HIV System Assessment with Longitudinal Treatment Cascade in KwaZulu-Natal, South Africa

Short title: Longitudinal HIV Treatment Cascade

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Abstract:

Introduction: While the HIV treatment cascade is a valuable tool in assessing the performance of health system management of HIV/AIDS, important improvements to its construction can be made. Traditional cascades lack the dimension of time to transition, which is a key measure of health systems performance. Underlying datasets are often constructed using disparate, and non-individually linked data sources. Many individually-linked cascades lack data concerning early stages, such as initial linkage to care after diagnosis. Use of cross-sectional analysis both imposes strong temporality assumptions. **Methods:** We use non-parametric competing-risk survival analysis to estimate the HIV treatment cascade, using the population-based cohort data that combines the information in population surveillance with clinical informatics systems. Six stages are defined: first positive HIV test, knowing status, linkage to car, eligibility for ART, initiation of ART, and immunological recovery. We estimate the time to reaching the next stage in the cascade in the presence of the competing risk of death at each stage. Data are from Africa Centre Demographic Information System, an HIV and health surveillance system individually linked to clinical records dataset in rural KwaZulu-Natal. **Results:** The population for this analysis consisted of 5,205 HIV positive individuals. Two years after testing positive in surveillance, 40.1% know their status, 17.3% are linked to care, 10.0% are eligible for ARTs, 6.1% initiate ARTs, and 2.6% are immunologically recovered. With regard to transitions between states early stages of the cascade (knowing status, linking to care, and eligibility for ART) are characterized by having relatively slow and steady transitions to the next stage. However, transitions to and from later stages (initiation and recovery) are characterized by high levels of retention and relatively quick and consistent transitions. Mortality has improved over time for all transition stages. However, rates of linking to care and initiation appear to be declining over time, with later years appearing to perform worse than earlier in the epidemic. **Conclusions:** There is a striking difference in the character of early stages of the cascade as compared to later stages. Counter-intuitively, as the roll-out of HIV interventions expands and services improve in an area, some measures of health systems performance may actually appear to worsen. This is likely to be due to fundamental shifts in the characteristics of the HIV positive population as the ART roll-out expands, including earlier detection of new infections and increasing reach into marginal populations. Linkage to care appears to be the most important current bottleneck in the cascade. Efforts should be focused on earlier linkage after diagnosis including mobilization and integration of clinical resources in rural South Africa.

Background

Despite great gains in the roll-out of antiretroviral therapy in the developing world, total coverage of ARTs among HIV infected individuals remains at only 63% of adults eligible for ARTs in the developing world.[1] Healthcare based on ART coverage is a critical component to managing the global HIV epidemic, and has been the cornerstone of global efforts to combat HIV.[2, 3] However, achieving high levels of coverage, and effective care beyond just minimal coverage, is a complex process with critical components across the healthcare system. The pathway from infection to continuing recovered health, often referred to as the treatment cascade or cascade of care, contains many important points of potential failure. Failure along the cascade yields loss of life for those infected,[4-10] increased infectivity,[11-14] and substantial economic burden.[15-18] Large numbers of people are failing along the cascade, resulting in the deaths of 800,000 people of causes related to HIV/AIDS in eastern and southern Africa in 2011.[1] As evidence grows supporting earlier initiation[19, 20] and treatment as prevention,[21] identifying failure points across the cascade becomes of even greater importance.

The HIV treatment cascade has been used to address the performance of the health care system with regard to HIV/AIDS, and identify specific steps requiring strengthening. The cascade breaks down the pathway from initial diagnosis through to immunological recovery on antiretroviral therapy, a state associated with good health and non-infectiousness. Identifying the stages in which people are less likely to transition to and from can generate inference on targets for intervention in order to improve the efficacy of the health care system overall. For example, if it is found that people who are linked into the health care system and are eligible for ARTs, but are not initiating ARTs, a policy maker may choose to invest in provider education initiatives. The inference draws depends on the stages generated. The World Health Organization suggests four stages: HIV testing, enrolment in care, ART initiation, and viral load suppression.[1] Several intermediary stages are likely important in addition, because large proportions of patients may fail to progress along the cascade due to failure to reach these stages, including knowing HIV status, eligibility for ART care,[22-28] and retention in care.[24, 25, 27-33]

Typically, such analyses have started at the time of presentation into clinical care, and represent cross-sectional data from each stage of the cascade. Cascades often utilizing data from different populations, with different denominators at each stage, and preclude a time to event analysis. Further, most such data derive from high-income areas of the world, away from the highest burden of infection.[34] Whilst useful, such an approach limits an understanding of the pathway taken by an infected individual through to high quality treatment.

By contrast, through linking a large demographic HIV surveillance site to the local primary health care facilities, we have the potential to plot the individual cascade pathway within a rural, high HIV prevalence region of KwaZulu-Natal, South Africa. An understanding of the gaps and barriers to care is vital to guide an effective response to the ingoing epidemic in sub Saharan Africa. As South Africa starts to adopt the WHO guidelines on initiating antiretroviral therapy at a CD4 <500/ul,[35] there is even more reason to bridge the current gaps in HIV treatment and care. Our longitudinally-based cascade of care concept yields greater depth of information and resolves the temporal and data assumptions described above. First, we define six stages after infection with HIV: diagnosis, knowing HIV status, linking to care, eligible for ART, initiation of ART, and immunological recovery. Next, we use a non-parametric survival analysis approach in order to estimate the time to reaching each of the stages, starting at time of the first positive HIV test. These data are then used to break the treatment cascade into each transition state longitudinally. This analysis shows that individuals have relatively high likelihoods of transitioning into initiation and recovery once they have been linked to care and become eligible for ART, as compared

to fairly low rates of knowing status and/or being linked to care. We also show that there has been shifts in the shape of the cascade over the years, illustrating changes in the demographics and health systems approaches to HIV over the past decade.

Methods

Study site and population

The population for this analysis is are HIV-infected individuals living within a 438 km^2, mostly rural area of the Umkanyakude in KwaZulu-Natal, South Africa near the rural city of Mtubatuba. The entire population living in this area is under continuous longitudinal health and demographic surveillance run by the Wellcome Trust Africa Centre for Health and Population Studies (Africa Centre Demographic Information System or ACDIS).[36] The area has a very high HIV prevalence, 28-29% in 2010.[37, 38] While most of the area is rural, there are several small townships within its borders. Household income is largely generated from a combination of government grants and employed wages, rather than from agriculture. The surveillance are contains six HIV treatment and care clinics, which are located on the premises of the local primary care clinics and started provided ART between 2005 and 2007; the sub-district includes a total of 17 HIV treatment and care clinics.[36] Importantly, the definition for individual eligibility for ARTs changed during the study period. Initially, eligibility was defined as having a CD4 count ≤ 200, or pregnant with a CD4 count ≤ 350.[39] South African guidelines changed in April, 2010 to recommending ART for HIV positive individuals with a CD4 count < 350 who are pregnant and/or have tuberculosis,[7, 40] and again in August 2011 to all patients with CD4 < 350.[7, 40, 41]

Dataset

This analysis utilizes two closely related data sources: ACDIS and ARTemis, a HIV treatment and care information system, which contains data on all patients enrolled in either pre-ART or ART in one of the 17 HIV treatment and care clinics within the sub-district, including visit dates and CD4 counts. . One of the main data collection components of ACDIS is an annual individual survey of all adults 15 years or older who live in the surveillance area. This survey which includes HIV testing, questions regarding whether a person knows his/her HIV status, and questions regarding sexual and health care seeking behaviors. The ACDIS is linked to ARTEMIS by personal identifiers, including South African ID numbers, sex, age, first name and last name.

Analysis

We use non-parametric competing-risk survival analysis to estimate the HIV treatment cascade, using the population-based cohort data that combines the information in ACDIS and ARTemis. We estimate the time to reaching the next stage in the cascade in the presence of the competing risk of death. Individuals are eligible to be included in this analysis if they ever tested HIV positive in the ACDIS surveillance system. The dates of all HIV cascade events (Table 1), are used to construct the time from one event in the cascade implying eligibility for the next event to that next event. The data on the next event for which an individual is eligible is either the date when the next event occurred or right-censored. For instance, knowledge of positive HIV status implies eligibility for linkage to care. We start counting person-time for the survival analysis of linkage to care from the first date when an HIV-infected individual in the surveillance reports that they know their status. The different events, i.e., the stages in the cascade, are defined in Table 1.

Table 1: Definition of stages

Event	Definition
First test positive	*Definition:* First positive HIV test *Estimation:* First recorded positive HIV test in the ACDIS surveillance system
Knows status	*Definition:* Patient knows his/her positive HIV status *Estimation:* The annual ACDIS survey includes a question which asks if the individual knows their HIV status. All individuals who respond positively after the date of their first recorded HIV test are marked as knowing their status on this date. The first recorded date in which an individual states knowing status in surveillance or has an HIV-related clinical event, such as attending HIV clinic, CD4 count, or initiating ARTs.
Linked to care	*Definition:* Patient engages with formal healthcare sector for HIV-related health care. *Estimation:* Individuals are recorded as having been linked to care on the first date in which they have a recorded HIV clinic visit, registration at a clinic, CD4 test, viral load count, or initiate ARTs.
Eligible for ART	*Definition:* Patient qualifies for ARTs, based on official guideline. *Estimation:* Individuals are considered eligible for ART on the first date in which they have a CD4 count which meets the eligibility criteria for ARTs during a CD4 count at the time of observation. The definition for eligibility from 2003 to March, 2010 is a CD4 count ≤ 200. [39] From April 2010 to July 2011, eligibility includes TB[1] or pregnancy with a CD4 count ≤ 350. August 2011 or later, eligibility includes all those with CD4 ≤ 350 [7, 40, 41]
Initiate ARTs	*Definition:* Initiation date of ART. *Estimation:* Individuals are recorded as having initiated based on ARTemis records of the initial date of ART prescription and/or distribution
Immunological recovery	*Definition:* Virological suppression and/or immunological recovery, HIV/AID reduced to clinically meaningful minimal level of illness *Estimation:* Recovery is estimated as having a CD4 count > 500 or a viral load undetectable levels (defined as <200 copies per mL[42])

The probability of an individual starting at one stage and transitioning to a subsequent stage is defined as a Kaplan-Meier curve for each transition stage. This transition set can also be considered as pre-ART (with first testing positive to initiation) and post-ART (after initiation of ART). Retention in all stages is defined as the number of HIV-related clinic events occurring before transitioning into the next stage, where a previous visit makes you eligible for a subsequent visit. In the case of pre-ART, this is only defined at the transition between eligibility for care and initiation, as a visit is considered qualification for transitioning into the "linked to care" stage.

Persons are allowed to have multiple transitions on the same day, and appear in the denominator for each stage transition. In an extreme example, if a person were to be diagnosed, and their next observed event is a CD4 count of 150 two months later, they would appear as having transitioned to the "knows status" stage 60 days after testing positive, transitioned to linked to care on the same day as knowing status (day 0), and would be counted as eligible for care on the same day as being linked to care (day 0). This updating of information conceptually preserves the conditionality aspect of the treatment cascade, in which individuals must go through each stage in order to reach the next stage. Each transition starts from the previous event, avoiding issues of "side doors"[43] into the cascade.

[1] Periods of TB are only given as TB start date in this dataset. Duration of TB is assumed to be 6 months from TB start date.

Results

Table 2 shows the descriptive statistics of the sample included in the analysis for three cohorts: all individuals testing positive between 2006 and 2011, and three cohorts testing positive in 2006-2007, 2008-2009, and 2010-2011, and the combined cohort dataset. 5,205 individuals were observed who tested positive for HIV at least once in the dataset and contribute towards this analysis. Of those, approximately 73% were female, with a mean age of 33. First CD4 count and CD4 count on eligibility increases for each cohort over time. This suggests that individuals are seeking care earlier and more frequently over time, and may be influenced by the loosening of eligibility rules for ART. Of particular note is the steady increase in first CD4 count from 270 among those first tested positive in 2006/2007 to 309 for the 2010/2011 cohort. While relaxing eligibility rules after April 2010 may help explain this, there remains a large average first CD4 count difference between the first two cohorts.

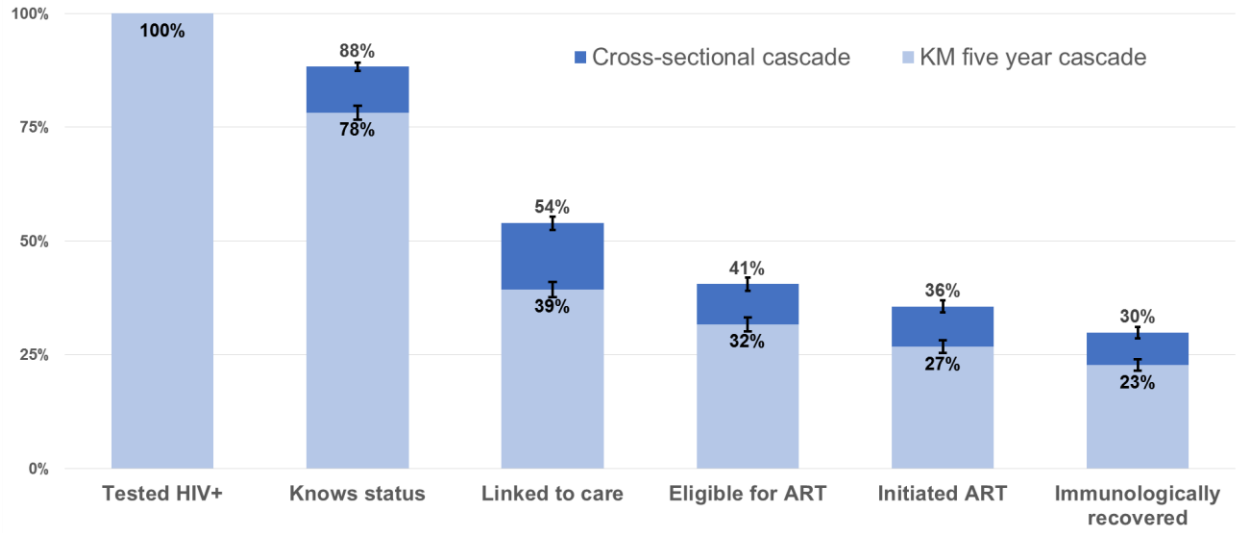
Table 2: Descriptive statistics

		First tested positive in years:		
	All	2006-2007	2008-2009	2010-2011
Female	0.73 (0.45)	0.73 (0.45)	0.71 (0.45)	0.74 (0.44)
Age	33 (12.4)	33.2 (12.9)	33.4 (12.8)	32.4 (11.6)
Years of education	8.09 (3.61)	7.87 (3.77)	7.91 (3.72)	8.44 (3.35)
Married ever	0.27 (0.44)	0.3 (0.46)	0.26 (0.44)	0.25 (0.43)
Currently employed	0.31 (0.46)	0.34 (0.47)	0.3 (0.46)	0.29 (0.46)
Pregnant ever	0.83 (0.38)	0.82 (0.38)	0.82 (0.38)	0.84 (0.36)
First CD4 Count	299 (222)	270 (212)	305 (230)	309 (220)
N	5,205	1,712	1,575	1,918

Note: mean (SD)

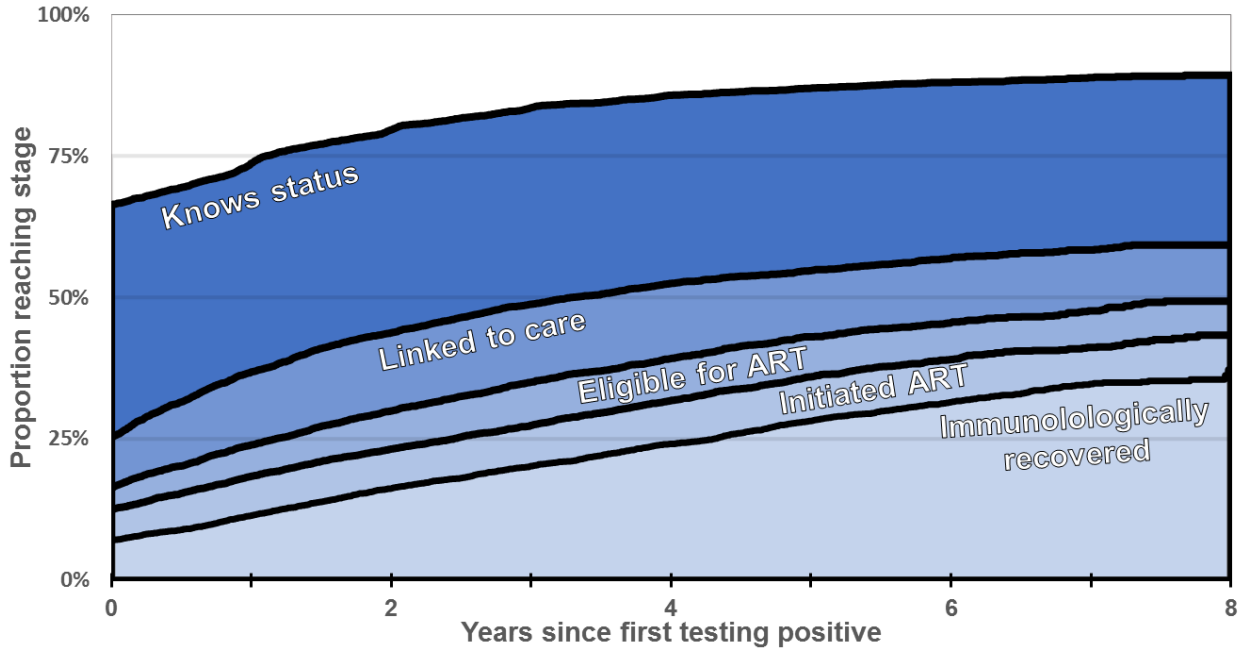
In order to simulate a cross-sectional treatment cascade was also created as a comparison to traditional cross-sectional cascades. The simulated cross-sectional distribution consisted of the last known status of all people known to be living among the full cohort. This is comparable to the distributions of persons in stages that would have occurred had a cross-sectional survey been performed. This is shown against the KM estimated achievement of each stage five years after first testing positive in Figure 1, among those who have not yet had a recorded cascade-related HIV event at the time of initial HIV detection in surveillance.

Figure 1: Simulated cross-sectional cascade vs. KM 5 year cascade



The KM variation effectively corrects for temporality assumptions. This shows a much more drastic drop in the proportion of people who are linked to care out of those testing positive for the first time in surveillance, with only 39% linked to care within 5 years.

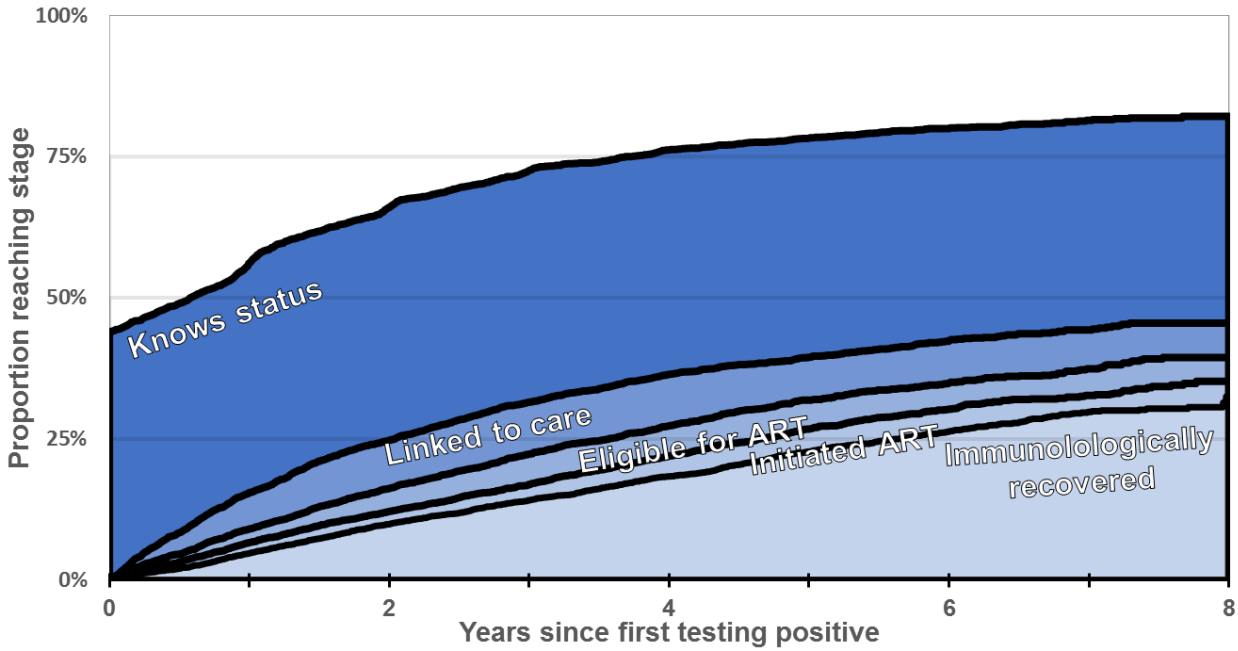
Figure 2: Longitudinal cascade cohort overview, 2006-2011 cohorts



The bottleneck at linkage to care is also seen in continuous time. Figure 2 shows the Kaplan-Meier-generated longitudinal cascade of care for all individuals, starting from the time at which they first tested positive, for all those whose first positive HIV test was between 2006 and 2011. At the time of initial detection in the surveillance dataset, 66% of individuals know their HIV status, 25% have been linked to care, 13% have initiated ART, and 7% have reached viral suppression / immunological recovery after initiation. These proportions increase steadily over time. Conditional on having been linked to care, the proportions of individuals who have reached later stages is relatively high, with over half of individuals who have been linked to care having reach immunological recovery within 5 years of initial detection in surveillance. A subgroup of those who have not yet reached a subsequent stage at time of detection is

shown in Figure 3, which extends the KM analysis from Figure 1 over continuous time. This is an estimation of time to event from initial infection, taking first detection in surveillance as a conservative estimate of time of infection. Only knowing status[2] reaches median time to event within eight years of detection.

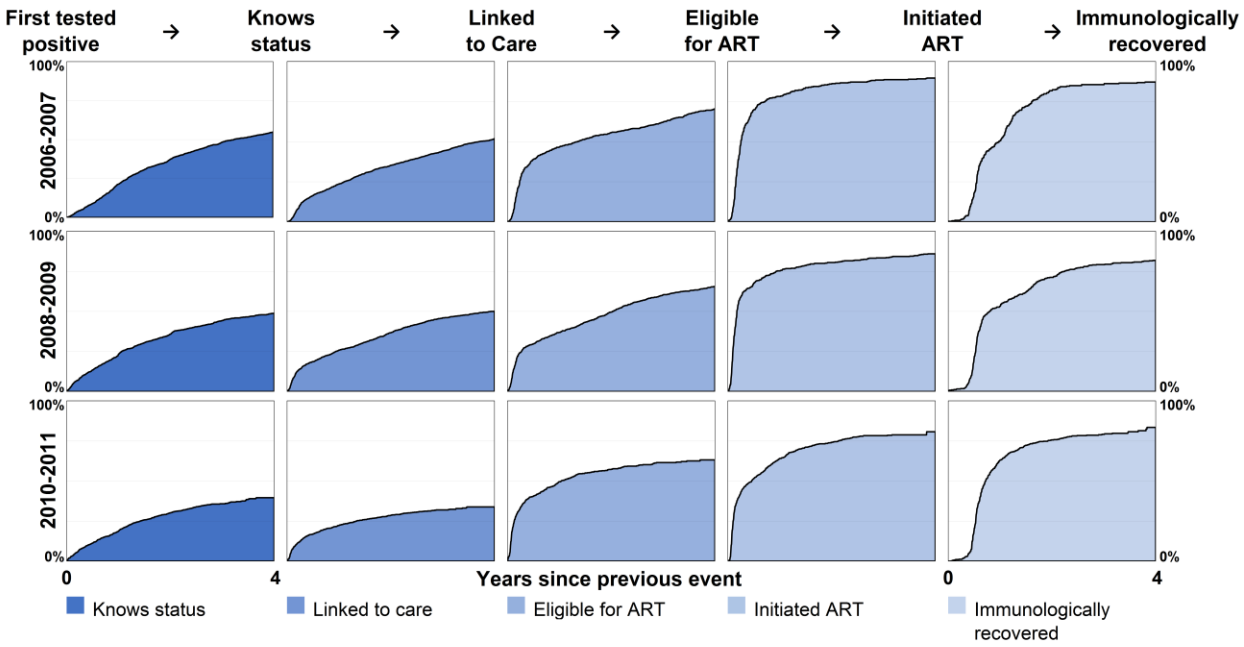
Figure 3: Longitudinal cascade from initial detection, 2006-2011 cohorts



While the previous two figures improve upon the cross-sectional cascade by correcting for and estimating temporality, these can be improved upon with time to event conditional on previous event. Figure 4 shows the full treatment cascade broken down by transitions between events. Each column shows one of the five stage transitions; each row shows data for a two calendar year period, in which the entry event would have occurred. The chart in the fourth column, second row, for example shows the transition from "Eligible for ART" to "Initiated ART" for those who became eligible for ART between 2008 and 2009 among those who had not yet initiated ART.

Figure 4: Transition to each stage by year, single state

[2] Knowing status appears as a transition on the first day is due to the construction of the first positive test and knowing status stages, in which both measures are assessed on the same day in surveillance. 44% of those who first tested positive on a given day also stated that they knew their status.

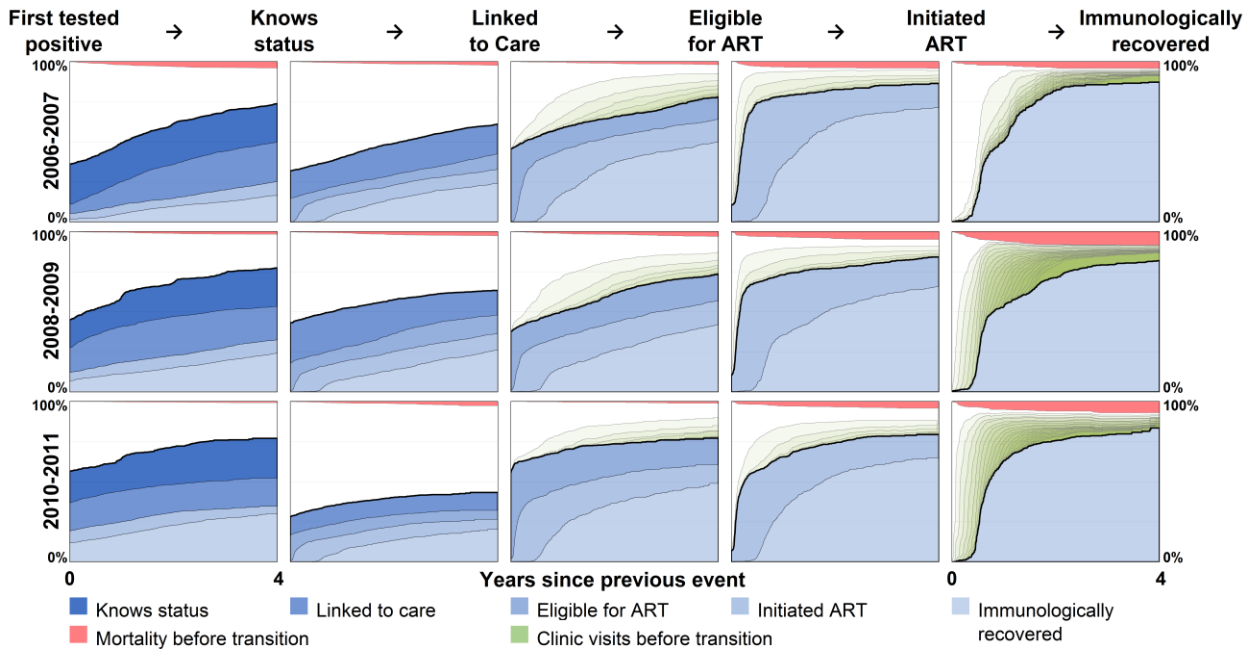


Several important insights emerge from this cascade chart. Firstly, there is a large difference in the pattern shown by the first two stage transitions as compared with the last two. The early transition are slow and steady, showing gradual and inconsistent times from first testing positive to knowing status and linking to care. The latter two transitions, however, show rapid and consistently timed. Those who are eligible for care typically initiate ARTs within a few months of testing eligible, with a median time to transition of approximately 3 months. Similarly, once initiated, the median individual reaches immunological recovery within one year after of initiation.

Going down the rows, there are some slight shifts in the transition stages over time. Counterintuitively, it appears as though the first transitions are actually slowing down over time, with individuals in these cohorts taking longer to transition into subsequent stages. Potential explanations of this are given in the discussion section. The slight dip in the transition from eligibility to initiation can largely be explained by the change in ART eligibility criteria during this last period. Finally, individuals who have started treatment appear to be recovering more consistently and more quickly, shifting from a median time to recovery of 12 among those who initiated ART in 2006-2007 to 8.5 months for those initiating in 2010-2011.

The longitudinal cascade in Figure 4 is useful for characterizing the difference in the transition probabilities out of each transition, but does not contain detail on to which stages people move, as well as subsequent stages. Figure 5 extends the analysis in Figure 4, showing both the proportion of people who have already reached subsequent stages at the beginning of each stage, as well as the probabilities of reaching every possible subsequent stage. About half of people who are linked to care are immediately eligible for ART, with slightly more people eligible in the 2010-2011 due to looser eligibility rules.

Figure 5: Transition to each stage by year, fully specified



Mortality and retention are also shown. Deaths and retention events (defined as clinic visits and/or laboratory events) are counted in each transition for each individual if they occur between between the beginning and ending stage, so that death and retention are specifically attributable to the transition. Deaths are occurring at later stages over time, with consistently lower proportions of deaths occurring at early stages. Retention is very high among those who have been linked to care, particularly among those who have initiated ART. Furthermore, retention improves over time, with larger proportions of people having several clinic visits before transitioning into subsequent stages.

Conclusions / Discussion

The longitudinal cascade of care in this region of KwaZulu-Natal shows two key findings. First, there is a striking difference in the character of early stages of the cascade as compared to later stages. In pre-ART stages, individuals become linked to care slowly and steadily, often transitioning to multiple stages in the same visit. Once a person has been tested to become eligible for ART, transitions tend to occur relatively rapidly and at consistent times from entering the stage. Furthermore, retention in these later stages is relatively high even for those who have not progressed to initiation or immunological recovery.

Secondly, and perhaps counter-intuitively, as the roll-out of HIV interventions expands and services improve in an area, some measures of health systems performance may actually appear to worsen. This apparent worsening can most likely be explained by some combination of several phenomenon. While early on in the roll-out of ARTs, there was a backlog of those who had been ill for some time, and thus would start ART immediately, individuals reaching a given stage in later years are more likely to have been infected relatively recently, reducing the incentive to engage in care. Secondly, care is expanding into populations which are more difficult to reach than early adopters, and may as such also be more difficult to engage in care. Understanding these shifts in the underlying composition of the AIDS epidemic is key as we shift from immediate scale up of ART to longer term strategies.[44]

This cohort also shows some striking differences with that of Alvarez-Uria 2013's study in India. While they find that the vast majority of HIV patients are entered into care and initiation ARTs do so within 3 months of diagnosis, our study suggests that fewer than 50% of those who are diagnosed positive for HIV are linked to care within even 5 years. This is very likely to do with the nature of the populations

involved. While Alvarez-Uria 2013 was studying a cohort among those who had sought care from one of three hospitals in a rural region of India, the ACDIS system draws from the entire population of its monitoring area in a surveillance setting. This latter population is likely a more realistic representation of a health system as a whole, avoiding biases associated with having a population who was already engaged in care.

The longitudinal cascade of care presented addresses three major criticisms of existing HIV treatment cascade designs. This analysis utilizes a single well-documented and individually linked data source for both all denominators/numerators and transition stages in rural South Africa. By extending the cascade of care over time, the longitudinal treatment cascade both avoids reliance on assumptions on the temporality of achieving stages and adds the critical component of time to event to each stage transition. The treatment cascade further improves on existing analyses by stratifying the cascade both over time to examine trends, and by each possible transition stage. This extra dimension is critical to making valid and useful inference on the development of HIV-related healthcare in the population.

As a result of these improvements, we are able to make several conclusions that may not be possible with traditional presentation of the cascade of care. We show, for example, that not only do high proportions of people in South Africa who are eligible for care actually receive care, which may be visible in a standard cascade, but that they do so very quickly after eligibility compared the transitions in other stages. While a cross-sectional cascade might show relatively high proportions of the HIV infected population as having been linked to care, the longitudinal cascade suggests long delays between both being diagnosed and knowing status and linking to care.

Two main policy prescriptions emerge from this analysis. First, new efforts focus on linking patients to care after diagnosis. Engagement in care is the largest bottleneck in the cascade in this population as compared with retention, ART initiation, and recovery once individuals are linked. In rural South Africa, this could take the form of increased mobility to clinical resources, bringing community health workers and testing facilities closer to the HIV infected population. Alternatively, synergies may be gained by linking testing with other public services and health care facilities, so that individuals may have HIV-related clinical visits in conjunction with services they would already be seeking. Second, as the expansion of ARTs gets closer to universal coverage, new patients may be both more likely to be newly infected. Policy should shift towards tactics to engagement and retention of HIV patients who have less severe disease, which could have impact on adherence.[45] This is a fundamental shift in the way in which low and middle income countries intensify HIV interventions. In South Africa, focus should be shifted from emergency intervention strategies and targeted expansion of ARTs to early detection and long-term retention strategies.

The longitudinal cascade also highlights the need for additional research regarding the determinants of transitioning through each stage, particularly regarding the factors influencing linkage to care. Further quantitative study can estimate changes in demographic characteristics which could have substantial impact on future health systems and improve identification of populations to be targeted at future interventions, such as age, distance to clinic, and education, of newly diagnosed individuals. Qualitative research will include examining changing social characteristics and attitudes towards ARTs and development of the roll-out over time.

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