaths. For the case of VL suppression status, suppressed VL was defined as having a VL <50 copies/mL and unsuppressed when VL ≥50 copies/mL. States' names and definitions were summarized in Table 6.1 below.

Table 6.1: State names and definitions

State number and name	Definitions
State 1: In care with unsuppressed VL	State 1 was defined as being in care and initiated on ART. In newly diagnosed PLHIV enrolled in care, ART was initiated without testing for VL, and the assumption is that at ART initiation, PLHIV had high VL (i.e., they had unsuppressed VL).
State 2: In care with suppressed VL	State 2 included PLHIV who were still in care and had achieved VL suppression (VL < 50 copies).
State 3: LTFU with unsuppressed VL	State 3 included PLHIV who started ART but were LTFU before they were virally suppressed, or the LTFU event was preceded by unsuppressed VL test.
State 4: Transfer with unsuppressed VL	State 4 included PLHIV who were initiated on ART but were transferred to other HIV clinics before a suppressed VL or unsuppressed VL preceded the transfer event.
State 5: Death with unsuppressed VL	State 5 included PLHIV who initiated ART but died before they achieved suppressed VL or unsuppressed VL preceding the death event. This state was absorbing, i.e., once entered, there was no out-of-state transition.
State 6: LTFU with suppressed VL	State 6 included PLHIV who were LTFU after achieving suppressed VL.
State 7: Transfer with suppressed VL	State 7 included PLHIV who transferred after suppressed VL.
State 8: Death with suppressed VL	State 8 included PLHIV who died with suppressed VL or a suppressed VL preceded by the death event. This was also an absorbing state.
State 9: Re-engaged with suppressed VL	State 9 included PLHIV who re-engaged in HIV care with suppressed VL. In this case, either PLHIV had suppressed VL at the return date or the suppressed VL test preceded the return date. PLHIV who re-engaged after transfer with suppressed VL were considered re-engaged with suppressed VL. In this study, re-engaging in HIV care was referred to as returning to care at the CDCI after either LTFU or transfer out.
State 10: Re-engage with unsuppressed VL	State 10 included PLHIV who re-engaged in care with unsuppressed VL. The re-engage state was constructed to separate those who remain in care throughout and those who have the behavior of moving in and out of care because the two have different future transition probabilities (32,111).

6.3.4. Multistate model description.

We formulated a multistate modeling framework with 10 mutually exclusive states having a total of 28 transitions. Follow-up started at the ART initiation date (baseline). In this model, most PLHIV started in state 1, except for a few PLHIV who initiated ART with suppressed VL (PLHIV had a VL test on the date of ART initiation and were suppressed), who started in state 2.

To avoid unreliable estimates (96), we restricted (not allowed) transitions that had few events (n <8 events). These transitions were from state 3→5 (n=4 events), state 6→8 (n=2 events), state 9→8 (n=2 events), and 10→5 (n=6 events). Because restricted transitions involved terminal events (death with and without suppressed VL), the events were dropped with no additional transition assumption. The decision to consider transitions with events ≥8 was made because the inclusion of 5-7 transition estimates was still unreliable.

The final multistate model used was a reversible 10-state model with 24 transitions, and reverse transitions were not allowed from states 5 and 8 because they are absorbing states (Figure 6.1). Transitions from LTFU to either transfer or death were captured based on tracing information of the LTFU participants available at the clinic. PLHIV was censored at the time of death or database closure, which was on January 16th, 2024.

6.3.5. Explanatory variables

Socio-demographic baseline variables included were sex, age (categorized as 10-19 years, 20-35 years, 36-49 years, and ≥50 years), and marital status (grouped as married or cohabiting, never married, and separated or divorced or widowed). Education level (grouped as none, primary school, and secondary and above), and occupation (categorized as farmers, employed, unemployed, and others). Distance estimated from the clinic to the ward of the PLHIV village of residence (grouped as ≤1 Km, 2-80 Km, and ≥81 Km).

Clinical baseline variables included body mass index (BMI). In PLHIV aged 10-18 years, BMI for ages was classified based on the Z-score, with values < -2 considered as wasted, those from -2 to 1 as normal, and those > 1 as overweight or obese (94). In PLHIV aged ≥ 19 years, the WHO categories (<18.5, 18.5 to < 25, ≥ 25 kg/m^2) were categorized as underweight, normal, and overweight or obese, respectively (95). CD4 cell counts in cells/mm^3 (categorized as <100, 100-199, 200-349, 350-499; ≥500) and WHO HIV clinical stages 1 to 4. Weight (in kilograms), CD4

cell counts, and WHO HIV stages were extracted within -24 to +4 weeks of the ART initiation date, with the preference being measurements taken before the ART initiation date.

Tuberculosis at ART initiation was defined as the detection of acid-fast bacilli or positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) from sputum or an extra-pulmonary sample, or prescription of anti-tuberculosis medication in the presence of an International Classification of Diseases (ICD)-10 code indicating tuberculosis (A15-A19) or clinical signs suggestive of tuberculosis and the start of anti-tuberculosis drugs within 3 months before and after ART initiation. Tuberculosis was considered unlikely if no prescription of anti-tuberculosis drugs and no clinical diagnosis was provided. In all other cases, tuberculosis was indeterminate and treated as missing data.

A subset dataset of PLHIV with VL test at the return after being LTFU with suppressed VL was created. The VL test is not often done at the return, and the assumption is that PLHIV discontinued ART when PLHIV was LTFU; therefore, they have unsuppressed VL. Only the first VL test available at the return was considered in PLHIV with multiple re-engagement VL tests.

6.3.6. Statistical analysis

Baseline variables were summarized using descriptive statistics. The McNemar test was performed to compare the difference between the proportion of suppressed VL before LTFU and the proportion of suppressed VL at the return after a period of being LTFU in the subset of PLHIV with the VL test at the return. To assess the transition between different states, continuous-time non-parametric multistate Markovian models were used in two stages (65,97,98). First, the Nelson-Aalen estimator was used to estimate baseline cumulative hazards as described in Eq.2 in Chapter Three (65,97). Subsequently, transition probabilities over time were estimated using the Aalen-Johansen estimator as explained in Eq.3 in Chapter Three (98). Thereafter, the expected length of stay in transient states was estimated using Eq.4 as explained in Chapter Three (99). Sensitivity analysis was performed in a multistate model with transfer out states (4 and 7) assumed to be absorbing states. Multivariable Cox proportional hazard models described in Eq.5 in Chapter Three were used to assess factors associated with different transitions (98). Data management and analysis were performed using Stata software version 14 (StataCorp LP, College Station, Texas, USA) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

6.4. Results

6.4.1. Participants' characteristics at baseline

In total, 13,002 PLHIV consented to KIULARCO. Of these, we excluded 824 transient PLHIV, 9368 PLHIV who enrolled before October 2017, 188 children under the age of 10 years, 140 who never initiated ART, 515 with ART exposure before enrolling in CDCI, and 8 who initiated ART in January 2024 (Figure 6.2). A total of 1,959 PLHIV were included in this analysis, with a median follow-up of 21 months (interquartile range: 6-45 months).

Over the years, the majority were female PLHIV with a proportion above 60% (Table 6.2). The majority of PLHIV who initiated ART were adults aged 20-35 years (more than 37% across the years), with the lowest being in adolescents (ranging between 4-5% across the years). Furthermore, low proportions of tuberculosis-positive cases were observed across the years (approximately 9%). Many PLHIV started ART with CD4 cell counts of 200-349 cells/mm^3 (23%). Over the years, the majority were initiated on ART while they were in WHO stage 1.

6.4.2. Summary of transition frequencies between states

The maximum follow-up time was approximately 6 years (from October 2017 to January 2024), with a median follow-up of 21 months (Interquartile range (IQR): 6 - 45 months). The summary of the transition frequencies summarised in Table S6.1 shows that out of the total 6563 transitions, the common transition was a transition from in care with unsuppressed VL to suppressed VL (16%). Comparing transfer and death with unsuppressed VL and suppressed VL, transfer and death with suppressed VL were less frequent compared to transfer with unsuppressed VL (1% versus 4% for transfer and 0.3% versus 1% for death). Furthermore, LTFU before and after achieving suppressed VL was different, with the most common transition being LTFU with suppressed VL (12%) compared to LTFU with unsuppressed VL (7%). Re-engagement in care was also frequent, comparing re-engagement after being LTFU before and after suppressed VL. Re-engagement with unsuppressed VL was common among those LTFU with suppressed VL (13%) compared to LTFU with unsuppressed VL (5%)

6.4.3. Average length of stay in transient states

The average length of time spent in the transient states was assessed. On average, PLHIV spent 9 months in care before achieving suppressed VL and 22 months in care with suppressed VL. After being LTFU with or without suppressed VL, on average, PLHIV spent 13 months out of care with unsuppressed VL and 17 months LTFU with suppressed VL. Furthermore, PLHIV who re-engaged in care with suppressed VL remained in that state longer (42 months) than those who re-engaged in care with unsuppressed VL (26 months).

6.4.4. Predicted transition probabilities between states

The analysis revealed a rapidly decreasing proportion of PLHIV remaining in care with unsuppressed VL from 0.56 (95% Confidence Interval (CI): 0.54-0.59) at 6 months to 0.15 (95% CI: 0.14-0.17) at 12 months (Figure 6.3a and Table 6.3). The proportion of continuing care with suppressed VL was high at 12 months (0.41; 95% CI: 0.39-0.43) and decreased thereafter. We also observed fairly low and constant probabilities of LTFU, transfer, and death with unsuppressed VL over time (Figure 6.3a).

After achieving suppressed VL, the proportion of PLHIV remaining in care with suppressed VL was high in the first 6 months (0.73 with 95% CI: 0.61-0.89) and decreased over time (Figure 6.3b and Table 6.3). On the other hand, the proportion of PLHIV who were LTFU with suppressed VL was low at 6 months (0.01 with 95% CI: 0.003-0.04), and slightly increased from 48 months up to 0.14 (95% CI: 0.10-0.19) at 60 months. Additionally, the probability of being in care with unsuppressed VL was slightly high in the first 6 months, with an estimate of 0.08 (95% CI: 0.03-0.22), and after 12 months, it remained low and constant over time. Over time, we observed a low proportion of transfer and death after achieving suppressed VL.

A different pattern of re-engagement in care after being LTFU with unsuppressed VL was observed (Figure 6.3c and Table 6.3). In the first 6 months, 0.46 (95% CI: 0.26-0.80) of the LTFU re-engaged with unsuppressed VL. Afterward, the probability of re-engaging with unsuppressed VL decreased up to 36 months, whereby the proportion increased gradually thereafter (Figure 6.3c). In contrast, the probability of re-engaging with suppressed VL was low in the first 6 months, with an estimate of 0.09 (95% CI: 0.04-0.19), and it increased to 0.46 (95% CI: 0.40-0.52) at 24 months and remained constant up to 60 months.

Transitions from LTFU with suppressed VL revealed interesting transition probabilities regarding re-engagement in care. The probability of re-engaging with unsuppressed VL was high in 6-12 months (Figure 6.3d), gradually decreased to 24 months, and thereafter remained constant over time. In contrast, the proportion of re-engaging with suppressed VL increased from 8-34 months and remained constant up to 48 months. We also observed a slightly increased proportion of transfer with suppressed VL at 12 months (0.11 with 95% CI: 0.02-0.78) (Table 6.3). However, the confidence intervals of point estimates were wide, indicating a potential for few data points for this transition, which was also evident in Table S6.1.

6.4.5. Sensitivity analysis

In a model with transfer states (states 4 and 7) as absorbing states, findings show low transition probabilities of being LTFU with and without suppressed VL and re-engaging with and without suppressed VL states compared to results of the model with a transient transfer state (Table S6.2 versus Table 6.3). Furthermore, the transition probabilities for being transferred with and without suppressed VL were high in the analysis with the transfer state as an absorbing state compared to the findings of the model with transient transfer states (Figure S6.1a-d versus Figure 6.3a-d).

6.4.6. Assessment of viral load at the return after being LTFU

In the sub-analysis of PLHIV with VL tests at the return (n=258), the proportion of suppressed VL at the return in care was 85% as compared to 53% before the previous LTFU event, and the difference was statistically significant (P<0.0001). Among PLHIV who had a VL test at the return, 122 (47%) were suppressed before and at the return, 96 (37%) were suppressed at re-engagement while they were LTFU with unsuppressed VL. Only 14 (5%) were unsuppressed at re-engage after being LTFU with suppressed VL. Of the 14 PLHIV, eight were re-suppressed in a median of 12 months with a range of 4-35 months.

6.4.7. Factors associated with transitions before suppressed viral load

Factors associated with the transition from unsuppressed to suppressed VL (state 1→2) are summarized in Table 6.4. Being female was associated with an increased hazard of achieving suppressed VL compared to male PLHIV (Hazard Ratio (HR) = 1.38; 95% Confidence Interval

(CI): 1.18-1.60). PLHIV aged 36-49 years had a reduced hazard of VL suppression compared to PLHIV aged 10-19 years (HR=0.66; 95% CI: 0,44-0.99). PLHIV who lived far from the clinic (≥81 km) were less likely to achieve suppressed VL compared to those who lived ≤1 km from the clinic (HR=0.69; 95% CI: 0.54-0.89). Being in WHO HIV stage 3 was associated with a reduced hazard of achieving suppressed VL compared to WHO HIV stage 1 (HR=0.80; 95% CI: 0.66-0.98). Furthermore, PLHIV who initiated ART in 2020-2021 and in 2022-2023 had an increased hazard of achieving suppressed VL compared to those who started ART in 2017-2019 (HR = 1.50; 95% CI: 1.29-1.75 and HR = 1.60; 95% CI: 1.32-1.95, respectively).

The assessment of re-engagement with unsuppressed VL after being LTFU with unsuppressed VL (state 3→10) showed PLHIV aged 20-35 years had a reduced hazard of re-engaging to care with unsuppressed VL (HR=0.44; 95% CI: 0.23-0.82) compared to those aged 10-19 years (Table S6.3). Living ≥81 km from the clinic was associated with an increased hazard of re-engaging with unsuppressed VL compared to those who lived in ≤1 km from the clinic (HR=1.62; 95% CI: 1.01-2.61). Additionally, being overweight or obese was associated with a reduced hazard of re-engaging with unsuppressed VL compared to PLHIV who had normal BMI (HR=0.68; 95% CI: 0.49-0.95). PLHIV who initiated ART in 2020-2021 had an increased hazard of re-engaging with unsuppressed VL compared to those initiated on ART in 2017-2019 (HR = 1.42; 95% CI:1.04-1.95).

6.4.8. Factors associated with transitions after suppressed viral load

Characteristics associated with transitions after achieving suppressed VL (state 2→6) are also summarized in Table 6.4. PLHIV who were separated or divorced or widowed were more likely to be LTFU compared to those who were married or cohabiting (HR=1.26; 95% CI: 1.05-1.51). PLHIV who were employed had an increased hazard of LTFU compared to farmers (HR=1.32; 95% CI: 1.05-1.67). Furthermore, PLHIV who initiated ART in recent years had an increased hazard of LTFU with suppressed VL compared to those who started ART in 2017-2019 (HR = 2.70; 95% CI: 2.21-3.30 for 2020-2021 and HR = 5.39; 3.93-7.40 for 2022-2023). However, we noted a wide confidence interval for those who started ART in 2022-2023. This is probably due to the effect of the small sample size in this transition.

Re-engaging with unsuppressed VL after being LTFU with suppressed VL (state 6→10) was also investigated and summarized in Table S6.3. Being overweight or obese was associated with a

reduced hazard of re-engaging with unsuppressed VL compared to those with normal BMI (HR = 0.83; 95% CI: 0.70-0.99). PLHIV who were initiated on ART in 2022-2023 had a reduced hazard of re-engaging with unsuppressed VL compared to those who started ART in 2017-2019 (HR = 0.59; 95% CI: 0.39-0.88). Furthermore, LTFU with suppressed VL after re-engaging with suppressed VL (state 9→6) was only related to the year of ART initiation, those who started ART recently had an increased hazard of LTFU with suppressed VL compared to those initiated on ART in 2017-2019 (HR = 4.31; 95% CI: 3.29-5.64 for 2020-2021 and HR = 9.92; 95% CI: 4.38-22.5 for 2022-2023). However, confidence intervals suggested a possibility of a small sample size for these transitions.

6.5. Discussion

In this large rural HIV cohort, we observed different patterns of engagement in care and changes in treatment outcomes during the "test and treat" period. The findings showed the majority achieving suppressed VL at 12 months (0.41). On average, PLHIV spent nine months in care with unsuppressed VL. After achieving a suppressed VL, the proportion of remaining in care was high in the first 6 months (0.73), and on average, PLHIV spent 22 months in care with a suppressed VL. Being female and recent ART initiation were associated with an increased hazard of suppressed VL. Furthermore, findings show a rapid decrease in the proportion of PLHIV remaining in the LTFU state before and after achieving suppressed VL within 12 months. Being overweight or obese was associated with a reduced hazard of re-engaging with unsuppressed VL after being LTFU with either suppressed or unsuppressed VL.

A good treatment outcome is expected in six months after ART initiation, and in this study, we observed a rapid increase in the proportion of suppressed VL in 6-12 months after ART initiation. This was suggestive of good treatment adherence within 12 months of ART initiation. This finding is similar to that of a large study conducted in East Africa (165). However, after two years, in this study, the proportion decreased, while in the East African study, the proportion was still high. This difference is probably due to the difference in PLHIV included. This study included PLIHV aged ≥10 years from a single rural HIV clinic, while the East African study included PLHIV aged ≥15 years from Tanzania, Kenya, and Uganda, and the findings represented the three countries. There is a possibility that PLHIV from different countries achieve suppressed VL and remain suppressed

differently over time. Analyses stratified by countries and residence (rural versus urban) would have provided more insight into the differences and similarities with this study.

The decreasing trend of the probabilities of remaining in care with suppressed VL was similar to a study conducted in Canada (31). However, in the Canadian study, the proportion of being in HIV care with suppressed VL and no gaps in care was above 50% even at 10 years. The difference could be explained by the differences in study settings. Our study included PLHIV aged ≥10 years, and it was conducted in a single rural HIV clinic in Tanzania, where ART treatment started in 2005, and in October 2017, the country rolled out the treat-all strategy. In the Canadian study, however, PLHIV included were from 8 cohorts, who were 18 years and above and on ART since January 2000, with at least one full year of ART experience at recruitment. The one-year ART experience increases the likelihood that PLHIV included were on ART for a long time, and this could influence the probability of remaining in care compared to this study. This is because a study conducted in Uganda, Kenya, Tanzania, and Nigeria revealed that PLHIV on ART for >4 years were less likely to miss their scheduled clinic visits compared to those on ART for <2 years (166).

We found different patterns of re-engagement in care among PLHIV who were LTFU with unsuppressed VL. The increasing proportion of re-engaging with suppressed VL in the first 24 months was suggestive of undocumented temporary self-transfer. A South African study found that 16% of the LTFU were undocumented transfers (167), and this was further supported by our finding of suppressed VL among PLHIV who were LTFU and re-engaged. Alternatively, there is a possibility that these PLHIV self-transferred to peripheral drug refill clinics, and they return to CDCI only for the VL test because the peripheral clinic may not have the capacity for VL testing. These PLHIV did not want to report they were transferred to other clinics because they wished to continue with VL tests and other routine HIV-related tests at CDCI. To reduce the potential overestimation of LTFU in the clinic, further investigation of PLHIV who LTFU and return only for VL and other tests is important.

The difference between males and females in achieving suppressed VL has been inconsistent. Similar to this study, a recent study conducted in France among PLHIV with acute infection found that women achieved suppressed VL and had increased CD4 cell counts faster than men (168). Others in Uganda showed that men were more likely to have a persistently high VL (35). It has been established that women have lower viremia compared to men (169), and probably during "test and treat", women initiated treatment with lower VL compared with men, hence fast VL

suppression. However, previous studies conducted in the early 2000s did not find evidence of a difference between men and women (170,171), but Donnelly et al. (171) showed that the difference between men and women was related to CD4 levels.

Similar to this study, previous studies did not find evidence of an association between being overweight or obese and poor VL suppression (172,173). However, previous studies showed that being underweight was associated with poor VL suppression (174,175). In this study, we found that being overweight or obese was associated with a reduced hazard of re-engaging with unsuppressed VL. Probably the established relationship of high BMI predicting increasing CD4 (172,176–178) over time would be related to a slower VL rebound in PLHIV who had higher BMI re-engaging in care after a period of being LTFU. Currently, the relationship between BMI and VL suppression among PLHIV re-engaging is understudied.

A higher hazard of achieving suppressed VL in those initiated on ART recently could be due to ART initiation while asymptomatic. Being asymptomatic could facilitate good treatment outcomes compared to those who initiated ART during the early phases of the "test and treat" era (2017-2019). The 2017-2019 time category has the potential of including PLHIV who were in the period of initiating ART by clinical or immunological indication, while in later years, probably the majority were diagnosed and immediately initiated on ART. Previous studies have shown that immediate ART initiation increased VL suppression (179), reduced AIDS-defining illnesses and HIV progression (180), and increased immune recovery (180,181). However, the increased hazard of LTFU with suppressed VL in PLHIV initiated on ART in 2020-2021 could be attributed to the COVID-19 pandemic, because during that time, people were scared of COVID-19 transmission in hospitals.

This study captured the cyclic nature of engagement in care with changes in treatment outcomes over time. To our knowledge, this is among the first studies that addressed the in and out of care transitions before and after achieving suppressed VL over time in rural sub-Saharan Africa. However, the study has some limitations. First, we could not explore some of the transitions, such as death before and after achieving suppressed VL, due to a few deaths. Second, there was a potential for a small sample size in the time of ART initiation variable because of the observed wide confidence intervals. Large studies or the Bayesian approach have the potential to further explore this topic using similar methods. Thirdly, the VL test was not often available at the return for those who disengaged and re-engaged in care. Future efforts to establish the actual effects

should involve VL testing upon the return to compare the two periods. Lastly, although LTFU and death states were treated separately, some deaths may not have been ascertained among individuals classified as LTFU.

6.6. Conclusion

Our findings show that the majority of PLHIV initiated on ART achieved VL within the first 12 months, and many remained in active care in the first 12 months. Additionally, re-engagement in care with suppressed VL while they were LTFU with unsuppressed VL was indicative of undocumented temporary self-transfer. This was probably due to the lack of a connected web-based HIV database in Tanzania that could have notified those in clinics about PLHIV receiving HIV services from other clinics. Emphasizing the development of a connected web-based HIV database is crucial for capturing self-transfer to reduce the potential under-reporting of transfers and overestimation of LTFU. On the other hand, PLHIV re-engaging in care with unsuppressed VL after being LTFU with suppressed VL suggests treatment discontinuation while out of care. Strengthening the effort of tracking PLHIV who are LTFU is crucial, especially in the first 12 months of achieving VL suppression.

6.7. Statements

6.7.1. Authors' contributions

A.V.K designed the study, conducted all analyses, and drafted the manuscript; A.M. and K.O. contributed to designing the study, supervised analyses, and reviewed the manuscript; T.R.G., M.W., F.V., E.L., and H.M. contributed to designing the study and reviewing the manuscript. All authors have read and approved the final manuscript.

6.7.2. Conflict of interest statement

Other authors have declared no conflict of interest, except A.V.K., who received a study leave allowance through the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) via the Ifakara Health Institute. In addition, this manuscript is part of her Ph.D., which was funded by the Consortium for Advanced Research Training in Africa (CARTA). Furthermore, Canton Basel-

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6.7.4. Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

6.7.5. Acknowledgments

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6.8. Figures and tables

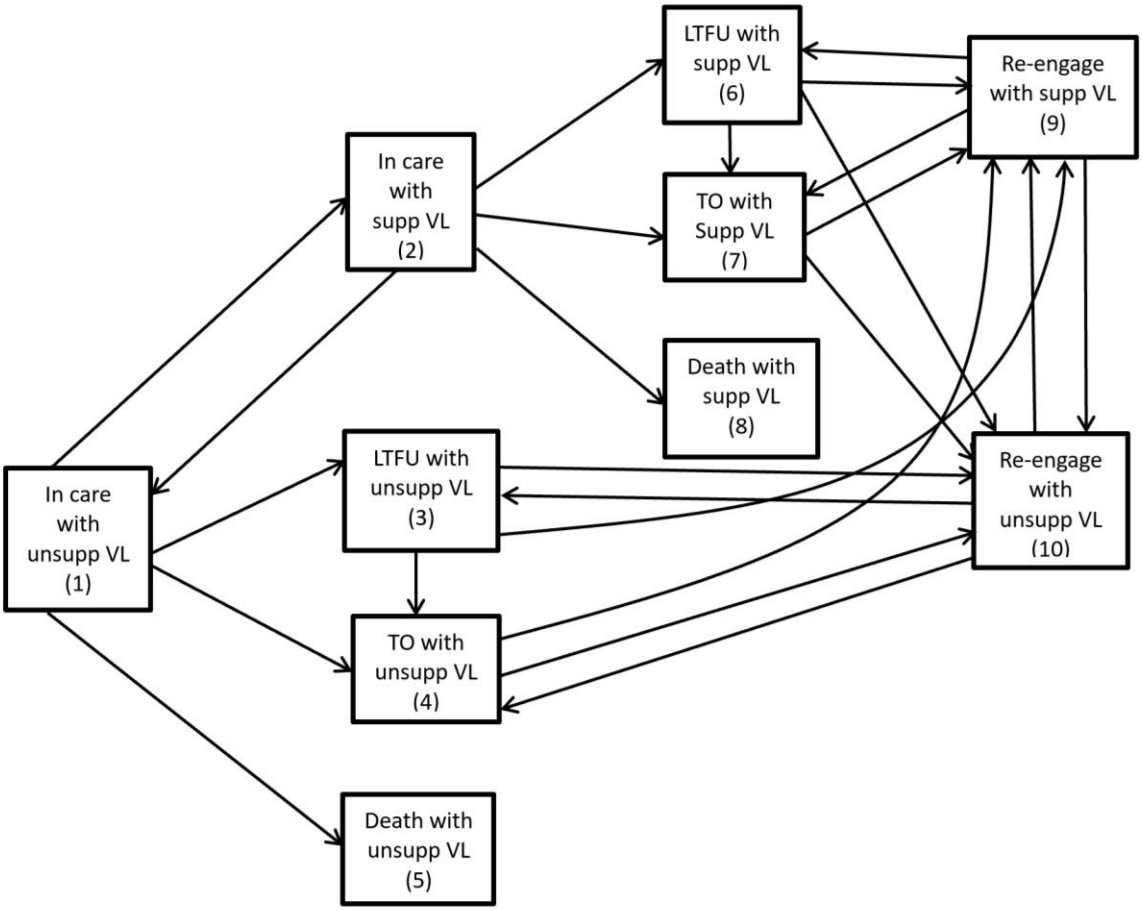

Figure 6.1: Multistate modeling framework for assessing treatment outcomes and engagement in care among PLHIV initiated on ART. Supp: Suppressed; unsupp: Unsuppressed; VL: Viral Load; LTFU: Loss to follow-up; TO: Transfer out

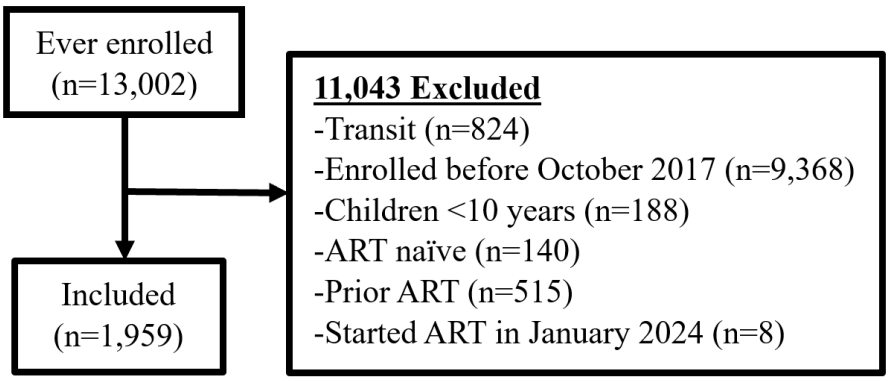

Figure 6.2: PLHIV inclusion flow chart. PLHIV: People living with HIV; ART: Antiretroviral Therapy

Table 6.2: Percentage distribution of characteristics at ART initiation of PLHIV who started ART from October 2017 to December 2023 (n=1959)

Characteristics	Year of ART initiation			Overall
	2017-2019	2020-2021	2022-2023	
Overall	923 (47.1)	599 (30.6)	437 (22.3)	1959 (100)
Sex				
Male	333 (36.1)	212 (35.4)	151 (34.6)	696 (35.5)
Female	590 (63.9)	387 (64.6)	286 (65.5)	1263 (64.5)
Age in years				
10 - 19	40 (4.3)	29 (4.8)	19 (4.4)	88 (4.5)
20 - 35	389 (42.2)	244 (40.7)	161 (36.8)	794 (40.5)
36 - 49	337 (36.5)	218 (36.4)	160 (36.6)	715 (36.5)
≥ 50	157 (17.0)	108 (18.0)	97 (22.2)	362 (18.5)
Marital status				
Married/cohabiting	564 (61.1)	383 (63.9)	239 (54.7)	1186 (60.5)
Never married	105 (11.4)	65 (10.9)	69 (15.8)	239 (12.2)
Separated/divorced/widowed	254 (27.5)	151 (25.2)	129 (29.5)	534 (27.3)
Education level				
None	92 (10.0)	68 (11.4)	60 (13.7)	220 (11.2)
Primary school	735 (79.6)	456 (76.1)	301 (68.9)	1492 (76.2)
Secondary and above/other	96 (10.4)	75 (12.5)	76 (17.4)	247 (12.6)
Occupation				
Farmer	731 (79.2)	456 (76.1)	317 (72.5)	1504 (76.7)
Employed	108 (11.7)	93 (15.5)	84 (19.2)	285 (14.6)
Unemployed	44 (4.8)	28 (4.7)	18 (4.1)	90 (4.6)
Other¥	40 (4.3)	22 (3.7)	18 (4.1)	80 (4.1)
Distance from the clinic in Km				
≤ 1	423 (45.8)	334 (55.8)	245 (56.1)	1002 (51.2)
2 - 80	352 (38.1)	182 (30.4)	137 (31.4)	671 (34.3)
≥ 81	118 (12.8)	49 (8.2)	24 (5.5)	191 (9.8)
Missing	30 (3.3)	34 (5.7)	31 (7.1)	95 (4.9)
Body mass index‡‡				
Normal	548 (59.4)	309 (51.6)	230 (52.6)	1087 (55.5)
Wasted/underweight*	122 (13.2)	57 (9.5)	55 (12.6)	234 (11.9)
Overweight/obese	228 (24.7)	211 (35.2)	115 (26.3)	554 (28.3)
Missing data	25 (2.7)	22 (3.7)	37 (8.5)	84 (4.3)
Tuberculosis status				
Unlikely	818 (88.6)	530 (88.5)	386 (88.3)	1734 (88.5)
Positive	80 (8.7)	55 (9.2)	39 (8.9)	174 (8.9)
Missing	25 (2.7)	14 (2.3)	12 (2.8)	51 (2.6)
CD4 Cell counts in cells/mm^3				
<100	169 (18.3)	113 (18.9)	99 (22.7)	381 (19.5)
100 - 199	145 (15.7)	86 (14.4)	68 (15.6)	299 (15.3)
200 - 349	229 (24.8)	129 (21.5)	87 (19.9)	445 (22.7)
350 - 499	137 (14.8)	77 (12.9)	78 (17.9)	292 (14.9)
≥500	195 (21.1)	124 (20.7)	67 (15.3)	386 (19.7)
Missing	48 (5.2)	70 (11.7)	38 (8.7)	156 (8.0)
WHO HIV stage				

Stage 1	449 (48.7)	350 (58.4)	224 (51.3)	1023 (52.2)
Stage 2	173 (18.7)	85 (14.9)	66 (15.1)	324 (16.5)
Stage 3	220 (23.8)	74 (12.4)	77 (11.7)	371 (18.9)
Stage 4	75 (8.1)	74 (12.4)	51 (11.7)	200 (10.2)
Missing	6 (0.6)	16 (2.7)	19 (4.4)	41 (2.1)

¶Totals may not add up to 100% because of rounding.
¥Included students and other occupations
‡In adolescents aged 10-19 years, body mass index for age was used for classification of nutrition status, and in PLHIV aged ≥19 years, body mass index for adults was used in defining nutrition status.
*The term "wasted" was defined in adolescents aged 10-18 years, and "underweight" was used for PLHIV aged ≥19 years
PLHIV: People living with HIV; ART: Antiretroviral Therapy.

Table 6.3: Transition probabilities with a 95% confidence interval from the different states at different selected time points

Time (Months)	In care with unsuppressed VL	From in-care with unsuppressed VL to			
		In care with suppressed VL	LTFU with unsuppressed VL	TO with unsuppressed VL	Death with unsuppressed VL
6	0.56 (0.54-0.59)	0.14 (0.13-0.16)	0.10 (0.08-0.12)	0.06 (0.04-0.08)	0.04 (0.03-0.05)
12	0.15 (0.14-0.17)	0.41 (0.39-0.43)	0.09 (0.07-0.11)	0.06 (0.04-0.08)	0.04 (0.03-0.05)
24	0.05 (0.04-0.06)	0.29 (0.27-0.32)	0.09 (0.07-0.11)	0.06 (0.04-0.09)	0.04 (0.03-0.05)
60	0.03 (0.02-0.04)	0.02 (0.01-0.03)	0.07 (0.04-0.11)	0	0.04 (0.04-0.05)
		From in care with suppressed VL to			
	In care with suppressed VL	In care with unsuppressed VL	LTFU with suppressed VL	TO with suppressed VL	Death with suppressed VL
6	0.73 (0.61-0.89)	0.08 (0.03-0.22)	0.01 (0.003-0.04)	0.07 (0.03-0.15)	0.07 (0.02-0.33)
12	0.68 (0.58-0.79)	0.05 (0.03-0.07)	0.04 (0.02-0.05)	0.04 (0.01-0.15)	0.08 (0.02-0.33)
24	0.40 (0.34-0.46)	0.04 (0.03-0.05)	0.05 (0.04-0.07)	0.04 (0.02-0.07)	0.08 (0.02-0.31)
60	0.02 (0.02-0.03)	0.03 (0.02-0.05)	0.14 (0.10-0.19)	0.003 (0.0004-0.02)	0.09 (0.02-0.31)
		From LTFU with unsuppressed VL to			
	Remained LTFU with unsuppressed VL	TO with unsuppressed VL	Death with unsuppressed VL¶	Re-engage with suppressed VL	Re-engage with unsuppressed VL
6	0.34 (0.19-0.63)	0.11 (0.04-0.26)	-	0.09 (0.04-0.19)	0.46 (0.26-0.80)
12	0.19 (0.14-0.26)	0.12 (0.07-0.21)	-	0.25 (0.19-0.34)	0.39 (0.31-0.48)
24	0.14 (0.11-0.18)	0.12 (0.08-0.19)	-	0.46 (0.40-0.52)	0.21 (0.17-0.25)
60	0.07 (0.05-0.12)	0	-	0.46 (0.39-0.53)	0.31 (0.26-0.39)
		From LTFU with suppressed VL to			
	Remained LTFU with suppressed VL	TO with suppressed VL	Death with suppressed VL¶	Re-engage with suppressed VL	Re-engage with unsuppressed VL
6	1	0	-	0	0
12	0.16 (0.02-0.69)	0.11 (0.02-0.78)	-	0.19 (0.09-0.41)	0.44 (0.27-0.72)
24	0.05 (0.03-0.07)	0.05 (0.01-0.19)	-	0.45 (0.39-0.52)	0.22 (0.18-0.28)
60	0.15 (0.11-0.21)	0.004 (0.005-0.03)	-	0.46 (0.39-0.53)	0.31 (0.26-0.38)

¶Transition not allowed due to a few transition frequencies (n < 8 frequencies)

VL: Viral Load; LTFU: Loss to follow-up; TO: Transfer out to other HIV clinics

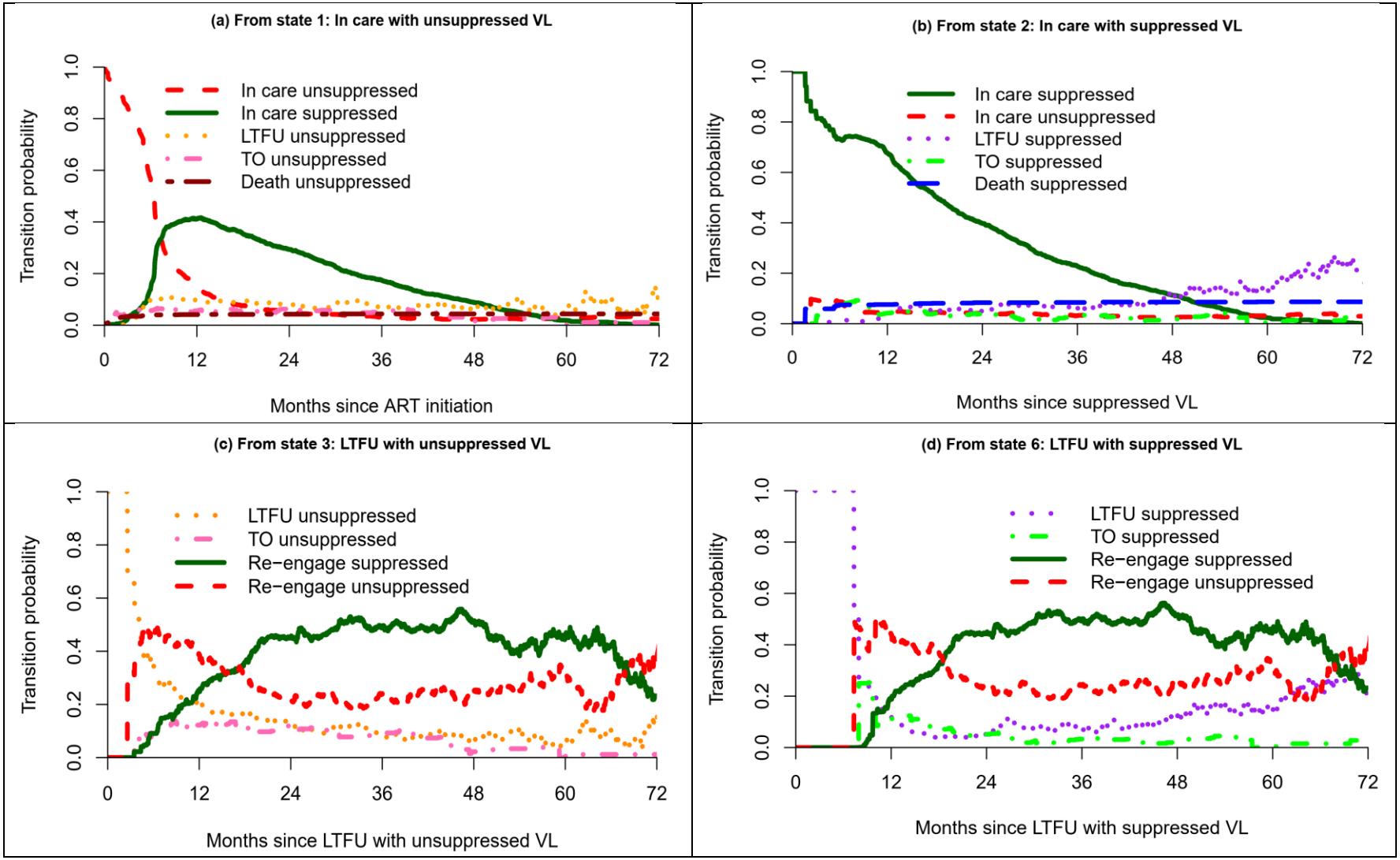

Figure 6.3: Transition probabilities estimated from different transient states. (a) Probabilities estimated since ART initiation with unsuppressed VL (state 1), (b) Probabilities estimated since retained in care and achieved suppressed VL (state 2), (c) Probabilities estimated since LTFU with unsuppressed VL (state 3), and (d) Probabilities estimated since LTFU with suppressed VL. ART: Antiretroviral Therapy; LTFU: Loss to follow-up; TO: Transfer out; VL: Viral load.

Table 6.4: Association of baseline characteristics with four major transitions among PLHIV aged ≥ 10 years who initiated ART from 2017 to 2023

Characteristics	Unsuppressed VL to Suppressed VL	Unsuppressed VL to LTFU with unsuppressed VL	Suppressed VL to LTFU with suppressed VL	LTFU with suppressed VL to Re-engage with suppressed VL
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
Sex				
Male	Ref	Ref	Ref	Ref
Female	1.38 [1.18-1.60]	0.83 [0.66-1.04]	0.92 [0.77-1.11]	1.29 [0.99-1.70]
Age in years				
10 - 19	Ref	Ref	Ref	Ref
20 - 35	0.69 [0.47-1.02]	1.07 [0.58-1.98]	1.06 [0.66-1.69]	1.16 [0.43-3.11]
36 - 49	0.66 [0.44-0.99]	0.90 [0.47-1.70]	1.12 [0.69-1.82]	1.27 [0.46-3.48]
≥ 50	0.66 [0.43-1.02]	0.62 [0.31-1.23]	0.91 [0.55-1.52]	1.33 [0.48-3.73]
Marital status				
Married/cohabiting	Ref	Ref	Ref	Ref
Never married	0.73 [0.58-0.93]	0.94 [0.66-1.36]	1.05 [0.79-1.40]	1.09 [0.67-1.67]
Separated/divorced/widowed	0.80 [0.69-0.94]	1.01 [0.79-1.30]	1.26 [1.05-1.51]	1.19 [0.90-1.57]
Education level				
None	Ref	Ref	Ref	Ref
Primary school	1.00 [0.79-1.26]	0.87 [0.62-1.21]	1.10 [0.83-1.46]	1.03 [0.63-1.67]
Secondary and above/other	1.15 [0.86-1.54]	0.70 [0.44-1.12]	1.09 [0.75-1.57]	1.17 [0.65-2.10]
Occupation				
Farmer	Ref	Ref	Ref	Ref
Employed	0.84 [0.69-1.02]	0.98 [0.71-1.33]	1.32 [1.05-1.67]	0.81 [0.55-1.19]
Unemployed and others	0.72 [0.54-097]	1.12 [0.74-1.71]	1.21 [0.86-1.69]	0.73 [0.39-1.37]
Distance from the clinic in Km				
≤ 1	Ref	Ref	Ref	Ref
2 - 80	0.87 [0.75-1.01]	1.12 [0.89-1.41]	1.02 [0.86-1.21]	1.29 [0.99-1.67]
≥ 81	0.69 [0.54-0.89]	1.22 [0.86-1.72]	1.15 [0.86-1.54]	1.20 [0.82-1.75]
Body mass index				
Normal	Ref	Ref	Ref	Ref
Wasted/underweight	1.06 [0.85-1.33]	0.72 [0.50-1.05]	1.17 [0.89-1.52]	1.02 [0.66-1.59]
Overweight/obese	0.99 [0.85-1.15]	0.76 [0.59-0.98]	1.10 [0.92-1.31]	1.24 [0.95-1.61]
Tuberculosis status				

Unlikely	Ref	Ref	Ref	Ref
Positive	0.76 [0.56-1.02]	0.89 [0.59-1.35]	0.91 [0.63-1.30]	1.24 [0.72-2.12]
CD4 Cell counts in cells/mm^3				
<100	Ref	Ref	Ref	Ref
100 - 199	1.15 [0.92-1.44]	0.81 [0.56-1.18]	1.15 [0.89-1.49]	1.08 [0.70-1.65]
200 - 349	1.12 [0.91-1.38]	1.06 [0.76-1.46]	0.89 [0.69-1.14]	1.04 [0.69-1.56]
350 - 499	1.06 [0.83-1.34]	1.10 [0.76-1.59]	1.07 [0.80-1.42]	1.00 [0.64-1.56]
≥ 500	0.97 [0.77-1.23]	1.31 [0.93-1.85]	0.91 [0.69-1.19]	0.84 [0.54-1.29]
WHO HIV stage				
Stage 1	Ref	Ref	Ref	Ref
Stage 2	0.91 [0.76-1.10]	0.98 [0.73-1.32]	0.93 [0.74-1.15]	0.72 [0.51-1.02]
Stage 3	0.80 [0.66-0.98]	1.06 [0.79-1.44]	0.93 [0.73-1.19]	0.91 [0.64-1.30]
Stage 4	1.20 [0.75-1.39]	1.34 [0.85-2.12]	0.93 [0.65-1.33]	0.75 [0.40-1.39]
Year of ART initiation				
2017-2019	Ref	Ref	Ref	Ref
2020-2021	1.50 [1.29-1.75]	1.16 [0.90-1.49]	2.70 [2.21-3.30]	1.09 [0.78-1.53]
2022-2023	1.60 [1.32-1.95]	1.02 [0.73-1.43]	5.39 [3.93-7.40]	0.89 [0.46-1.74]

aHR: Adjusted hazard ratio; CI: Confidence interval; VL: Viral Load; LTFU: Lost to follow-up; Ref: Reference category

6.9. Supplementary figures and tables

Table S6.1: Transition frequencies and their corresponding percentages (total transitions = 6,563)

From	To										Total
	In care with unsupp	In care with supp VL	LTFU with unsupp	TO with unsupp	Death with unsupp	LTFU with supp VL	TO with supp VL	Death with supp VL	Re-engage with supp VL	Re-engage with supp VL	
In care with unsupp VL	0	1066 (16.2)	475 (7.2)	244 (3.7)	82 (1.3)	0	0	0	0	0	1867 (28.5)
Retained with supp VL	212 (3.2)	0	0	0	0	758 (11.6)	82 (1.3)	19 (0.3)	0	0	1071 (16.3)
LTFU with unsupp VL	0	0	0	54 (0.8)	0	0	0	0	248 (3.8)	331 (5.0)	633 (9.6)
TO with unsupp VL	0	0	0	0	0	0	0	0	8 (0.1)	48 (0.7)	56 (0.9)
LTFU with supp VL	0	0	0	0	0	0	46 (0.7)	0	338 (5.2)	873 (13.3)	1257 (19.2)
TO with supp VL	0	0	0	0	0	0	0	0	8 (0.1)	21 (0.3)	29 (0.4)
Re-engage with supp VL	0	0	0	0	0	665 (10.1)	33 (0.5)	0	0	9 (0.1)	707 (10.8)
Re-engage with unsupp VL	0	0	493 (7.5)	44 (0.7)	0	0	0	0	406 (6.2)	0	943 (14.4)

unsupp: Unsuppressed; Supp: Suppressed; VL: Viral Load; LTFU: Loss to follow-up; TO: Transfer out

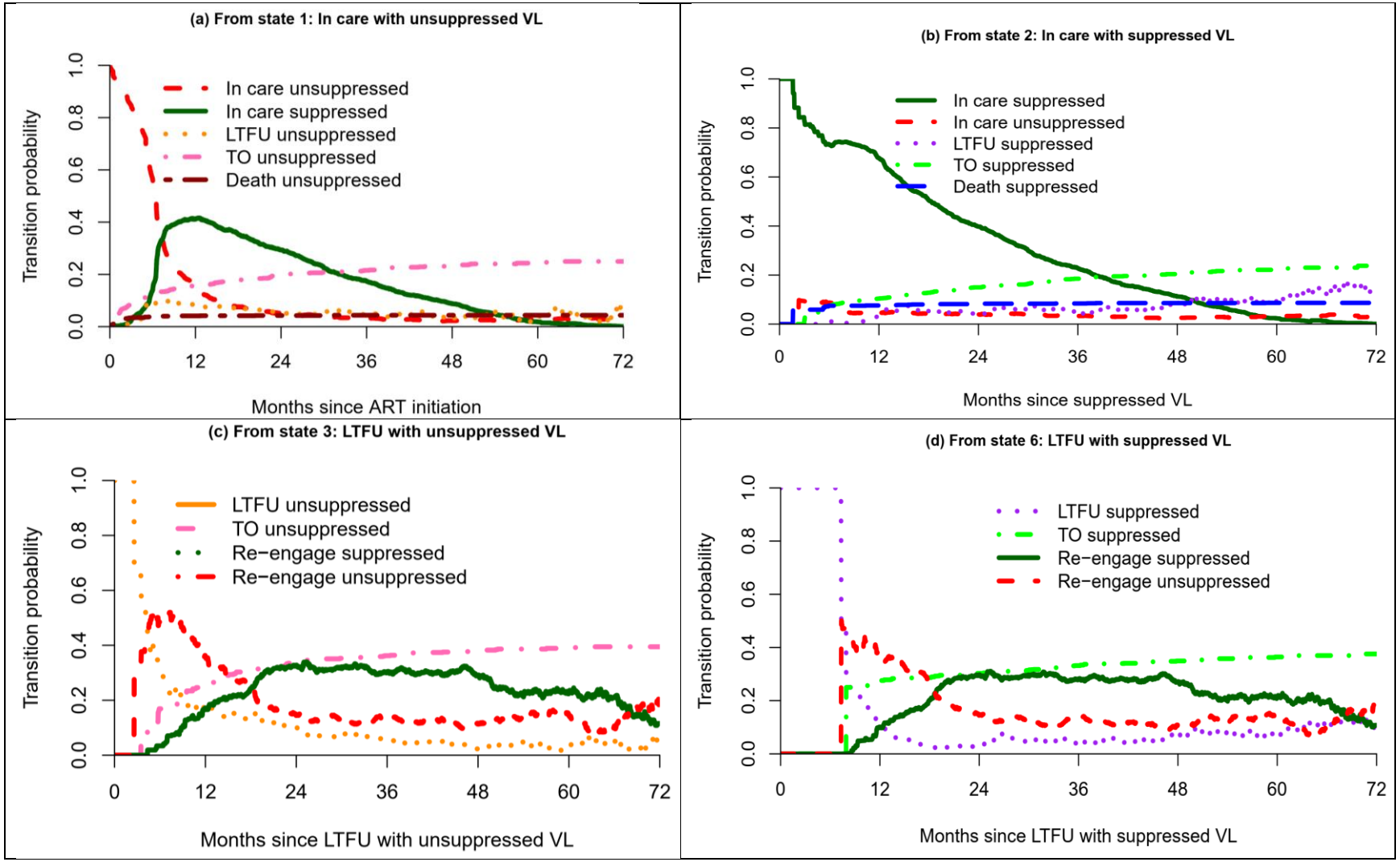

Figure S6.1: Transition probabilities estimated from different transient states in a model that considered transfer out as an absorbing state. (a) Probabilities estimated since ART initiation with unsuppressed VL (state 1), (b) Probabilities estimated since achieved suppressed VL and retained in care (state 2), (c) Probabilities estimated since LTFU with unsuppressed VL (state 3), and (d) Probabilities estimated since LTFU with suppressed VL. ART: Antiretroviral Therapy; LTFU: Loss to follow-up; TO: Transfer out; VL: Viral load.

Table S6.2: Transition probabilities with a 95% confidence interval from the different states at different selected time points in a model that considered transfer as an absorbing state for sensitivity analysis

Time (Months)	In care with unsuppressed VL	From in-care with unsuppressed VL to			
		In care with suppressed VL	LTFU with unsuppressed VL	TO with unsuppressed VL	Death with unsuppressed VL
6	0.56 (0.54-0.59)	0.14 (0.13-0.16)	0.09 (0.08-0.11)	0.13 (0.11-0.14)	0.04 (0.03-0.05)
12	0.15 (0.14-0.17)	0.41 (0.39-0.43)	0.08 (0.06-0.10)	0.16 (0.14-0.18)	0.04 (0.03-0.05)
24	0.05 (0.04-0.06)	0.29 (0.27-0.32)	0.06 (0.05-0.08)	0.20 (0.18-0.22)	0.04 (0.03-0.05)
60	0.03 (0.02-0.04)	0.02 (0.01-0.03)	0.04 (0.02-0.07)	0.24 (0.22-0.27)	0.04 (0.03-0.05)
		From in care with suppressed VL to			
	In care with suppressed VL	In care with unsuppressed VL	LTFU with suppressed VL	TO with suppressed VL	Death with suppressed VL
6	0.73 (0.61-0.89)	0.08 (0.03-0.22)	0.01 (0.003-0.04)	0.07 (0.03-0.15)	0.07 (0.02-0.33)
12	0.68 (0.58-0.79)	0.05 (0.03-0.07)	0.04 (0.02-0.05)	0.10 (0.06-0.18)	0.08 (0.02-0.33)
24	0.40 (0.34-0.46)	0.04 (0.03-0.05)	0.04 (0.03-0.06)	0.15 (0.10-0.22)	0.08 (0.02-0.31)
60	0.02 (0.02-0.03)	0.03 (0.02-0.05)	0.09 (0.07-0.13)	0.22 (0.17-0.29)	0.09 (0.02-0.31)
		From LTFU with unsuppressed VL to			
	Remained LTFU with unsuppressed VL	TO with unsuppressed VL	Death with unsuppressed VL¶	Re-engage with suppressed VL	Re-engage with unsuppressed VL
6	0.31 (0.15-0.64)	0.17 (0.07-0.40)	-	0.03 (0.01-0.14)	0.48 (0.25-0.95)
12	0.17 (0.11-0.24)	0.26 (0.15-0.44)	-	0.17 (0.12-0.25)	0.36 (0.24-0.53)
24	0.10 (0.07-0.14)	0.34 (0.23-0.49)	-	0.33 (0.26-0.41)	0.14 (0.11-0.19)
60	0.03 (0.02-0.06)	0.39 (0.29-0.53)	-	0.23 (0.18-0.30)	0.14 (0.11-0.19)
		From LTFU with suppressed VL to			
	Remained LTFU with suppressed VL	TO with suppressed VL	Death with suppressed VL¶	Re-engage with suppressed VL	Re-engage with unsuppressed VL
6	1	0	-	0	0
12	0.11 (0.02-0.72)	0.28 (0.05-1.00)	-	0.10 (0.04-0.28)	0.38 (0.17-0.83)
24	0.03 (0.01-0.06)	0.30 (0.06-1.00)	-	0.30 (0.15-0.58)	0.14 (0.07-0.28)
60	0.07 (0.03-0.15)	0.36 (0.11-1.00)	-	0.21 (0.11-0.42)	0.13 (0.07-0.27)

¶Transition not allowed due to a few transition frequencies (n < 8 frequencies)
VL: Viral Load; LTFU: Loss to follow-up; TO: Transfer out to other HIV clinics

Table S6.3: Association of baseline characteristics with other transitions among PLHIV aged ≥ 10 years who initiated ART from 2017 to 2023

Characteristics	LTFU with suppressed VL to Re-engage with unsuppressed VL	Re-engage with suppressed VL to LTFU with suppressed VL	Re-engage with unsuppressed VL to LTFU with unsuppressed VL	LTFU with unsuppressed VL to Re-engage with unsuppressed VL
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
Sex				
Male	Ref	Ref	Ref	Ref
Female	1.11 [0.94-1.31]	0.97 [0.80-1.16]	0.98 [0.79-1.22]	1.16 [0.87-1.54]
Age in years				
10 - 19	Ref	Ref	Ref	Ref
20 - 35	0.95 [0.56-1.60]	1.08 [0.61-1.94]	0.74 [0.43-1.28]	0.44 [0.23-0.82]
36 - 49	1.42 [0.83-2.43]	1.18 [0.65-2.16]	0.69 [0.40-1.22]	0.55 [0.29-1.04]
≥ 50	1.21 [0.70-2.12]	1.01 [0.54-1.91]	0.58 [0.31-1.08]	0.51 [0.24-1.07]
Marital status				
Married/cohabiting	Ref	Ref	Ref	Ref
Never married	1.06 [0.80-1.41]	0.91 [0.66-1.24]	0.96 [0.68-1.37]	0.64 [0.40-1.05]
Separated/divorced/widowed	0.90 [0.75-1.08]	0.88 [0.71-1.08]	1.16 [0.91-1.47]	1.23 [0.89-1.70]
Education level				
None	Ref	Ref	Ref	Ref
Primary school	0.79 [0.9-1.05]	0.90 [0.64-1.26]	0.83 [0.58-1.18]	0.96 [0.61-1.51]
Secondary and above/other	0.82 [0.58-1.16]	1.01 [0.67-1.51]	0.68 [0.42-1.09]	0.80 [0.43-1.48]
Occupation				
Farmer	Ref	Ref	Ref	Ref
Employed	0.95 [0.76-1.20]	1.18 [0.92-1.52]	1.12 [0.84-1.50]	1.04 [0.72-1.50]
Unemployed and others	1.26 [0.90-1.78]	1.13 [0.77-1.67]	1.15 [0.75-1.78]	0.73 [0.45-1.21]
Distance from the clinic in Km				
≤1	Ref	Ref	Ref	Ref
2 - 80	0.92 [0.78-1.08]	0.84 [0.69-1.01]	0.94 [0.75-1.18]	0.77 [0.57-1.03]
≥ 81	0.69 [0.52-0.90]	1.13 [0.84-1.51]	1.03 [0.71-1.49]	1.62 [1.01-2.61]
Body mass index				
Normal	Ref	Ref	Ref	Ref
Wasted/underweight	0.82 [0.62-1.08]	1.23 [0.90-1.68]	0.94 [0.67-1.34]	0.87 [0.51-1.49]
Overweight/obese	0.83 [0.70-0.99]	0.92 [0.76-1.12]	0.99 [0.78-1.26]	0.68 [0.49-0.95]

Tuberculosis status				
Unlikely	Ref	Ref	Ref	Ref
Positive	1.13 [0.80-1.58]	0.85 [0.56-1.30]	0.95 [0.61-1.48]	0.79 [0.43-1.46]
CD4 Cell counts in cells/mm^3				
<100	Ref	Ref	Ref	Ref
100 - 199	0.80 [0.61-1.04]	1.30 [0.76-1.40]	1.11 [0.79-1.56]	1.17 [0.72-1.88]
200 - 349	1.03 [0.81-1.31]	1.09 [0.82-1.44]	1.15 [0.84-1.57]	1.00 [0.65-1.53]
350 - 499	0.94 [0.72-1.23]	1.20 [0.88-1.63]	0.97 [0.66-1.41]	0.80 [0.48-1.33]
≥500	0.87 [0.67-1.14]	1.22 [0.90-1.65]	1.16 [0.82-1.64]	0.98 [0.61-1.57]
WHO HIV stage				
Stage 1	Ref	Ref	Ref	Ref
Stage 2	0.93 [0.75-1.15]	1.43 [1.11-1.85]	1.23 [0.92-1.63]	1.09 [0.75-1.60]
Stage 3	0.94 [0.75-1.18]	1.18 [0.90-1.54]	1.21 [0.91-1.59]	0.81 [0.56-1.16]
Stage 4	1.07 [0.75-1.53]	2.11 [1.32-3.38]	1.14 [0.70-1.85]	0.89 [0.44-1.79]
Year of ART initiation				
2017-2019	Ref	Ref	Ref	Ref
2020-2021	0.92 [0.75-1.12]	4.31 [3.29-5.64]	1.99 [1.51-2.63]	1.42 [1.04-1.95]
2022-2023	0.59 [0.39-0.88]	9.92 [4.38-22.5]	3.85 [1.93-7.67]	1.14 [0.56-2.30]

aHR: Adjusted hazard ratio; CI: Confidence interval; VL: Viral load; LTFU: Lost to follow-up; Ref: Reference category

CHAPTER SEVEN: General discussion and conclusions

7.0. Introduction to the chapter

This chapter discusses the major findings from different studies that responded to project objectives and compares them with existing literature on the topic. The first objective of the project was to conduct a systematic literature review of statistical methods used in the assessment of the HIV care cascade and continuum of care. The review identified and synthesized statistical methods used to evaluate the HIV cascade and continuum of care. The systematic scoping review found that the majority of the cascade assessments applied cross-sectional methods, and cascade evaluations using longitudinal methods are emerging in the literature, with the application of different types of longitudinal methods.

The second objective was to describe the transition dynamics along the cascade and continuum of care among PLHIV enrolled at the CDCI, Tanzania, between 2005 and 2022. In repeated cross-sectional analyses, the proportion of ART initiation increased over time. The majority of the PLHIV who were on ART and retained in care were virally suppressed. However, the longitudinal models assessed the same group of PLHIV, showing that in-and-out of care transitions were common. Across the different guideline years, the proportion of deaths also decreased over time.

Objective three was about modeling transition probabilities along the HIV care cascade and continuum care among PLHIV enrolled in care at the CDCI, Tanzania, between 2005 and 2022. Findings revealed that being on ART at baseline was associated with a reduced hazard of LTFU and an increased hazard of return to care after being LTFU. Being female was related to a reduced hazard of LTFU and re-engagement after being transferred.

Objective four assessed the treatment outcomes and engagement in care, and factors associated among PLHIV enrolled in care at the CDCI, Tanzania, from 2017 to 2024. In this objective, PLHIV initiated on ART during “test and treat” were investigated for viral load outcomes. Findings showed that, even during the era of “test and treat”, PLHIV moved in-and-out of care before and after achieving suppressed VL. Being female was associated with an increased hazard of achieving suppressed VL compared to male PLHIV. Furthermore, PLHIV who were in WHO HIV stage 3 had a reduced hazard of achieving VL suppression compared to those in WHO HIV stage 1. PLHIV aged 20-35 years (compared to those aged 10-19 years) and being overweight or obese

(compared to normal BMI) had a reduced hazard of re-engaging with unsuppressed VL after being LTFU with unsuppressed VL.

This chapter is organized as follows: first, all the major findings of the project were discussed in comparison with existing literature and possible underlying mechanisms. Later, the project conclusion and recommendations from various studies were also identified to guide future studies on the topic. Lastly, the Chapter was closed with the contribution of this Ph.D.

7.1. Overall discussion

The majority of the articles reviewed used only the cross-sectional methods during the assessment of the HIV cascade and continuum of care (93%), despite the existing concerns and the limitations of the design methods (15,17). The few articles that used longitudinal design methods (7%) often assessed the engagement in care, and very few used both cross-sectional and longitudinal design methods (73,104,137). In longitudinal assessments, methods used included repeated cross-section, repeated measures, classical survival methods, competing risks, and multistate models. These different methods were responding to different objectives depending on the cascade evaluation goal. So far, there is no methodological guideline that could be used by the program data manager and cascade assessors on how and when to use certain longitudinal methods for HIV cascade and continuum of care assessment.

There was a clear lack of connection between the cross-sectional and longitudinal assessments because of the different quantities estimated. Some of the longitudinal cascade assessments that used multistate models did not consider stages such as linkage to HIV care and treatment clinics, ART status, and VL or CD4 of the assessed PLHIV like in cross-sectional cascade (14,31,54,66). Instead, engagement in care states such as retention in care, LTFU or disengagements, transfer, and deaths were often used. This made it difficult to compare the findings of cross-sectional and longitudinal cascades because different quantities were assessed. A recently published article that assessed longitudinal cascade using multistate models used a modeling framework that included both ART and VL suppression status states (164,165). Moreover, Bakoyannis et al (165) showed a way of obtaining estimates of cross-sectional cascade using a multistate modeling framework. Their approach provided a better understanding of the progress and additional tools for researchers

interested in comparing the cross-sectional and longitudinal cascade findings in a multistate modelling framework.

Over the years, knowledge about HIV and clinical practices has improved. These improvements were also integrated into HIV and AIDS management guidelines worldwide. The impact of these changes over time was also observed in this project. In a study that assessed the transition dynamics along the cascade, one of the key findings was the achievement of the third 95% of the 2025 UNAIDS target by September 2022 among PLHIV on ART and retained in care at the CDCI. The estimate was similar to the 2023 Tanzanian cascade assessment, which showed that 92% of PLHIV on ART were suppressed (43). Furthermore, cascade assessment stratified by time showed improved ART initiation and treatment response outcomes over time. Findings show that the proportion of ART initiation increased from 67% in April 2005-January 2009 to 96% in April 2019-September 2022, and good treatment outcomes increased from 32% to 82% in the same period. These results were similar to studies done in South Africa (73), Australia (182), the UK and Ireland (150), Canada (42), and Oman (137).

The optimal benefit of ART is dependent on good treatment adherence, which is also affected by intermittent LTFU during treatment. Despite the apparent excellent progress shown in the cross-sectional cascade, PLHIV enrolled in care transitioned in-and-out of care frequently over time. In the first 12 months of enrollment, 24% were LTFU, while 34% of the LTFU returned to care by 12 months after being LTFU. The proportion of re-engagement after being LTFU decreased over time, and it was similar to a recent study conducted in Zambia (183). This result suggests a reduced chance of return when PLHIV spends a longer time out of care, which may indicate undocumented self-transfer or death.

Most of the assessments on re-engagement in care are focused on return to care after being LTFU (184), and very few have investigated re-engaging after transfer to another HIV clinic (185). In this project, re-engagement in care also occurred among PLHIV who were transferred out and later returned to care at CDCI. In this setting, PLHIV may return to care after transfer because of the nature of the CDCI clinic. The CDCI is located at the regional referral hospital, which has HIV-specialized medical doctors and a laboratory for HIV-related tests. Therefore, PLHIV who were transferred to the nearby clinics can return or be referred to CDCI if they need a higher level of HIV service. This is different from other settings that used transfer as an absorbing state because

once PLHIV is transferred, they do not return, or the return information was not captured well in databases (14,32).

Even though the second study of this project showed PLHIV on ART had a reduced hazard of LTFU, a third study that focused on PLHIV on ART, LTFU was common before and after achieving suppressed VL. The pattern of re-engagement was broadly similar. Studies that assessed PLHIV returning to care after a period of disengagement have shown various reasons for disengaging from care, including denial of HIV status, disclosure issues, advanced HIV, mental health problems, lack of social support, unexpected transfer due to change of employment (especially for young adults), and ART side effects (186,187). Furthermore, it is likely that PLHIV who were LTFU with unsuppressed VL and returned with suppressed VL were temporary self-transfers that were not documented at the CDCI. Beeman et al (188) have also shown that transfer out was used as a method to re-engage after a period of LTFU. These LTFU PLHIV usually start with a new HIV test from a different clinic and pretend to be newly diagnosed. Efforts to ensure HIV clinics are connected using technology are crucial to capture these self-transfers after LTFU events.

PLHIV returned to care for various reasons and different characteristics. PLHIV who were temporarily LTFU after achieving suppressed VL and returning with suppressed VL might have had two probable reasons for maintaining good treatment outcomes. First, one would be a temporary self-transfer with continuation of medication from elsewhere. The second would be that LTFU had a very high CD4 cell count and probably very low viremia (<50 copies/mL) before becoming LTFU and returned to care early before VL rebound. Studies that used analytical treatment interruption (ATI) methods have reported time for confirmed VL rebound ranging between 2 and 12 weeks (189–191), and depending on PLHIV characteristics, sometimes as long as 48 weeks when their CD4 >500 cells/mm^3 and VL <50 copies/mL (190). However, LTFU PLHIV individuals are not necessarily the same as PLHIV involved in ATI studies, because those in ATI studies are carefully selected and frequently monitored for confirmed VL rebound (192). Further investigation of PLHIV who LTFU and return with suppressed VL using mixed methods is critical for a better understanding of drivers of good treatment outcomes after the period of LTFU.

VL suppression improves the well-being of PLHIV on treatment and reduces the risk of opportunistic infection. However, this benefit requires PLHIV to continue with medication for controlling virus replication. Unfortunately, PLHIV who achieve viral suppression do not feel they are sick and eventually become at risk of ART interruption (187). In this project, the third study also shows that among PLHIV who were LTFU after achieving suppressed VL, some returned with unsuppressed VL, and others maintained suppressed VL. This is suggestive of an ongoing challenge of maintaining durable suppressed VL over time, even during a "test and treat" period, which was also observed in a small proportion of PLHIV in central Uganda (35).

In this project, female PLHIV, whether on ART or not, had a reduced hazard of LTFU compared to male PLHIV. Generally, female PLHIV have shown good HIV service uptake compared to male PLHIV (193–196). The reasons for poor engagement in care among male PLHIV are gender and masculinity norms, stigma, absence of men-friendly services, poverty, inappropriate behavior of female nurses, fear of HIV diagnosis, and confidentiality concerns (197–200). Consequently, men often are late in terms of treatment initiation (194) and often start treatment with advanced HIV disease (195), leading to an increased risk of mortality (194). To address the challenges of men's involvement in HIV care and treatment clinics, several interventions to encourage men's involvement have been proposed, including community-based outreach, supporting adherence through community-based ART provision, men's dialogue and adherence clubs, and community-based adherence groups (198,199,201). The community-based interventions, which are flexible enough to include men-friendly time for services, ART provision, counseling, and privacy, have the potential to reduce stigma, transport costs, and confidentiality concerns (199,201).

The effect of age was dependent on the transition under consideration. In the study that assessed the progress of the cascade and transition dynamics, in adults, PLHIV aged $\geq$ 31 years had a reduced hazard of LTFU and were more likely to re-engage after transfer. PLHIV aged 31-49 years at enrolment had an increased hazard of re-engaging. This finding was similar to a study done in Lilongwe, Malawi (202), but it was different from a study done in Mali, which showed no age effect on PLHIV re-engaging after being LTFU (203). Additionally, PLHIV aged 20-35 years at ART initiation had a reduced hazard of re-engaging with suppressed VL after being LTFU with suppressed VL. This is suggestive of treatment discontinuation while not in care. Treatment discontinuation has the consequence of VL rebound (204) and onward HIV transmission.

Lack of family, partner, or social support affects treatment adherence and clinic continuation. In the second study of this project, PLHIV who were never married had an increased hazard of LTFU and reduced hazard of return to care after being LTFU compared to those who were married or cohabiting. In qualitative studies that assessed reasons for LTFU, one of the reasons identified was the lack of family and social support (205–207). PLHIV interviewed about the facilitators of retention in care have reported that social support (such as appointment reminders, treatment adherence support, and food support) encouraged them to continue with HIV care and treatment (208). Furthermore, studies reported stigma as a barrier to retention; one of their findings was that some PLHIV opted to skip their scheduled appointments because they feared that their HIV status would be disclosed during their clinical, laboratory, and drug prescription visits (208). Interventions for improving retention should consider the individual characteristics of the PLHIV, including their social life. For example, PLHIV who never married may have experienced rejection in society and/or been considered less important. HIV diagnosis in this group further complicates their life due to the stigma that comes with the diagnosis.

Living far from the clinic is always linked with an increased hazard of LTFU in both quantitative and qualitative studies (21,187,206,209). However, some PLHIV would prefer to receive their services from clinics far from their living area because of fear of status disclosure when they are not ready to disclose. It was interesting to observe that PLHIV living far away had an increased hazard of return to care after being LTFU. A possible explanation for the increased hazard of return could be HIV progression and symptoms of opportunistic infections. Studies that evaluated PLHIV returning to care after being LTFU have reported that PLHIV returned while they were sicker (210), and others found that the majority had advanced HIV at the return (211). For the case of CDCI, PLHIV lived far from the clinic and had disease progression, while LTFU may have returned specifically because of the superior HIV services available at CDCI, either on their own or by referral from other HIV clinics.

7.2. Conclusions, recommendations, and research implications

In this project, from the review study, it was clear how the cross-sectional and longitudinal assessments provided different findings of the HIV cascade and continuum of care evaluation. The empirical analyses that started from standard methods to advanced methods showed how these

methods complement each other for a better understanding of the HIV cascade and engagement in care. The cascade evaluations that include longitudinal assessments of engagement in care using multistate models generate detailed and comprehensive evaluations of the program with additional areas and time points to intervene.

The scoping review found a variety of cross-sectional and longitudinal design methods applied in the evaluation of the HIV cascade and continuum of care. However, HIV cascade researchers and program managers do not have detailed and step-by-step guidelines on which method is suitable for which type of cascade evaluation goal. Currently, there is great emphasis on the application of longitudinal methods and multistate models, and their applications are emerging in the literature, with various methods being used. These methods are now widely accepted, but their application is still low due to the complexity of data management of the unstructured longitudinal data collected routinely from HIV clinics. To increase the uptake of these methods at the program level and beyond (country and regional levels), a methodological guideline on steps from objectives, dataset preparation, analysis, interpretation of results, and reporting is of paramount importance for future detailed cascade and engagement in care assessments.

In the empirical assessments, the application of various methods identified in the review has shown how richly the routinely collected data from HIV clinics could be used to inform various policies and strategies to improve the HIV service uptake. In cross-sectional analyses, as expected, across different guideline years, the proportion of ART initiation increased, with 96% of the PLHIV enrolled in the current HIV and AIDS management guidelines being initiated on ART. Furthermore, by September 2022, 95% of the PLHIV who were on treatment and retained in care were virally suppressed (VL <1000 copies/mL). This indicates good progress with the UNAIDS 2025 targets being achieved very early in the clinic. However, in these analyses, PLHIV who were LTFU, transferred to other clinics, or died were considered not in active care at analysis time and were excluded. Because PLHIV experienced intermittent LTFU episodes at different stages of the cascade, the cross-sectional cascade analyses do not fully represent the true proportions of PLHIV with the desired outcomes.

The advanced methods utilized longitudinal data provided valuable information about the existing dynamics of engagement in care, which often is not reported in cross-sectional analyses. The application of multistate models provided a unique opportunity for further investigation of the

cascade and engagement in care of the enrolled PLHIV from the start of the cohort. The findings of these analyses (applied to the same PLHIV used in cross-sectional analyses) showed that the proportion of PLHIV remaining in care without any event decreased over time. Furthermore, PLHIV had high rates of intermittent LTFU, with approximately one-third of the LTFU returning to care within 12 months after being LTFU. Healthcare providers should actively trace PLHIV who LTFU within 12 months to establish whether PLHIV discontinued medication or transferred to other HIV clinics. Furthermore, the identified time points with higher rates of return to care are informative for intervention design and resource allocation to improve engagement in care.

The large proportion of PLHIV who achieved suppression within 6-12 months was suggestive of good treatment adherence of the majority initiated on ART. Furthermore, PLHIV with suppressed VL on average spent 22 months in care. The achievement of suppressed VL is not challenging in this clinic, but sustaining suppressed VL is difficult when PLHIV individuals are out-of-care. Immediate tracing of PLHIV who were suppressed and have missed their scheduled visit for at least 7 days (as recommended by WHO (212)) is very important to ascertain their treatment adherence challenges and re-initiate ART to prevent VL rebound, HIV progression, and death. Additionally, upon the return to care, PLHIV receive enhanced counseling sessions to improve treatment adherence. During these sessions, healthcare providers should make additional efforts to understand the PLHIV perspective as to why they have difficulty continuing HIV treatment. From this information, providers may design a supportive system for treatment adherence according to the identified challenges.

Among PLHIV who were initiated on ART, different patterns of re-engagement in care before and after achieving suppressed VL were observed. For example, PLHIV returned to care with suppressed VL was suggestive of undocumented self-transfer. Currently, in Tanzania, there are no well-established ways for the clinics to capture these self-transfers in real time. The Tanzanian Ministry of Health, NASHCoP, and HIV stakeholders could extend the existing data collection system to be a web-based database. This system will allow clinics to capture self-transferred clients. This approach will reduce the overestimation of the LTFU proportions and the underestimation of transfer proportions. On the other hand, those who returned to care with unsuppressed VL after being suppressed probably experienced treatment interruption. Counseling on the risk of treatment interruption and VL rebound should be integrated into routine HIV care.

These counseling sessions should aim to prevent treatment discontinuation when PLHIV are informed about the suppressed VL and should be provided during the ART initiation and after achieving suppressed VL. Furthermore, mixed methods research in rural Tanzania setting should be considered to gain more insights from PLHIV who may have discontinued medication to inform future intervention design.

The project identified various baseline characteristics associated with different transitions that can guide policy-makers, decision-makers, and researchers for a focused intervention design and funding. PLHIV who will require additional considerations to improve their retention in care or treatment outcomes include males, adolescents, young adults, employed, PLHIV living far from the clinic, and those who were never married. These factors were suggestive that different groups of PLHIV may have different support needs for improving engagement in care and treatment outcomes. Intervention packages that focus on the various needs of these PLHIV would help to improve engagement in care and improve treatment outcomes in the future.

7.3. Ph.D. contribution

This Ph.D. project is among the first to provide a comprehensive assessment of the HIV care cascade and continuum of care at the sub-national level and in rural Tanzania, accounting for patients' various transitions along the cascade. The assessments captured the dynamics of engagement in care and provided a complete picture of the HIV cascade progress in terms of time points where there are a lot of gaps in care, how long PLHIV stays out of care, and when they re-engage in care. The information will guide decision-makers of the clinic and NASHCoP on priority areas for resource allocation because this information is not available in national surveys. After all, the surveys are not powered for sub-national level estimates.

Additionally, HIV program managers of the clinics will benefit from these detailed assessments because they will guide them in areas and subgroups of PLHIV that require close attention to improve cascade progress. The information generated in this project is useful in improving the HIV cascade and continuum of care policy and guidelines for cascade assessments in the country. Materials of this Ph.D. can be used as input in the development of a program methodological guide for data managers and analysts of the HIV cascade and continuum of care in Tanzania and beyond.

Findings from a single clinic have shown the advantage of applying advanced methods in understanding the progress of the HIV cascade and continuum of care. These methods can easily be extended to national-level estimates that will utilize routine data collected from HIV clinics. Extending these methods to national-level estimates will provide a complete picture of the progress, and the decision-makers and policy-makers of the Tanzanian Ministry of Health and NASHCoP will plan based on the findings of the comprehensive assessment. Through this approach, the knowledge will also be transferred to the program managers of various institutions.

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9.0. APPENDICES

9.1. Ph.D. ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms AV Kalinjuma
School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

E-mail: avedastus@gmail.com

CC: Supervisor: Drs K Otwombe and F Vanobberghen
<otwombek@phru.co.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/04/20

REF: R14/49

PROTOCOL NO: **M211165** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Transition dynamics and treatment outcomes amongst HIV-positive patients of Ifakara, Tanzania: a comprehensive analysis for optimizing the existing longitudinal cohort data*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms AV Kalinjuma

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M211165

NAME: (Principal Investigator) Ms AV Kalinjuma

DEPARTMENT: School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

PROJECT TITLE: *Transition dynamics and treatment outcomes amongst HIV-positive patients of Ifakara, Tanzania: a comprehensive analysis for optimizing the existing longitudinal cohort data*

DATE CONSIDERED: 2021/11/26

DECISION: Approved unconditionally

CONDITIONS:

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Drs K Otwombe and F Vanobberghen

APPROVED BY: Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2022/04/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

21/04/2022
Date

9.2. Declaration of co-authors

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, [Aneth Vedastus Kalinjuma], student number [2449789], declare that this Thesis~~/Dissertation/Research~~ Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis~~/Dissertation/Research~~ Report .

Signature of Student …… …… **Date**……05-02-2025……

Name of Primary Supervisor……Prof. Kennedy Otwombe……..

Signature of Primary Supervisor …… ……**Date**……05 Feb 2025……..

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of ~~his/~~her Thesis~~/Dissertation/Research~~ Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for ~~his/~~her degree purposes.

Article 1: Title: Statistical methods applied for the assessment of the HIV cascade and continuum of care: a systematic scoping review

Journal name, year, volume and page numbers: BMJ Open, 2023, Volume 13, issue 11

Authors	Name	Signature	Date
1st author	Aneth Vedastus Kalinjuma		05-02-2025
2nd author	Tracy Renée Glass		10 Feb 2025
3rd author	Honorati Masanja	DocuSigned by:	2/11/2025
4th author	Maja Weisser	728BE860CB8A417...	06.02.2025
5th author	Amina Suleiman Msengwa		10.02.2025
6th author	Fiona Vanobberghen	Fiona Vanobberghen	06 Feb 2025
7th author	Kennedy Otwombe		05 Feb 2025

Comments by primary supervisor:

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Article 2: Title: Progress of HIV care cascade and transition dynamics along the continuum of care among persons living with HIV in Ifakara, Tanzania: A prospective study

Journal name, year, volume and page numbers: BMC Infectious Diseases (Manuscript under revie

Authors	Name	Signature	Date
1st author	Aneth Vedastus Kalinjuma		05-02-2025
2nd author	Aaloke Mody		10 Feb 2025
3rd author	Tracy Renée Glass		10 Feb 2025
4th author	Maja Weisser	DocuSigned by: 6F9ADEF4B824455...	2/11/2025
5th author	Ezekiel Luoga		07/02/2025
6th author	Honorati Masanja	DocuSigned by: 728BE860CB8A417...	2/11/2025
7th author	Fiona Vanobberghen		06 Feb 2025
8th author	Kennedy Otwombe		05 Feb 2025

Comments by primary supervisor:

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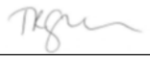
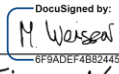
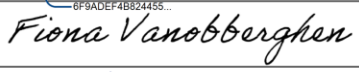
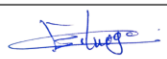
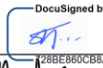
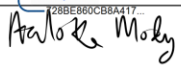
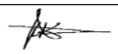
Article 3: Title: Treatment outcomes and engagement in care among persons living with HIV in Ifakara, Tanzania: A multistate modeling study

Journal name, year, volume and page numbers: Manuscript drafted

Authors	Name	Signature	Date
1st author	Aneth Vedastus Kalinjuma		05-02-2025
2nd author	Tracy Renée Glass		10 Feb 2025
3rd author	Maja Weisser		2/11/2025
4th author	Fiona Vanobberghen		06 Feb 2025
5th author	Ezekiel Luoga		07/02/2024
6th author	Honorati Masanja		2/11/2025
7th author	Aaloke Mody		10 Feb 2025
8th author	Kennedy Otwombe		05 Feb 2025

Comments by primary supervisor:

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9.3. Published paper 1: Systematic scoping review

Open access Original research

BMJ Open

Statistical methods applied for the assessment of the HIV cascade and continuum of care: a systematic scoping review

Aneth Vedastus Kalinjuma ,[1,2] Tracy Renée Glass,[3,4] Honorati Masanja,[1] Maja Weisser,[1,3,5] Amina Suleiman Msengwa,[6] Fiona Vanobberghen,[3,4] Kennedy Otwombe [2,7]

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ABSTRACT

Objectives This scoping review aims to identify and synthesise existing statistical methods used to assess the progress of HIV treatment programmes in terms of the HIV cascade and continuum of care among people living with HIV (PLHIV).

Design Systematic scoping review.

Data sources Published articles were retrieved from PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete and Excerpta Medica dataBASE (EMBASE) databases between April and July 2022. We also strategically search using the Google Scholar search engine and reference lists of published articles.

Eligibility criteria This scoping review included original English articles that estimated and described the HIV cascade and continuum of care progress in PLHIV. The review considered quantitative articles that evaluated either HIV care cascade progress in terms of the Joint United Nations Programme on HIV and AIDS targets or the dynamics of engagement in HIV care.

Data extraction and synthesis The first author and the librarian developed database search queries and screened the retrieved titles and abstracts. Two independent reviewers and the first author extracted data using a standardised data extraction tool. The data analysis was descriptive and the findings are presented in tables and visuals.

Results This review included 300 articles. Cross-sectional study design methods were the most commonly used to assess the HIV care cascade (n=279, 93%). In cross-sectional and longitudinal studies, the majority used proportions to describe individuals at each cascade stage (276/279 (99%) and 20/21 (95%), respectively). In longitudinal studies, the time spent in cascade stages, transition probabilities and cumulative incidence functions was estimated. The logistic regression model was common in both cross-sectional (101/279, 36%) and longitudinal studies (7/21, 33%). Of the 21 articles that used a longitudinal design, six articles used multistate models, which included non-parametric, parametric, continuous-time, time-homogeneous and discrete-time multistate Markov models.

Conclusions Most literature on the HIV cascade and continuum of care arises from cross-sectional studies. The use of longitudinal study design methods in the HIV cascade is growing because such methods can provide additional information about transition dynamics along the cascade. Therefore, a methodological guide for applying different types of longitudinal design methods to the HIV continuum of care assessments is warranted.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review is one of the largest and most recent systematic scoping reviews conducted on the methods used to assess the HIV cascade and continuum of care with wide coverage and diversity.
⇒ The review highlights areas with limited research in terms of methods and their applications to the HIV cascade and continuum of care, and it provides recommendations for future research.
⇒ This review was limited to articles published in English. Therefore, the impact of including other languages in this review is unknown.
⇒ The review included published articles. However, the pattern study findings would not be expected to change if grey literature were included.

INTRODUCTION

The HIV care cascade is a framework that describes the stages of people living with HIV (PLHIV) transitioning through HIV infection, diagnosis, linkage to care, initiation of antiretroviral therapy (ART), retention in care and viral load suppression.[1 2] This framework characterises and quantifies the proportion of PLHIV in each stage of the cascade.[3 4] It is a useful tool for monitoring the uptake of HIV services and the progress of HIV treatment programmes.[5–7]

In the literature, the terms 'HIV care cascade' and 'HIV continuum of care' are used interchangeably,[4 5 8 9] but Kay *et al*[10] distinguished the two concepts. They defined the 'HIV continuum of care' as a dynamic and bidirectional engagement in HIV care,

whereas the 'HIV care cascade' was defined as a static and cross-sectional representation of HIV care stages at the population level. In recent years, many researchers have embraced these concepts, and the distinction between them has been recognised in literature, particularly after the Joint United Nations Programme on HIV and AIDS (UNAIDS) announced the 90-90-90 targets for HIV for 2020[11] and 95-95-95 targets for 2025.[12] The 95-95-95 target states that 95% of PLHIV know their HIV status, 95% of those diagnosed are initiated on ART and 95% of those on ART are virally suppressed.

Currently, most HIV treatment programme assessments and evaluations are performed following the HIV care cascade approach, which aims to report progress towards UNAIDS targets for 2020 or 2025.[13–22] These assessments often apply descriptive statistics and show progress at a particular time point, referred to as a cross-sectional design. In recent years, assessments of the HIV cascade and continuum of care that use a longitudinal design have been increasingly featured in the published literature. In these applications, methods such as multistate models,[3 5] competing risk methods[23] and the distribution time spent in each cascade stage[24] were used. The existence of various methods and their applications in the HIV cascade and continuum of care evaluation call for a review that identifies the statistical methods used in these assessments.

Different types of reviews exist on this topic, the majority of which focus on synthesising estimates for each HIV care cascade stage. These reviews mainly focused on HIV testing, engagement in care and treatment,[25 26] cascades among alcohol users,[27] longitudinal methods for assessing retention in care[28] and cascades among people who inject methadone drug.[29] Others reviewed cascade stage definitions,[30] measures of patient engagement in HIV care,[31] cascade experiences among indigenous people,[32] cascades among adolescents and young adults[33] and cascades among children and adolescents.[34]

Currently, few systematic reviews have synthesised methods used to assess the HIV cascade and continuum of care progress. The first systematic review was conducted by Medland *et al*[35] and published in 2015. At that time, few cascade articles were published, and most studies used descriptive statistics in a cross-sectional study design. Granich *et al*[36] conducted a review of methods and the status of progress towards the UNAIDS 90-90-90 from 2010 to 2016, and they showed that different methods were used. However, they focused mainly on articles that used a cross-sectional study design and methods used to determine indicators and data sources. In 2021, Vourli *et al*[37] published a systematic review that highlighted the importance of expanding the scope of cascade assessment to include time to the next cascade stage. In these reviews, the components of the statistical methods applied to the HIV cascade and continuum of care assessments were limited. Therefore, this systematic scoping review aimed to identify and summarise the statistical methods used to assess HIV treatment programme progress in terms of the HIV cascade and continuum of care among PLHIV using both cross-sectional and longitudinal study designs.

METHODS

Review protocol

The scoping review protocol was developed from November to December 2021, following the Joanna Briggs Institute System for the Unified Management, Assessment, and Review of Information Manual for Evidence Synthesis (Scoping Review Chapter).[38]

Eligibility criteria

This scoping review included original articles written in English that focused on estimating and describing the HIV cascade and continuum of care among PLHIV. Specifically, the review considered quantitative articles that either evaluated or assessed the HIV care cascade in terms of UNAIDS targets or the dynamics of engagement in HIV care and treatment clinics for the HIV continuum of care. Mixed-methods articles were included if the quantitative component was well described (ie, the method used to assess the cascade and results of the cascade were presented in the article). The review excluded articles comparing the HIV care cascade with other cascades, such as the tuberculosis care cascade, hepatitis cascade and prevention of mother-to-child transmission of HIV. The review further excluded review and meta-analysis articles, opinions, editorials, commentary articles and non-peer-reviewed articles (because the methods sections were not well-described). Finally, the review did not include published conference abstracts or proceedings, because the methods were typically not provided in sufficient detail.

Search strategy

The development of an electronic bibliographical database search strategy began with a pilot phase, whereby review concepts were searched independently in PubMed and Google Scholar. The retrieved relevant titles and abstracts were screened to identify keywords to include in the development of electronic database search queries. The database search query was first developed in English using the PubMed database and adapted to the Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete and Excerpta Medica dataBASE (EMBASE) databases as needed (online supplemental table S1). The database search dates were from April to July 2022.

Source of the evidence selection process

Titles and abstracts were retrieved from all three databases, and duplicates were removed based on the digital object identifier and article content. Titles and abstracts were screened for eligibility by the lead author and irrelevant articles were excluded. All potentially relevant full-text articles were downloaded for review. The first author and two independent reviewers each conducted a full-text

review of all articles, during which the review criteria were applied. The article search and assessment of inclusion and exclusion criteria were summarised and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews flow diagram.[39]

Data extraction and data entry process

The extracted information included the first author's name and publication year, type of participants, age, country, sample size, study design, study level of representation and data source. Other extracted information included cascade stages, cascade size, cascade staging methods and statistical methods used to assess the HIV cascade and continuum of care (online supplemental table S2). All extracted information was first entered into an Excel spreadsheet. The data extraction tool was modified and revised whenever necessary, depending on new information available in the articles and its relevance to this review. The first author reviewed all extracted data. Disagreements between reviewers were resolved by consensus. After finalising the data collection template, an electronic data capture system was developed using open data kit (ODK), and data entry was performed by the reviewers. The information entered into ODK was pooled in Excel with a comma-separated value file format using the ODK briefcase.

Data items

The variables used in this review included publication year, which included three groups: 2011–2014, referring to the time between the first cascade report and before the announcement of the UNAIDS 90-90-90 targets; 2015–2019, following the UNAIDS 90-90-90 targets announcement and the implementation time and 2020–2022 (by July), representing the reporting time for the UNAIDS 90-90-90 targets and the implementation of the new UNAIDS 95-95-95 targets. The study site was country-specific if a study was conducted in one country and regionally if a study was conducted in at least two countries. The study regions included Asia and Europe, North and South America, sub-Saharan Africa and global (a single report that included multiple regions).

A cross-sectional study design included articles that presented cascade results at a single time point. A longitudinal design included articles that presented cascade outcomes either repeatedly over time (ie, repeated cross-sectional study design), or prospective or retrospective study designs (including cohort data).[40] In this review, studies that included cascade assessments using both cross-sectional and longitudinal designs were included in the longitudinal study design group, because cross-sectional analyses can be considered a subset of longitudinal analyses.

Other variables included data sources (cohort, laboratory test records, hospital records, surveys, surveillance and clinical trial data) and study level of representation, which was grouped into facility, subdistrict/town/municipality/city; state/province; population (when a study estimated the number of PLHIV, diagnosed and linkage to care); community/district/county; regional; country and global studies. Another variable was the sample size (the number of diagnosed PLHIV assessed). The sample size was grouped into four categories: <1000, 1000–5000, 6000–10 000 and >10 000. The types of participants were grouped into all PLHIV, children only, adolescents, adults, HIV key populations, prisoners, veterans, refugees and the military. The HIV key populations included men who had sex with men, female sex workers, people who inject drugs, and transgender men and women. Finally, the statistical methods applied in the different articles were grouped into two categories: descriptive statistics and regression models. Variables such as study design, data sources, types of participants and statistical methods were allowed for multiple responses; the obtained responses were converted into multiple individual variables with binary responses.

Stage names with similar meanings were reorganised to formulate simple cascade stage names, such as HIV infection (PLHIV), diagnosis, linkage to care, loss to follow-up (LTFU), retention in care, transfer to other HIV clinics, ART eligibility, on ART, viral load suppression and death. Articles that used a longitudinal design and multistate models had slightly different names for their cascade stages. In this case, stage names were used as they were written by the authors. The size of the cascade and continuum of care frameworks was categorised into four groups based on the number of stages assessed. The four categories were extralarge cascades (>six stages), large cascades (five to six stages), medium cascades (four stages) and small cascades (≤three stages).

The cascade frameworks used were grouped into six: the Centers for Disease Control and Prevention (CDC) 2011 cascade framework (including PLHIV, diagnosis, linkage to care, retention in care, ART status and viral load suppression status stages[2]). CDC with five stages (starting from the diagnosis, linkage to care, retention in care, ART status and viral load suppression status stage), and CDC with four stages (starting from linkage to care, retention in care, ART status and viral load suppression status stages). Gourlay and others in 2017 (here abbreviated as Gourlay 2017) included PLHIV, diagnosis, ART status and viral load suppression stages.[41] Gourlay 2017 with three stages started from the diagnosis. Other cascade formulations included stages such as ART eligibility, clinical staging, ART adherence, LTFU/disengagement, engagement in care, death, transfer out, CD4 testing, current use of ART and history of ART. The cascade staging method used was grouped into three categories: dependent (also known as conditional), independent and a combination of the two. In the dependent method, PLHIV are eligible for the next cascade stage if they are in the previous cascade stage, whereas in the independent method, each cascade stage was derived independently of the prior cascade stage.[42]

Data analysis and presentation

The review findings were analysed and summarised using summary statistics, such as counts with percentages, medians with IQRs, and data ranges. Results were presented using tables. The geographical distribution of articles by country was summarised using world maps. Maps were plotted for country-specific articles (excluding 28 regional articles). The constructed cascade and continuum of care frameworks were summarised in terms of the size and cascade stages used. Types of cascade framework used were summarised using counts with percentage. The frameworks of a subset of articles that used a longitudinal study design and multistate models were compiled to document similarities, differences and existing gaps. All data management and statistical analyses were performed using Stata software V.14 (StataCorp LP, College Station, Texas, USA).

Patient and public involvement

Patients and/or the public were not involved.

RESULTS

Description of the article selection process

The search query retrieved 5805 titles and abstracts from all three databases, 5495 titles were excluded in the title and abstract screening stages (figure 1). The 310 abstracts were identified as meriting full-text reviews, of which 300 articles were included (online supplemental table S3).

Characteristics of articles

The majority of the 300 articles were published between 2015 and 2019 (n=177, 63%) (table 1). Various PLHIV groups were assessed, including children, adolescents, adults, migrants, prisoners, veterans, the military and HIV key populations. HIV key populations were reported in 74 articles, which included men having sex with men (n=35, 47%), female sex workers (n=19, 26%), people who inject drugs (n=20, 27%), and transgender men (n=8, 11%) and women (n=19, 26%).

Assessments of the HIV cascade and continuum of care were performed using cross-sectional (279/300, 93%) and longitudinal (21/300, 7%) designs (table 1). The review included 28 studies conducted in regions or globally. Many of these studies were conducted in Asia and Europe (n=11, 39%) and in sub-Saharan Africa (n=11, 39%). Focusing on country-specific studies, most of the articles that used a cross-sectional study design were from the USA, Canada, Zimbabwe and South Africa (these countries each contributed between 9 and 83 of 252 studies) (figure 2). Articles that used a longitudinal study design were mainly from the USA (6/20 studies).

Various data sources have been used to describe the HIV cascade and continuum of care. In the 279 articles that used a cross-sectional study design, the survey data source was common (n=110, 39%), whereas, in the 21 articles that used a longitudinal design, the cohort data source was often used (n=10, 48%) (table 1). The sample size varied across articles, with the smallest study including 22 hard-to-reach individuals and the largest study including 37.9 million PLHIV (UNAIDS report of 170 countries). In articles that used a cross-sectional study design, the median sample size was 1721 PLHIV (IQR: 524–8744), whereas in articles that used a longitudinal design, the median was 3311 PLHIV (IQR: 1080–11 510). Articles that used a cross-sectional study design had various levels of representation, with many being subdistrict/town/municipality/city-based studies (68/278, 25%), while for articles that used a longitudinal design, the majority were facility-based studies (6/18, 33%).

HIV cascade and continuum of care stages

In general, a median of four cascade stages (IQR: 3–5) was used (table 2). The smallest cascade had two stages, and the largest cascade had nine stages. Both Cross-sectional studies and longitudinal studies used large cascades (five to six stages) (95/279, 34% and 7/21, 33% respectively) and small cascades (≤three stages) (94/279, 34% and 7/21, 33% respectively). In articles that used a longitudinal design, the larger the cascade size the larger the median sample size. However, there was no clear pattern between sample size and the number of stages used in articles that used cross-sectional study design methods (online supplemental figure S1).

In articles that used a cross-sectional study design, 12% (34/279) used Gourlay 2017 cascade framework (table 2). The CDC 2011 cascade framework was used in various forms: 15/279 (5%) studies used all six stages, and others used the shorter form with either five stages (9/279, 3%) or four stages (11/279, 4%). In 21 articles that used a longitudinal study design, few used CDC 2011 framework (n=1, 5%) and Gourlay 2017 (n=1, 5%). In all articles reviewed, 71% (190/267) used dependent staging methods. In articles that used a cross-sectional study design, only 7% (17/255) used both dependent and independent methods (table 2).

In both study designs, common stages were PLHIV, diagnosis, linkage to care, ART status, viral load suppression, death and LTFU (online supplemental table S4). In articles that used a longitudinal design, some used other stages such as optimal care, suboptimal care, disengaged and no ART. Lastly, two articles used a longitudinal design with formulated stages in combination with either ART status or CD4 cell count (online supplemental figure S2).

Statistical methods applied

In the descriptive analyses, the majority of articles used proportions to describe participants at each cascade stage (cross-sectional design (276/279, 99%) and longitudinal design (20/21, 95%)) (table 3). Articles that used a longitudinal study design often estimated transition probabilities between cascade stages (5/21, 24%), which was rare among studies that used a cross-sectional design (1/279, 0.4%). Furthermore, the time spent in each cascade stage (5/21, 24%) and the Kaplan-Meier or cumulative incidence function (5/21, 24%) were often estimated in the

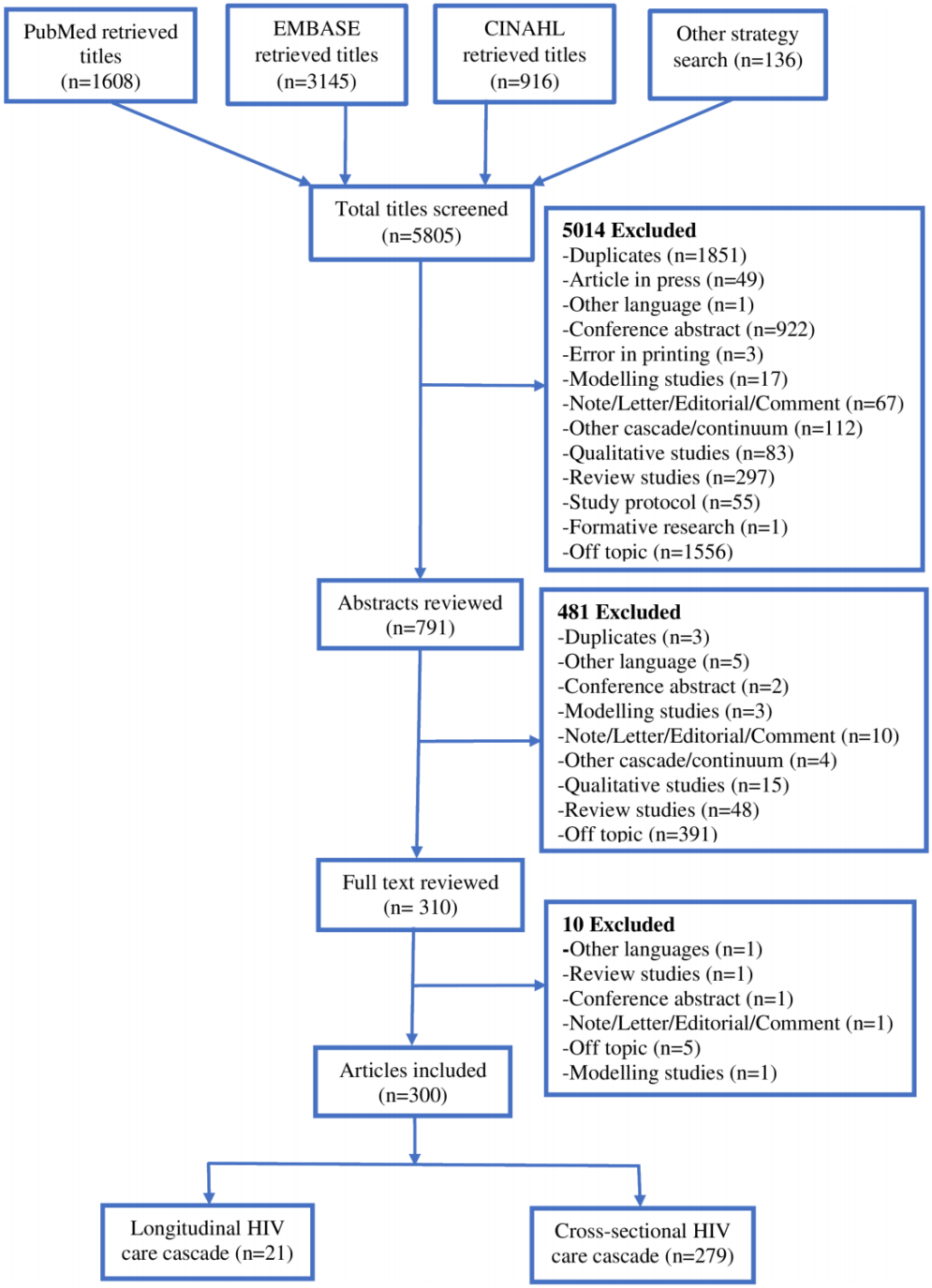

Figure 1 Flow chart of the inclusion and exclusion of research articles. CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica dataBASE.

Table 1 Characteristics of articles included in the scoping review (n=300)

Characteristics of articles	Cross-sectional	Longitudinal*	Overall
Papers included†	279/300 (93.0%)	21/300 (7.0%)	300/300 (100%)
Publication year			
2011–2014 (before 90-90-90)‡	18/279 (6.5%)	0/21 (0%)	18/300 (6.0%)
2015–2019 (post 90-90-90)	177/279 (63.4%)	14/21 (66.7%)	191/300 (63.7%)
2020–2022 (reporting of both)§	84/279 (30.1%)	7/21 (33.3%)	91/300 (30.3%)
Regional studies (involved ≥two countries)			
Asia and Europe	10/27 (37.4%)	1/1 (100%)	11/28 (39.3%)
North and South America	5/27 (18.5%)	0/1 (0%)	5/28 (17.9%)
Sub-Saharan Africa	11/27 (40.7%)	0/1 (0%)	11/28 (39.3 %)
Global¶	1/27 (3.7%)	0/1 (0%)	1/28 (3.6%)
Type of participants**			
Mixture (all PLHIV)	47/279 (16.9%)	3/21 (14.3%)	50/300 (16.7%)
Children only	10/279 (3.6%)	1/21 (4.8%)	11/300 (3.7%)
Adolescents	29/279 (10.4%)	5/21 (23.8%)	34/300 (11.3%)
Adult	127/279 (45.5%)	14/21 (66.7%)	141/300 (47.0%)
Key population	72/279 (25.8%)	2/21 (9.5%)	74/300 (24.7%)
Migrants	5/279 (1.8%)	0/21 (0%)	5/300 (1.7%)
Prisoners	2/279 (0.7%)	0/21 (0%)	2/300 (0.7%)
Veterans	2/279 (0.7%)	0/21 (0%)	2/300 (0.7%)
Refugees	0/279 (0%)	1/21 (4.8%)	1/300 (0.3%)
Military	0/279 (0%)	1/21 (4.8%)	1/300 (0.3%)
Types of HIV key population**,††			
Men having sex with men	33/72 (45.8%)	2/2 (100%)	35/74 (47.3%)
Female sex workers	19/72 (26.4%	0/2 (0%)	19/74 (25.7%)
People who inject drugs	20/72 (27.8%)	0/2 (0%)	20/74 (27.0%)
Transgender women	19/72 (26.4%)	0/2 (0%)	19/74 (25.7%)
Transgender men	7/72 (9.7%)	1/2 (50.0%)	8/74 (10.8%)
Data sources**			
Cohort data	65/279 (23.3%)	10/21 (47.6%)	75/300 (25.0%)
Laboratory test records	11/279 (3.9%)	0/21 (0%)	11/300 (3.7%)
Hospital medical records	55/279 (19.7%)	5/21 (23.8%)	60/300 (20.0%)
Survey data	110/279 (39.4%)	3/21 (14.3%)	113/300 (37.7%)
Surveillance data	70/279 (25.1%)	3/21 (14.3%)	73/300 (24.3%)
Clinical trials data	4/279 (1.4%)	1/21 (4.8%)	5/300 (1.7%)
Others‡‡	19/279 (6.8%)	3/21 (14.3%)	22/300 (7.3%)
Sample size, median (IQR)	1721 (524–8744)	3311 (1080–11510)	1862 (545–8859)
Sample size range (minimum, maximum)	22–39 000 000	100–92 215	22–39 000 000
Sample size (number of participants)			
<1000	103/279 (37.3%)	5/21 (21.8%)	108/297 (36.4%)
1000–5000	85/279 (30.8%)	7/21 (33.3%)	92/297 (31.0%)
6000–10 000	24/279 (8.7%)	3/21 (14.3%)	27/297 (9.1%)
>10 000	64/279 (23.2%)	6/21 (28.6%)	70/297 (23.6%)
Level of representation			
Facility§§	51/278 (18.4%)	6/18 (33.3%)	57/296 (19.3%)
Subdistrict/town/municipality/city	68/278 (24.5%)	2/18 (11.1%)	70/296 (23.7%)

Continued

Table 1 Continued

Characteristics of articles	Cross-sectional	Longitudinal*	Overall
State/province	36/278 (13.0%)	0/18 (0%)	36/296 (12.2%)
Population¶¶	52/278 (18.7%)	2/18 (11.1%)	54/296 (18.2%)
Community/district/county	31/278 (11.2%)	3/18 (16.7%)	34/296 (11.5%)
Regional	17/278 (6.1%)	2/18 (11.1%)	19/296 (6.4%)
Country	22/278 (7.9%)	3/18 (16.7%)	25/296 (8.5%)
Global¶	1/278 (0.4%)	0/18 (0%)	1/296 (0.3%)

*Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses.
†Row percentage.
‡The UNAIDS 90-90-90 target of the year 2020 stated that 90% of PLHIV know their HIV status, 90% of the diagnosed positive are initiated on ART and 90% of those on ART are virally suppressed.
§Articles published in 2020-2022 assessed both UNAIDS targets for 2020 (90-90-90) and 2025 (95-95-95).
¶Global studies are the studies included multiple regions such as Europe, Asia, America and sub-Saharan Africa.
**Percentage was estimated for each type of response and the report in this table is for 'yes' for all binary response variables processed from multiple responses variables.
††Analysis was restricted among the articles reported in the key population participants (n=74).
‡‡Other data sources largely included clinic and programme registries, databases, different types of medical records, consortiums, population estimates reports, social insurance schemes and AIDS programme databases.
§§Ficility-level studies at a health facility or clinic or hospital-based studies.
¶¶Population studies are the studies that included population-level cascade stages which included PLHIV, diagnosis and linkage to care.
ART, antiretroviral therapy; IQR, interquartile range; PLHIV, people living with HIV; UNAIDS, Joint United Nations Programme on HIV and AIDS.

longitudinal studies. Approximately 28% (84/300) of the included articles used simple test statistics, such as the χ^2 test, Fisher's exact test, t-test, Wilcoxon rank-sum test and Kruskal-Wallis test.

To assess the association between cascade stages or transitions and participant characteristics, 176/300 (59%) of the included articles performed regression analysis. The regression models used in the reviewed articles primarily considered discrete and survival outcomes (table 3). In the articles that used a cross-sectional study design, the logistic regression model was common (101/279, 36%). In studies that used a longitudinal design, logistic and Cox proportional hazard models were commonly used (33% (7/21) and 19% (4/21), respectively).

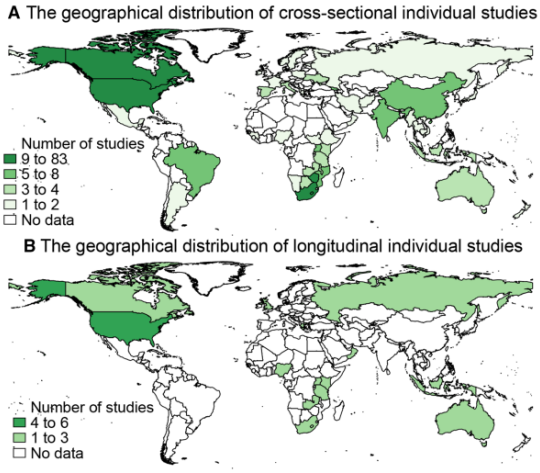

Figure 2 The geographical location distribution of country-specific studies of cross-sectional (n=252) and longitudinal (n=20) studies (regional studies, such as sub-Saharan Africa or Asia and Europe, were excluded).

Longitudinal design with multistate models

Among the 21 articles that used a longitudinal study design, different analysis methods were used. Articles that used longitudinal analysis methods were mainly in five groups (online supplemental table S5): classic survival analyses (n=2), survival analysis with competing risk methods (n=5), repeated cross-sectional and time spent in each cascade method (n=2), survival analysis with multistate models (n=6) and repeated measure analysis methods (n=1).

In articles that used a longitudinal study design and multistate models (n=6), five types of multistate models were used. These included non-parametric multistate; parametric, continuous-time multistate; time-homogeneous Markov models; discrete-time multistate Markov and general multistate models (table 4). Three articles adopted the Markov process, and one study considered the Markov process with first-order dependence. In almost all reviewed articles (n=5), the assessment of the care cascade started at enrolment in HIV care, and one article considered ART initiation as the baseline. Regardless of the type of multistate model used, death was considered an absorbing state in all the reviewed articles. Other absorbing states included LTFU

Table 2 Summary of various forms of outcomes used in the articles included in the scoping review (n=300)

Outcome	Cross-sectional	Longitudinal*	Overall
Number of cascade stages, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)
Size of the HIV care cascade			
Extralarge cascade (>six stages)	15/279 (5.4%)	1/21 (4.8%)	16/300 (5.3%)
Large cascade (five to six stages)	95/279 (34.1%)	7/21 (33.3%)	102/300 (34.0%)
Medium cascade (four stages)	75/279 (26.8%)	6/21 (28.6%)	81/300 (27.0%)
Small cascade (≤three stages)	94/279 (33.7%)	7/21 (33.3%)	101/300 (33.7%)
Sample size by size of the HIV care cascade, median (IQR)			
Extralarge cascade (>six stages)	3295 (595–7489)	NA†	3674 (645–10315)
Large cascade (five to six stages)	1418 (500–7843)	7810 (1532–32242)	1532 (592–8382)
Medium cascade (four stages)	2355 (440–10076)	3287 (2196–6850)	2617 (463–9829)
Small cascade (≤three stages)	1999 (579–9150)	476 (175–11510)	1931 (528–9150)
Types of cascade framework used			
CDC 2011‡	15/279 (5.4%)	1/21 (4.8%)	16/300 (5.3%)
Gourlay 2017§	34/279 (12.2%)	1/21 (4.8%)	35/300 (11.7%)
CDC 2011 with five stages¶	9/279 (3.2%)	0/21 (0%)	9/300 (3.0%)
CDC 2011 with four stages**	11/279 (3.9%)	0/21 (0%)	11/300 (3.8%)
Gourlay 2017 with three stages††	12/279 (4.3%)	0/21 (0%)	12/300 (4.0%)
Other‡‡	198/279 (71.0%)	19/21 (90.5%)	217/300 (72.3%)
Cascade staging approaches§§			
Dependent¶¶	183/255 (71.8%)	7/12 (58.3%)	190/267 (71.2%)
Independent***	55/255 (21.6%)	4/12 (33.3%)	59/267 (22.1%)
Both dependent and independent	17/255 (6.9%)	1/12 (8.3%)	18/267 (6.7%)

*Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses.
†NA is not applicable because there was one study under this group with a sample size of 23227.
‡Six cascade stages were used as follows: PLHIV, diagnosis, linkage in care, retention in care, on ART and viral load suppression.
§Four stages were used as follows: PLHIV, diagnosis, on ART and viral load suppression.
¶The cascade adopted stages like CDC 2011, but the assessment started from the diagnosis stage
**The cascade adopted stages like CDC 2011, but the assessment started from linkage to care stage.
††The cascade adopted stages like Gourlay 2017, but the assessments started from the diagnosis.
‡‡Other cascade formulations that included other stages and longitudinal frameworks.
§§Studies used longitudinal and multistate models or survival analyses; staging methods for each cascade stage are not applicable.
¶¶In the dependent method, PLHIV are eligible for the next cascade stage if they achieved the prior cascade stage.
***In the independent method, each cascade stage is derived independently of the prior cascade stage.
ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; PLHIV, people living with HIV.

and transfer to other HIV clinics. Three studies used a model that allowed back and forth for LTFU and disengagement states (online supplemental figure S2).

DISCUSSION

The findings of this scoping review showed that cross-sectional study design methods were most commonly used to assess the progress of HIV service uptake and treatment responses (93%). The reviewed articles were mainly available at the subnational level. The articles used a cross-sectional study design covering a wide range of PLHIV, including children, adolescents, adults, migrants, prisoners and key populations. In general, the cascade size had a median of four stages (IQR: 3–5). The dependent staging method was often used in articles with a cross-sectional study design. Various longitudinal design methods were used, including repeated cross-sectional, repeated measures and survival analyses. In articles that used a longitudinal study design and multistate methods (n=6 out of 21 articles), only three articles used analytical frameworks that integrated the in- and out-of-care movements of PLHIV enrolled in care. Although cascade researchers pointed out challenges of using a cross-sectional design in 2015,[4 6] articles using a longitudinal

Table 3 Statistical methods used in articles included in the scoping review (n=300)

Methods	Cross-sectional	Longitudinal*	Overall
Descriptive statistics†			
Proportion for each stage of the HIV care cascade	276/279 (98.9%)	20/21 (95.2%)	296/300 (98.7%)
Simple test statistics‡	78/279 (28.0%)	6/21 (28.6%)	84/300 (28.0%)
Time spent in each stage of the HIV care cascade	7/279 (2.5%)	5/21 (23.8%)	12/300 (4.0%)
Transition probabilities§	1/279 (0.4%)	5/21 (23.8%)	6/300 (2.0%)
Kaplan-Meier or cumulative incidence function	0/279 (0%)	5/21 (23.8%)	5/300 (1.7%)
Regression models†			
Logistic model	101/279 (36.2%)	7/21 (33.3%)	108/300 (36.0%)
Cox Proportional Hazard model	15/279 (5.4%)	4/21 (19.1%)	19/300 (6.3%)
Poisson model	32/279 (11.5%)	0/21 (0%)	32/300 (10.7%)
Competing risk model	3/279 (1.1%)	0/21 (0%)	3/300 (1.0%)
Generalised linear model	10/279 (3.5%)	0/21 (0%)	10/300 (3.3%)
Weighted and unweighted linear model	4/279 (1.4%)	0/21 (0%)	4/300 (1.3%)
Log-binomial regression model	5/279 (1.8%)	0/21 (0%)	5/300 (1.7%)
Multinomial regression model	0/279 (0%)	3/21 (14.3%)	3/300 (1.0%)
Generalised estimating equation model	1/279 (0.4%)	0/21 (0%)	1/300 (0.3%)
Other models¶	19/279 (6.8%)	2/21 (9.5%)	21/300 (7.0%)

*Longitudinal design articles included articles that conducted both longitudinal and cross-sectional analyses.
†Percentage was estimated for each type of response and the report in this table is for yes for all binary response variables processed from multiple responses variables
‡Simple test statistics used included the χ^2 test, Fisher's exact test, t-test, Wilcoxon rank -sum test and Kruskal-Wallis test.
§Transition probability is a predicted probability of moving between two consecutive states in a given time.
¶Other models applied were ARIMA or SARIMA, Bayesian hierarchical models, bivariable and multivariable regression, generalised additive model, negative binomial model, generalised linear mixed model and spectrum model.
ARIMA, Autoregressive Intergrated Moving Average model; PH, Proportional Hazard; SARIMA, Seasonal Autoregressive Intergrated Moving Average model.

design and addressing the in- and out-of-care pathways in cascade assessments are scarce. The major reason being these methods require advanced data management and analysis skills.[43 44]

Several authors have proposed different types of frameworks that include various pathways through the HIV cascade and continuum of care. The 'HIV States and Transition' framework was formulated to capture the interaction of PLHIV with HIV testing, care and treatment services at a given time.[6] It has two key features: mutually exclusive states (cascade stages) and transitions between states. This framework was adapted by the articles that expanded the cascade assessment using longitudinal design with multistate methods (online supplemental figure S2).[5 8 45–47] Others proposed the 'Comprehensive HIV Care Cascade', which is a framework formulated by combining stages used in the standard HIV care cascade with the additional consideration of poor outcomes (LTFU or death before or after ART initiation).[48] The 'Cyclical Cascade of HIV Care' was proposed to capture the non-linearity of PLHIV engagement in HIV treatment clinics.[49] The framework also maintained stages of the standard HIV care cascade (diagnosis, linkage and ART initiation) with additional stages of early retention (<6 months) and long retention (>6 months). Disengagement was incorporated with the possibility of re-engaging in care.

In this review, less than half (n=83, 28%) used either the CDC 2011 or Gourlay 2017 cascade frameworks to quantify and describe the HIV cascade and continuum of care. Other researchers modified the cascade for various reasons. First, data availability, which affects mostly stages included; for example, some studies started with PLHIV linked in care,[50–52] while others did not have viral load data.[53] In articles that used longitudinal design and multistate methods, the lack of transfer-out information[8] and failure to capture re-engagement in care after LTFU[46] affected the inclusion of these stages. Second, the HIV management guidelines used during the cascade assessments changed over time. This resulted in the inclusion of cascade stages such as ART eligibility[54] and CD4 testing.[55] Third, additional information on the cascade. This was the case when ART status was further divided into two stages ever on ART or history of ART use and current use of ART.[56–58] Others added the ART adherence stage[56 59 60] or used the retention stage in both pre-ART and post-ART initiation.[61] Lastly, addressing the in- and out-of-care transitions. In assessments that used a longitudinal design with

Table 4 Articles that used longitudinal study design and multistate model (n=6)

Methods	Number of articles
Baseline*	
Enrolment/recruitment	5
ART initiation	1
Reason for censoring†	
End of follow-up	2
Transfer, death, and follow-up	1
Transfer out, death, and status less than 12 months	1
Absorbing‡ state	
Death	2
Death and LTFU	2
Death and transfer out	2
Types of multistate models	
Non-parametric§ multistate model	1
Parametric¶, continuous-time** multistate	1
Time-homogeneous†† Markov model	1
Discrete-time‡‡ multistate Markov model	2
General multistate model	1
Multistate model assumptions	
First-order dependence	1
Markov process§§	2
Markov, first-order dependence	1
Missing data techniques	
Multiple imputations	2
Missing data indicator	3

*Baseline is the time at which the assessment of the cascade started.
†Censoring occurs when the exact survival time is unknown from the start until the end of the study.
‡Absorbing state is a state in which once visited no out-of-state transition is possible.
§Non-parametric model is the model that does not take any distribution assumption.
¶Parametric model is the model that follows a certain distribution, for example, exponential and Weibull.
**Continuous-time model is the model used in a dataset collected in unequal-spaced time.
††Time-homogenous model is the model that assumes transition intensity rates are constant over time.
‡‡Descrite-time model is the model used in a dataset collected in the equally spaced time interval.
§§Markov assumption is the assumption used in multistate models that assumes the future transition is only dependent on the current state.
ART, antiretroviral therapy; LTFU, loss to follow-up.

multistate methods, engagement in care was expanded to capture PLHIV who were LTFU or disengaged from care and later returned to care.[5 45]

Almost all articles quantified the cascade using the proportion of PLHIV achieving each cascade stage. Quantification was done either by using a dependent or independent staging method.[17] The independent staging method is often used in combination with the dependent method, but it is used mainly to assess the proportion of PLHIV with suppressed viral load.[62] This is because the independent staging method reflects the actual uptake of health services,[63] while dependent staging methods mainly focus on PLHIV retained in care.[16 64] Furthermore, approximately 60% of the articles performed regression analyses to examine the relationship between patient characteristics and either each of the cascade stages[54 65–68] or a few selected cascade stages.[69–73] In these assessments, modifiable characteristics were identified to plan for interventions that will improve cascade progress in stages with poor progress.

This review revealed different longitudinal design methods. Assessments were mostly conducted using survival methods. These were mainly in three groups: classic survival analysis, competing risk methods and multistate models. Competing risk methods were used primarily used to estimate the cumulative probabilities function of each stage,[17 23] whereas, in multistate methods, the aim was to capture all possible transitions between stages.[5 47]

The multistate methods used included parametric and non-parametric multistate, continuous-time and discrete-time multistate, and general multistate models. A multistate model is a continuous-time stochastic process that allows individuals to move between a finite number of states.[74] In the HIV cascade and continuum of care, states correspond to the HIV cascade stages.[5 6 45] In multistate modelling frameworks, states can be either transient (participants can move in and out of the state) or absorbing (no transition is possible out of the state).[75] In this review, articles that used multistate models considered death and transfer to other HIV clinics as absorbing states. Depending on the availability of data, LTFU and disengagement from care were allowed to be transient or absorbing states (online supplemental figure S2).

This review is among the largest and most recent systematic scoping reviews conducted on the methods used to assess the HIV cascade and continuum of care with extensive coverage and diversity. Furthermore, because of its coverage, the review identifies areas with limited research in terms of methods and their applications to the HIV cascade and continuum of care and provides recommendations for future studies. However, there were some limitations. First, this review was restricted to English articles. The impact of including other languages in this review is unknown, but areas with a high burden of HIV are mostly anglophone countries. Therefore, the pattern of review findings is not expected to change. Second, the review included peer-reviewed articles. The impact of omitting grey literature is also unknown, but because cross-sectional design methods are widely used, the conclusion of this review is unlikely to be affected by the missed grey literature.

CONCLUSION

Most studies on the HIV cascade and continuum of care applied cross-sectional study design methods. The use of longitudinal study design methods in the assessment of the HIV cascade is increasing. These methods provide additional information about the transition dynamics along the cascade, establish detailed progress and identify additional areas for interventions. Multistate modelling frameworks can be viewed as extensions of established cross-sectional design frameworks regarding engagement in HIV care, but further work is needed to integrate ART status and viral load suppression status into these frameworks. Therefore, a methodological guide on the application of different types of longitudinal design methods in the HIV cascade and continuum care and their corresponding frameworks is needed to guide future studies.

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9.4. Status of journal submission of paper 2: Cascade progress manuscript