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IMPLEMENTATION SCIENCE (E GENG, SECTION EDITOR)

Novel Longitudinal Methods for Assessing Retention in Care: a Synthetic Review

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Abstract

Purpose of Review Retention in care is both dynamic and longitudinal in nature, but current approaches to retention often reduce these complex histories into cross-sectional metrics that obscure the nuanced experiences of patients receiving HIV care. In this review, we discuss contemporary approaches to assessing retention in care that captures its dynamic nature and the methodological and data considerations to do so.

Recent Findings Enhancing retention measurements either through patient tracing or "big data" approaches (including probabilistic matching) to link databases from different sources can be used to assess longitudinal retention from the perspective of the patient when they transition in and out of care and access care at different facilities. Novel longitudinal analytic approaches such as multi-state and group-based trajectory analyses are designed specifically for assessing metrics that can change over time such as retention in care. Multi-state analyses capture the transitions individuals make in between different retention states over time and provide a comprehensive depiction of longitudinal population-level outcomes. Group-based trajectory analyses can identify patient subgroups that follow distinctive retention trajectories over time and highlight the heterogeneity of retention patterns across the population.

Summary Emerging approaches to longitudinally measure retention in care provide nuanced assessments that reveal unique insights into different care gaps at different time points over an individuals' treatment. These methods help meet the needs of the current scientific agenda for retention and reveal important opportunities for developing more tailored interventions that target the varied care challenges patients may face over the course of lifelong treatment.

Keywords Retention in care · Multi-state analysis · Group-based trajectory analysis · Loss to follow-up · Transfer · Reengagement

Introduction

The current global progress in expanding HIV testing and rapid initiation of antiretroviral therapy to all persons living with HIV implies that the scientific agenda to characterize and enhance retention in care is more important than ever. To make progress, however, current epidemiological analyses of retention must make use of available analytical approaches that move beyond depicting the cascade as a linear sequence of events—diagnosis, linkage to care, ART initiation, retention, and viral suppression—in which patients flow through in a single, forward direction. The reality, however, is that retention is in fact rarely linear: in the real world, patients frequently transition in and out of care and between different levels of engagement over time [1–5, 6••, 7–9, 10••, 11••, 12]. Retention and engagement are better conceived of as dynamic processes that may take on different longitudinal patterns (Fig. 1) and, as such, require the appropriate analytical approaches to capture these nuanced

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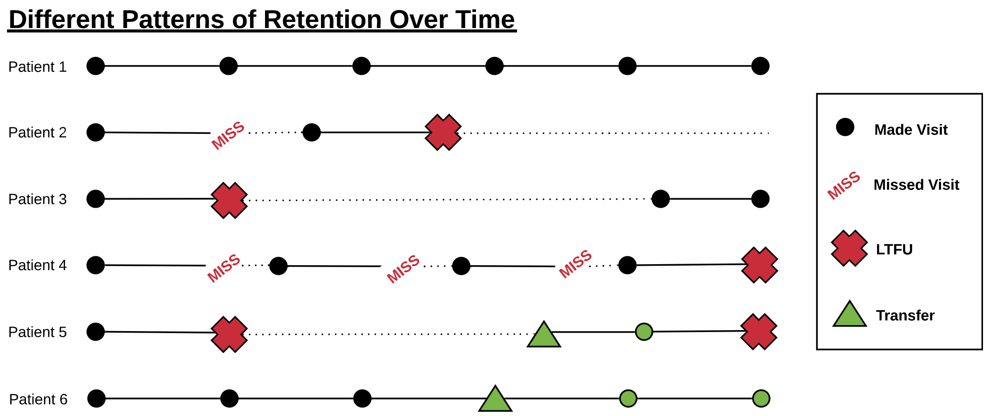

Fig. 1 Different patterns of retention over time. Retention in care is an assessment of an individuals' inherently longitudinal and dynamic experience of accessing HIV care. This figure depicts several potential retention trajectories characterized by patterns across several dimensions over time: making visits, missing visits, becoming lost to follow-up, transferring clinics, and returning back into care

features. Still, the current analytic approaches often reduce these highly dimensional patient histories into cross-sectional estimates from a single time point and also obscure heterogeneity in the different patterns and types of retention behaviors across patients. By overlooking both the dynamic and longitudinal nature of retention in care, current approaches may miss opportunities to deepen our assessments of the actual rich and nuanced longitudinal experience of patients receiving HIV care [1–5, 6••, 7–9, 10••, 11••, 12].

In this review, we discuss methods that are increasingly used, but still relatively uncommon in the HIV literature, to account for longitudinal and dynamic care experiences over time [3, 6••, 13••, 14••]. We first discuss advances in data collection and measurements to capture the longitudinal care experience from the patient perspective. We then emphasize two methods—multi-state and group-based trajectory analyses—that are designed specifically for assessing dynamic metrics that change over time and examine the data needs and methodological considerations for using them. Multi-state models characterize the patient transitions either into or out of "states" over time and are able to examine combined dynamics of multiple cascade steps (such as retention and viral suppression) over time at the population level. Trajectory analyses decompose a population over time into distinct groups defined by the heterogeneity in their longitudinal patient experiences. By enabling greater visibility into variation at any one time point as well as variation over time, these methods uncover more complex patient behaviors. These approaches can thus help public health respond in more nuanced ways to the varied needs of different patient groups and advance a scientific agenda around retention in care that is more cognizant of the distinctive patient experiences even in a public health setting.

Traditional Cross-sectional Metrics of Retention in Care

Retention in care can be conceptualized as individuals' adherence to appropriate care, treatment, and monitoring over a period of time [15]. Several commonly used retention metrics have been proposed and are used to varying extents across the literature and in practice. These include missed visits (i.e., scheduled visits which patients did not keep), visit adherence (i.e., the proportion of scheduled visits that were kept), visit constancy (i.e., the proportion of time intervals with at least one completed clinic visit), and gaps in care (i.e., not having a visit for a defined period of time) [15]. These metrics—although originally conceptualized using data based on attendance at clinic visits—can also be extended to include data from pharmacy refills or laboratory monitoring [12, 16–18, 19••, 20, 21••]. Each metric has its own advantages and limitations when considering the availability of appropriate data, ease of analysis, association with longer-term clinical outcomes, and the prevailing question at hand [22–28]. Still, all reduce the dynamic and longitudinal nature of retention into measurements that can be assessed cross-sectionally at a single time point, which can lead to missed opportunities to understand nuanced patient behavior and potentially even misleading conclusions under certain circumstances [7, 10••, 29].

Enhancing Data Sources and Measurements for Retention in Care from the Patient Perspective

Emerging strategies for measuring retention have emphasized retention metrics that are both longitudinal and also measured from the perspective of the patient. This first requires the appropriate data to do so. Currently, retention in care is often assessed by whether a patient continues to make visits, receive medication, or obtain labs at their original clinic or health system [16, 30]. The underlying assumption is then that patients are not receiving care if they are not going to their original clinic, thus measuring retention only from the perspective of a single clinic or health system and not the individual patients. In reality, however, a patient may transfer between clinics, get medications at different pharmacies, or obtain labs from outside the network. Contemporary approaches to assessing retention have emphasized strategies for developing longitudinal datasets that measure retention from the patient experience even as they access care in different places.

Using patient tracing to ascertain outcomes among those who are considered lost to follow-up (LTFU) has emerged as a critical tool for more comprehensive assessments of retention in care. Patients are frequently mobile and need to transition care between facilities. Several studies that have used patient tracing to ascertain outcomes among those LTFU have demonstrated that a substantial proportion of those considered LTFU from their original clinic report that they eventually end up transferring to a new facility [5, 31–38]. Still, it is important to note that, though patients eventually transfer to a new facility, cross-sectional metrics of transfer can still belie the full picture. In one study examining outcomes among those who reported transferring, a majority of patients that transferred only did so after a prolonged gap in care [11••]. Furthermore, once reaching their new clinic, they experienced delays in treatment reinitiation. Thus, capturing this full journey and incorporating the periods of time when patients have gaps in care are keys to understanding the retention experience from the patient perspective.

Beyond patient tracing, big data approaches have led to promising solutions for creating more patient-centered datasets that track retention from the patient perspective even as they access care at different venues. Retention in care often utilizes measurements such as clinic visits, pharmacy refills, and laboratory values, each of which provides unique insights into different aspects of care from accessing treatment to getting appropriate monitoring but is often stored in separate databases [16, 30]. Developing full longitudinal patient history that tracks patients as they receive care in different settings (and also times when they are not receiving care) requires linking together all records from different clinics, pharmacies, and laboratories, ideally, using a universal patient identifier such as a social security number or even biometric data [39–41]. This approach has been employed on smaller scales to identify out-of-care patients in order to target attempts to reengage them back into care [42–45]. Researchers in South Carolina have also sought to link together multiple regional databases—including inpatient and outpatient insurance claims data sources, the state electronic HIV/AIDS reporting system, and data from the state corrections database—extend this approach further to generate a comprehensive and representative longitudinal database [46]. Similarly, researchers have used South Africa's national laboratory monitoring system to create longitudinal patient records in order to examine retention in a manner that incorporated transfers [19••, 20, 21••]. A key innovation in the approach done in South Africa was the use of probabilistic matching to link patient records from programmatic data under circumstances where there is no universal patient identifier and names, dates of birth, and sex may contain nicknames, typographical errors, and/or transpositions/inversions that preclude exact matching [19••, 47, 48]. The first iteration of the database only incorporates laboratory values—using it as a proxy for being in care—but future work will also seek to link it to clinic- and pharmacy-based patient records [49], thereby creating a comprehensive longitudinal patient record.

Using Multi-state Analytic Methods to Capture Transitions in between Retention States

Multi-state analytic methods extend widely used longitudinal survival analysis because they readily account for the fact that patients may experience multiple transitions between different care states over time [50–53]. Kaplan-Meier methods—the most commonly used method for survival analyses—only asses time to a single event. Competing risk approaches extend this approach by assessing the time to multiple potential events, but only considers the first event to occur [54]. The reality, however, is that patients' treatment journey and retention in care are often a series of events [1–5, 6••, 7–9, 10••, 11••]. Although someone may become lost to follow-up, they may then reengage back into care after some time, either at their original clinic or at a new facility. Multi-state analyses are designed precisely to provide estimates under circumstances where patients flow through multiple states over time (Fig. 2) but observation time is unequal and patient censoring is also required [50–53]. Thus, these methods better reflect the realities of patient retention and synthesize the cumulative experience of patients' treatment histories at the population level.

There are several concrete ways in which estimates derived from multi-state analyses can extend insights gleaned from standard longitudinal methods. First, they can provide a comprehensive depiction of the different states of patients will be in over time and estimate the proportion of the population that will be in a given state at any particular time (Fig. 3). For example, there may be higher proportions of LTFU in early time periods, but the proportion who have reengaged in care (and then considered in care) may then increase over time as more people come back to care [6••]. This is in contrast to typical survival analyses that only examine how many people have transitioned to the next event (e.g., ever experience loss to follow-up). It also improves on cross-sectional approaches because it is longitudinal and appropriately accommodates circumstances where the amount of observation time for all individuals is not equal and where censoring is required. Illustrative examples from the literature have sought to characterize the longitudinal patient experience after linkage to care—including retention in care in the periods prior to and after ART initiation—in cohorts from public health HIV clinics in Zambia [6••, 55], South Africa [14••], Indonesia [56], and the USA [57••]. In addition to providing a complete picture of the whole cohort over time, multi-state analyses allow one to examine outcomes among those patients entering

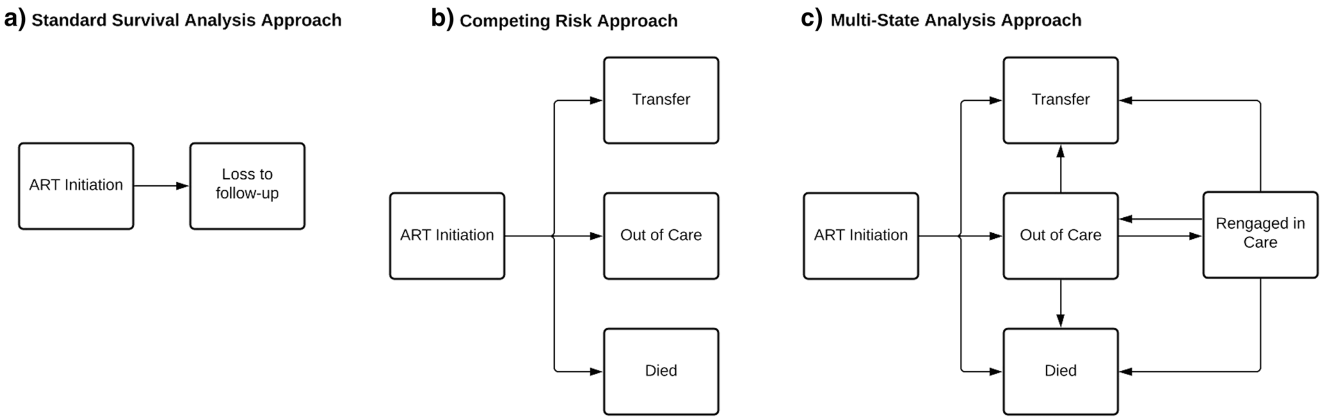

Fig. 2 Comparison of transition frameworks for retention in care using standard survival analyses, competing risk approaches, and multi-state approaches. In standard survival analyses, one is assessing the time to single event. In competing risk approaches, one can assess time to multiple different events, but only a single transition can be evaluated for each individual. In contrast, using multi-state analytic approaches, individuals may transition between various different states over time without any limitations as to the types or numbers of transitions an individual can make. Of note, in all examples, individuals can also be censored (not depicted), but this is done under the assumption that censoring is uninformative (i.e., those who are being censored and no longer under observation have an equal probability of having events as those that remain in the analysis), which may not be valid under many circumstances

a specific state, to characterize specific types of transitions and how transition rates change over time, and to identify predictors of different types of transitions. For example, one can examine both the rates and predictors of first becoming LTFU, and then also estimate these same metrics for patients reengaging back into care. Examples from the USA [58, 59], Canada [60, 61], and Kenya [62] have used multi-state analyses to assess rates of transitions between varying levels of engagement in care and their predictors, such as stress, adherence, or time out of care. Analyses by Lee et al. [58, 62], for example, highlight that individuals often return to care after short-term disengagement, but those disengaged for longer periods often remain disengaged, indicating that distinct strategies may be needed depending on how long one has been out of care. Ultimately, multi-state analyses can thoroughly characterize each individual transition but then also synthesizes them all into a comprehensive depiction of longitudinal patient outcomes. These results can reveal nuanced insights for identifying specific timepoints and transitions that might provide unique opportunities for intervention.

This suite of methods is grounded in the state-transition framework which is used to describe the relationships

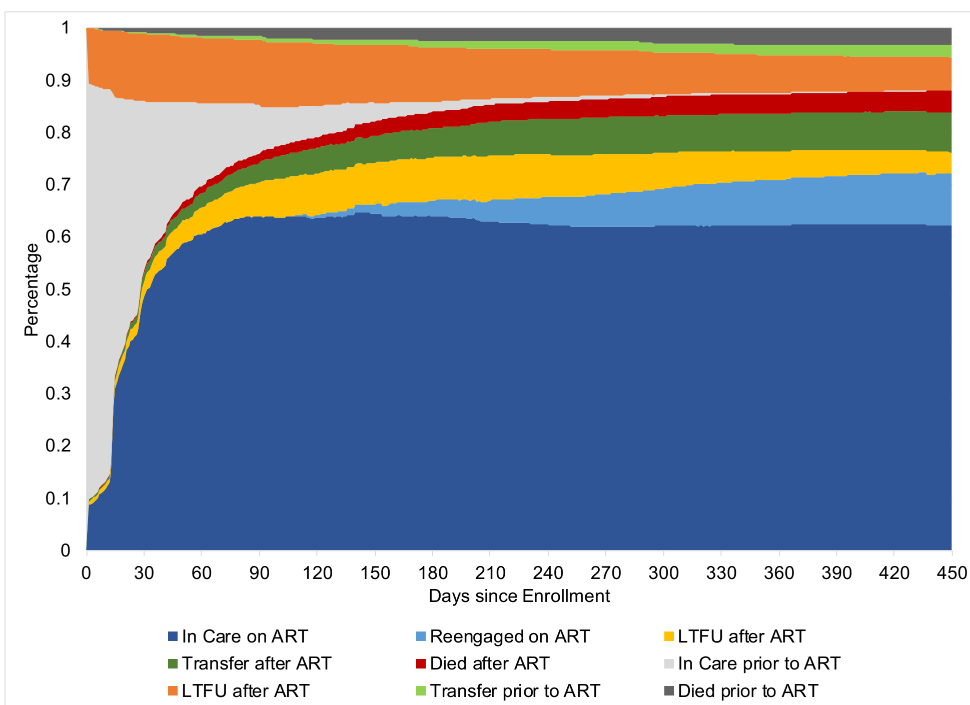

Fig. 3 Example of multi-state analysis for retention in care. This figure presents a hypothetical example of a multi-state analysis of outcomes after persons living with HIV link to care. Individual states are defined at each timepoint by whether an individual has been initiated on ART, their current care status (i.e., whether they are in care, LTFU, reengaged after LTFU, or have transferred), and whether they have died. This figure is adapted from Mody et al. (2020) [6••]

between a set of mutually exclusive and exhaustive states that fully capture the potential experiences of a patient (Fig. 2) [50–53]. These states may be either absorbing (i.e., once a person enters that state, it does not change) or non-absorbing (i.e., a person can transition out of that state at a later time). For example, when a patient is currently in care (i.e., non-absorbing state), they may become lost to follow-up, transfer to a new facility, or die. Similarly, once they are lost to follow-up (i.e., non-absorbing state), they may reengage back into care, transfer to a new facility, or die. In contrast, death is an absorbing state as patients cannot transition to a new state once they have died. When defining the states in the state-transition framework, incorporating individuals' past experiences (e.g., "reengaged in care after being lost" as opposed to "in care") can help to better capture these rich individual experiences. The flexibility in defining the appropriate state-transition framework is a particular advantage of multi-state methods, but a key consideration is having longitudinal patient data where the timing of each specific transition in the state-transition framework can be identified. Based on this framework, one then estimates all the possible transitions patients make between these different states in a multi-state analysis. Estimation methods for multi-state analyses may be based on either parametric (i.e., transition rates assumed to follow a specific functional form that can be parameterized) or non-parametric (e.g., no functional form for transition rates assumed [e.g., Aalen-Johansen methods]) approaches [50–53]. Additionally, in synthesizing estimates from each transition into a complete picture, it is important to note that the Markov assumption (i.e., once a patient enters a particular state, it is only their current state and not their prior history that influences their outcomes) is often required, but can be overcome by incorporating past history into the state-transition framework or using robust variances [50–53, 63]. Research to refine estimation methods and the underlying assumptions is ongoing.

Identifying Distinct Trajectories of Retention using Group-Based Trajectory Analysis

Group-based trajectory analysis offers another novel method for characterizing retention that helps to highlight two important features: (1) how retention changes over time and (2) how different patient subgroups may have distinctive patterns of change over time. This method—which is a form of latent class analysis—can be used to identify subgroups of patients that have unique trajectories of retention trajectories (Fig. 1). The main underlying assumption is that the overall population is made up of distinct, but unobserved (i.e., latent), subpopulations with different behavioral patterns and that these methods can empirically uncover these subgroups using the observed data [64, 65]. The benefits of this method are that it clearly delineates unique trajectories patients may follow as they change over time, unlike other methods—including multi-state analyses—that present population-level averages of outcomes. Furthermore, it demonstrates the heterogeneity in these trajectories across distinctive patient subgroups. Illustrative examples from the literature have used group-based trajectory modelling to examine trajectories of retention in care [13••, 66••, 67••, 68], adherence (including PrEP) [69, 70], viral loads [71–74], and CD4 counts [75], but this method can be used to identify trajectories of any relevant metric that may fluctuate over time [76–79].

Understanding this type of heterogeneity advances our understanding of retention in several ways. First, it highlights different subgroups that are expected to represent generalizable archetypal patterns of behaviors with shared underlying determinants (Fig. 4). For example, one study from Zambia identified that approximately 50% of patients remain engaged in care consistently, 20% become LTFU and remain out of care, while another 30% have more intermittent engagement and move in and out of care over time [66••]. Similar patterns and insights have also been gleaned from studies in different settings and also using different metrics of retention [13••, 66••, 67••, 68–75]. As the underpinning of group-based trajectory analysis is that these different groups have distinct behavioral determinants driving their trajectories [64, 65], this also suggests that these groups may likely require different things from the health system [80–83]. Patients doing consistently well can have their care de-escalated, which is currently the rationale behind the so-called differentiated service delivery [84, 85]. Those who become LTFU and remain out of care likely need the most intensive intervention, but their trajectories also indicate that opportunities to intervene at the clinic may be limited (e.g., only during the first few visits when it will not yet be clear which trajectory they will follow) [66••, 83]. This may indicate the need for well-conceptualized programs that can successfully reach patients in the community. Second, the trajectories themselves also can identify unique opportunities for intervention that has yet to be fully exploited. For example, patients coming in and out of care can be intervened on at the time of reengagement [83, 86–88]. Third, characterizing these trajectories provides unique opportunities to risk-stratify patients based on their observed behaviors. In the study from Zambia, different retention trajectories were highly associated with patient mortality and much more so than typical sociodemographic predictors such as age and sex. This is important to note because risk stratifying based on observed patient behavior—rather than simply using sociodemographic characteristics—may be a much more effective and efficient way of targeting resource-intensive interventions. Lastly, identifying unique trajectories also presents opportunities for novel study designs. For example, one mixed-methods study on PrEP adherence first used group-based trajectory analysis to categorize patients into trajectories

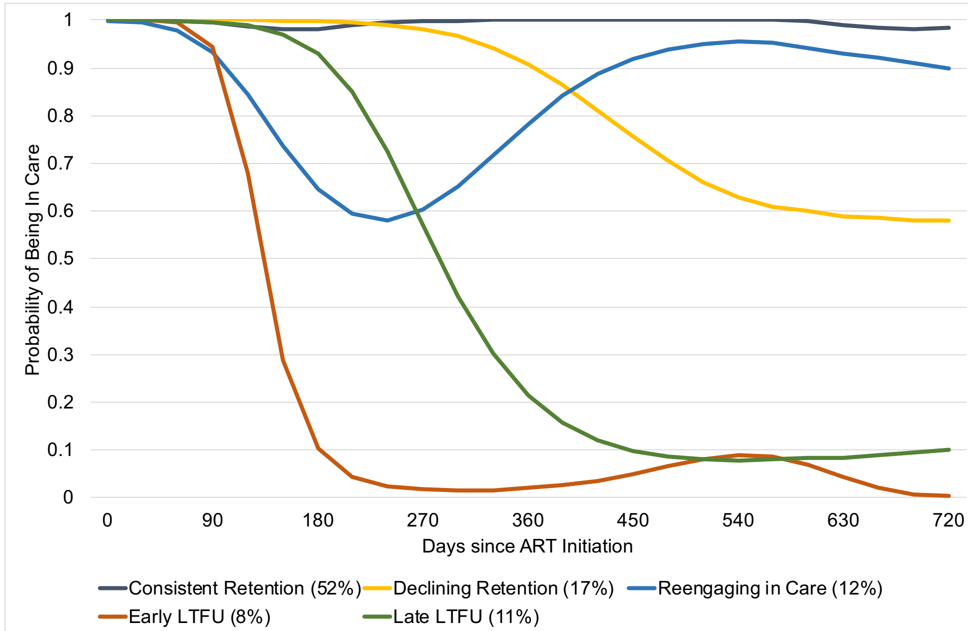

Fig. 4 Example of unique retention trajectories. This figure presents a hypothetical example of identified retention trajectories and the proportion of the population expected to be in each trajectory group using group-based trajectory analysis. Trajectories represent the probability that an individual in that trajectory group will be in care (i.e., not LTFU) at any time point (and not the specific trajectory of any one individual). This figure is adapted from Mody et al. (2019) [66••]

and then used qualitative methods to better understand the determinants of these patient journeys across trajectories [70]. Thus, characterizing different trajectories reveals several untapped opportunities for improving the outcomes along the HIV care continuum by better targeting and tailoring interventions toward patients' distinctive needs.

In group-based trajectory analysis, one first uses the observed data to empirically identify the different retention patterns over time (i.e., trajectories), and then categorizes each individual into the trajectory group to which they are most likely to belong (based on their observed data) [64, 65]. Statistically, group-based trajectory models use maximum likelihood estimation to empirically estimate both the trajectory shape of each group and also the proportion of individuals in each group that creates the best fit for the observed data [64, 65]. Group-based trajectory models not only can be used to model a single metric over time but also can be extended to identify groups of individuals that follow similar trajectories with respect to more than one metric (i.e., joint trajectories of multi-trajectories) [64, 65, 89]. Since characteristics of the trajectory groups are not known a priori and are empirically derived from the observed data, the key steps in the modelling process involve choosing a final model by systematically assessing various model specifications and comparing their metrics of how well they fit the data. Specifically, the number of trajectory groups as well as the shape of trajectories—which are modelled using a flexible polynomial that is either linear, quadratic, or cubic—are not known a priori and must be systematically assessed to identify which specifications lead to the optimal fit. Typically, one first varies the number of groups to identify the optimal number of trajectory groups and then varies the order of the trajectory polynomials. In choosing the final model, the goal is to identify a model that is optimized for both fit and parsimony, which helps to prevent overfitting while still choosing a model that captures the complexity in the data. This is typically done using metrics such as Bayesian information criterion (BIC), Akaike information criteria (AIC), and bootstrapped Lo-Mendell-Rubin or Vuong-Lo-Mendell-Rubin likelihood ratio tests, but, critically, should also take into account the interpretability of the classes based on contextual knowledge [64, 65, 89, 90].

After identifying the final model, the next step is to estimate the probabilities of an individual belonging to a specific trajectory group given their observed engagement patterns (i.e., their posterior probabilities) based on an application of Bayes' Theorem [64, 65, 89]. Once the posterior probabilities are estimated, there are several ways to assign trajectory group membership for each individual so that analyses examining predictors of trajectory group membership or using trajectory group membership as the exposure can be performed. These include assigning individuals to the group to which they most likely belong based on posterior probabilities (i.e., the maximal probability rule) or using multiple imputation based on posterior probabilities (i.e., multiple pseudo-class draws); methodological research into the most appropriate methods for accounting for uncertainty in trajectory group assignments is going [91, 92]. As a final step, one then should examine the adequacy, fit, and consistency of the trajectory model and group assignments using well-established metrics. These include (1) comparing the proportion assigned to each latent class using maximal probability rule versus the estimated distribution from the initial model, (2) estimating the average posterior probability for individuals assigned to each class using the maximal probability rule, and (3) calculating the entropy statistic, an indicator of separation between latent classes [64, 65, 90].

There are several key considerations when conducting group-based trajectory modelling. First, outcomes must be relatively complete and specified at routine intervals. When missing data is present, it utilizes the maximum likelihood function to fill in the missing data, based on a missing at random (MAR) assumption. The MAR assumption, however, may not be valid in certain situations such as when there is a significant amount of censoring in the data [64, 65, 89, 90]. Second, it is important to note that trajectory groups and trajectory group membership are empirical—based on the best fit to the observed data—and not actually an innate characteristic. Validating findings in an external dataset (or at least using cross-validation with the existing data) can help support that identified trajectories are reproducible and generalizable beyond the observed data.

Conclusion

Retention in care is a dynamic process and individuals frequently transition between different retention states over the course of their treatment history. Emerging approaches have allowed for more nuanced characterizations of the experiences of patients receiving HIV care over time by (1) optimizing data sources and measurements to capture longitudinal retention experience as individuals transfer in and out of care and access care through different venues and (2) using novel methodological approaches developed to better capture these longitudinal histories. Leveraging these more contemporary approaches to help meet the current needs for the scientific agenda for retention in care by (1) delineating more specific care gaps at different time points over an individuals' treatment and (2) revealing important heterogeneity in the different patterns of retention individuals' experiences. Ultimately, improving our understanding of retention in care in this manner can help to guide future research agendas and HIV treatment programs in developing more tailored interventions that more effectively target the varied care challenges patients may face over the course of lifelong treatment—a key step in implementing more patient-centered HIV care.

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Declarations

Conflict of Interest The authors declare no competing interest.

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Papers of particular interest, published recently, have been highlighted as:
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