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Quantifying the HIV Treatment Cascade in a South African Health Sub-district by Gender: Retrospective Cohort Study

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Abstract

Objectives: To quantify the HIV care cascade in a Cape Town sub-district to understand rates of linkage to and engagement in HIV care.

Methods: We used routinely collected data to reconstruct the treatment cascade for 8,382 infected individuals who tested HIV+ in 2012/13. We obtained data on patient gender, year of initial HIV-positive test, age at testing and initial CD4 cell count and defined five stages of the HIV care cascade. We quantified attrition across cascade stages.

Results: Two-thirds of the sample (5,646) were women. Males were older at time of first testing (36.5 versus 31.3 years) and had more advanced HIV disease at diagnosis (298 versus 404 CD4 cells/ μ L for women). The median duration of follow-up was 818 days. Among women, 90.5% attended an initial HIV care visit, 54.6% became eligible for antiretroviral therapy under local guidelines during follow-up, 49.3% initiated ART, and 45.6% achieved a therapeutic response. Among men, 88.0% attended an initial HIV care visit, 67.4% became ART eligible during follow-up, 48.0% initiated ART, and 42.4% achieved a therapeutic response. Approximately 3% of women and 5% of men died during follow-up.

Conclusions: We were able to reconstruct the HIV treatment cascade using routinely-collected data. In this setting, rates of engagement in care differ by gender in key stages of the cascade, with men faring worse than women at each cascade point. This highlights the need for interventions aimed at encouraging earlier testing, linkage, ART initiation, and retention among men.

Keywords

HIV treatment cascade; linkage to care; gender differences; South Africa

Introduction

HIV/AIDS continues to exert a large burden worldwide, with a disproportionately adverse impact in sub-Saharan Africa (SSA)(1). Of approximately 1.7 million new infections and 770,000 deaths attributed to HIV in 2018, 51% and 42%, respectively, occurred in SSA(1). With approximately 7.7 million infected adults, South Africa is home to the world's largest number of people living with HIV, accounting for just over 20% of the infected global population (1, 2). While there are more HIV-infected women than men in South Africa, men form a substantially larger fraction of those who are either unaware of their HIV-positive status or are aware but not engaging in HIV care (3). In predominantly heterosexually-driven generalized HIV epidemics such as South Africa's, gender differentials in engagement in HIV care may have considerable impact on infection transmission if men are less likely to know their HIV status or engage in HIV care (4).

Across southern Africa, disproportionately fewer men test for HIV or access antiretroviral therapy (ART), and those who do are less likely to adhere continuously to treatment than women (5, 6). Relative to women, men usually present for care later, and initiate ART with more advanced disease and more complications (7). For example, in South Africa, 52% of HIV infected women are on ART, compared to 43% of men (8) and in one South African study, nearly 30% of men had stage four HIV disease at entry to a care program compared to only 20% of women (9). Additionally, while approximately 55% of people living with HIV in South Africa are female, more than two-thirds of individuals receiving ART in public sector facilities are female, a situation that is closely mirrored elsewhere in SSA (10). In Rakai, Uganda, men were significantly less likely to enroll into a program of freely provided HIV care: among men, 38% did not enroll within six months after referral, whereas 29% of women did (11).

The continuum of HIV care, also referred to as the HIV treatment cascade, is a conceptual framework that facilitates understanding of the dynamic interactions between individuals and the healthcare system, from diagnosis through linkage to care, drug adherence, retention in care, and ultimately sustained viral suppression (12–14). In addition to describing the flow of patients through these stages of the continuum, information from such a continuum of care can quantify differences in outcomes at each continuum stage by major characteristics such as gender. While disparities by gender in a range of HIV care indicators have been noted in SSA, the stages along the treatment cascade at which the largest disparities occur have not yet been fully described. Understanding the gender perspectives of engagement in HIV care is important because it is widely recognized that the development, implementation and evaluation of gender-responsive approaches to prevention and treatment help advance the goal of eradicating the infection (6, 10, 15). Gender inequality is a major driver of the HIV epidemic and the gender risk profile is uneven (16). Learning how gender

relates to HIV care seeking at various stages in the continuum may provide significant practical insights into how to optimize engagement in care.

HIV cascades derived from routine datasets are often proxy cascades, as individuals often cannot be followed through the cascade in the absence of unique patient identifiers. The Western Cape dataset is therefore unique in South Africa as patients are assigned unique identifiers that allow patients to be followed across clinics and clinical encounters. In this study, we use routinely collected clinical data from a care system in Cape Town to understand variations in engagement in care by gender and age.

Methods

Study design, setting, and data sources

We performed a retrospective cohort study of 8,382 HIV-infected individuals in the Klipfontein health sub-district who were tracked by constructing a longitudinal cascade of care using routinely available electronic records. The Klipfontein health sub-district, located in Cape Town, is one of 32 in South Africa's Western Cape Province. In 2011, it had a population of approximately 384,000 living in 97,000 households; about half the population is considered Coloured, and 45% are Black African (17).

As part of a data harmonization effort by the Western Cape Province, we accessed de-identified data through the Provincial Health Data Centre (PHDC) of the Western Cape Department of Health. We obtained clinical, pharmacy, laboratory, and vital status data from all clinics in Klipfontein, which were linked by the PHDC using a range of identifiers, including a unique patient identifier (18). There are 15 health facilities that provide HIV testing in Klipfontein, and several non-governmental organizations promote and perform testing, referring those with positive results to the clinics for treatment and longer term care. The majority of visits to general medical clinics in the Klipfontein health sub-district can be ascertained from administrative and clinical data sources, and unique patient numbers permit consistent identification of each individual across clinics. The entry point into this analysis was a clinical encounter at any Klipfontein clinic in which an HIV-positive diagnosis was documented for the first time, confirmed by logging of a first CD4 cell count result into the laboratory database. We included individuals in the study if they were older than 15 years at the time of that encounter, during 2012 and 2013. Our analyses covered the period in which patients were in follow-up care between January 2012 and December 2016.

Measures

We obtained data on patients' gender, year of initial HIV-positive test, age at testing and initial CD4 cell count. We defined five stages of the HIV cascade: (i) HIV diagnosis (confirmed by an entry of a first CD4 cell count result in the laboratory database), (ii) enrolment (linkage) to HIV care, (iii) eligibility for ART either at enrolment or at any point during follow-up, (iv) ART initiation, and (v) therapeutic response. The definitions of each of the cascade stages are outlined in Table 1. The CD4 threshold for ART eligibility changed over time in accordance to prevailing South African guidelines, as noted in the footnote to Table 1. Only 51.5% of participants had at least one viral load test; since the data were

limited, we defined a successful therapeutic response following previous studies as either the World Health Organization (WHO) definition of less than 1,000 viral copies per milliliter or a CD4 count exceeding 500 cells per microliter (19). We also described each patient's outcome at the end of the study period as either still in care, transferred to other facilities outside Klipfontein for care, lost to follow-up or died. Loss to follow up was defined as no record in the database after December 31, 2015 with no documentation of death or clinic transfer.

Statistical analysis

The aim of our analysis was to compare both the cross-sectional and longitudinal clinical stages of the cascade of care for males and females in Klipfontein. Therefore, we quantified patient attrition from care across stages beginning from HIV diagnosis and determined the probability of transitioning from one stage to the next over a 4.5-year period. Individuals were censored on the final day of follow-up for the study. We described the fractions of females and males in each respective stage of the cascade and used a Cox proportional hazards model to assess the effect of gender on the probability of transitioning to the next cascade stage, adjusting for CD4 cell count and year of first HIV-positive test.

Ethical Approval

The study was approved by the relevant Institutional Review Boards at the University of Cape Town (study number 320/2015) and Brown University (study number 15–056). The data received from the Department of Health were de-identified and contained no personal identifying information.

Results

In the Klipfontein sub-district, 8,382 people received their first positive HIV test during 2012 or 2013 and were included in this analysis. Table 2 shows patient characteristics by year of HIV test. The majority of the sample was women (67.4%); women were on average 5.2 years younger than men (31.3 v 36.5; $p < 0.001$). Women had less advanced HIV disease at study entry, with the mean CD4 count more than 100 cells higher than that for men (404 v 298; $p < 0.001$). A larger proportion of men compared to women had CD4 counts less than 200 at baseline (39% v 12.7%; $p < 0.001$.) Mean CD4 count for men did not change when comparing those who had their first CD4 test in 2012 versus those who did so in 2013 (298 v 297, $p = 0.885$), but it increased for women during that same time period (394 v 416; $p = 0.002$). The median follow-up duration for women was 1,008 days, compared to 903 days for men ($p < 0.001$). 51.5% of participants had one or more viral load test results.

Discussion

Using routinely-collected data, we successfully reconstructed the HIV treatment cascade in a South African health sub-district, and examined gender differences in movement through key stages of the cascade. We found that men are disadvantaged in their access to and effective use of ART: compared with women, men were less likely to be linked to HIV care

and to start ART, and more likely to die. Men were also less likely to achieve a therapeutic response than women.

Post-diagnosis linkage to care and treatment initiation in this population were particular bottlenecks and offered opportunities for cascade “leakage” (23). Although nearly 90% of people in our sample who tested for HIV were successfully linked to care, less than half initiated HIV treatment. Other studies have reported similarly low rates of linkage to care and treatment initiation. A recent population-based study of ART for prevention found that frequent home-based testing and immediate initiation of ART failed to decrease HIV incidence largely because of the low rate of linkage to care (24). Three other universal test and treat (UTT) trials showed that despite substantial effort, achieving universal coverage remains exceedingly difficult (25).

A noticeable gap in the treatment cascade is between being linked to care and actually initiating ART. This step was made considerably more complicated by changing guidelines for treatment initiation throughout the study. At the beginning of the study in 2012, the South African policy for treatment initiation was a baseline CD4 threshold of 350 CD4 cells per μL ; in January 2015 that threshold changed to 500 cells per μL (with immediate treatment for those with Hepatitis B, Tuberculosis, and those pregnant, breastfeeding or within 1 year post-partum) (20–22). Many African countries call for treatment initiation regardless of CD4 cell count, and in September 2016 South Africa’s guidelines changed to call for universal treatment for anyone living with HIV (18, 20, 21). While beyond the scope of this analysis, the elimination of a CD4 cell threshold for treatment initiation may well smooth the transition by eliminating the “ART eligible” step since anyone with a HIV-positive test would be eligible to start ART. Close monitoring of the program following the elimination of CD4 threshold will be important and may yield improvements because of the elimination of the time and confusion associated with being HIV positive but “not yet eligible” for treatment.

Our data provide further evidence of the urgent need to address men’s access to HIV testing, treatment and successful transitioning through the HIV treatment cascade, especially in the context of the African epidemic. We noted disparities along the HIV treatment cascade between men and women, particularly in the areas of ART eligibility and initiation. Our data indicate that many more men than women were eligible to start ART, possibly indicating men tested for HIV later after infection; and of those who were eligible for ART, many fewer men started treatment. Interventions to encourage men to get tested for HIV, to link to treatment and to achieve viral suppression are urgently needed if we are going to be successful at reaching UNAIDS’ 90-90-90 targets of 90% of infected people knowing their HIV status, 90% of those being on treatment and 90% of those on treatment achieving viral suppression. To help alleviate these disparities, a range of interventions that employ a combination of behavioral, peer-centered, and healthcare provider-oriented strategies may be required to sustainably alleviate gender differentials in the cascade of care (15, 26, 27).

Since our study data were gleaned from existing health service records, we were limited by the available data. In particular, the study would have been enriched by more behavioural and demographic information on the participants, including socioeconomic and risk

behavior information, which were unfortunately not available. Our study is also limited by the fact that the entry point is having received an HIV test in the health sub-district. Because residents of the sub-district are able to get tested for HIV at a variety of sites – both within and beyond the borders of the sub-district, we were unable to calculate the first part of the HIV cascade, which is the proportion of the population that tests for HIV. Most treatment cascade studies – unless they are population-based – are similarly unable to quantify this proportion (19).

In addition, since our study only used data from the City of Cape Town and the Western Cape Province, it is likely that some study participants who were labelled lost-to-follow-up may actually have transferred to clinics outside of the City of Cape Town and Western Cape Province. As a result, we likely over-estimate the number of people lost-to-follow-up since some of those people would have switched clinics and are now successfully on ART in another Province. A national database is necessary to allow the tracking of individuals who switch clinics between Provinces and would result in a more robust estimation of the true rate of loss-to-follow-up in South African ART programmes.

Conclusions

Using routinely-collected data, we were able to reconstruct the HIV treatment cascade in one South African health sub-district. We observed improvements in the program over time for women but not for men, with women who tested in 2013 showing an increase in CD4 cell counts compared to women who tested in 2012. Among men however, there was no difference in CD4 cell counts among those who tested earlier compared to those who tested later. In addition, at each stage of the HIV treatment cascade, men did worse than women, highlighting the urgent need for effective interventions - particularly aimed at men – that can facilitate more successful transitions through the steps of the HIV treatment cascade.

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Figure 1:

HIV Treatment Cascade in the Entire Health sub-District (N=8,382)*

*Each stage in the treatment cascade is calculated as the number of people in that stage divided by the total number of people tested for HIV.

Figure 2:

Treatment Cascade by Gender (Total N=8,382; Male N=2,736, Female N=5,646)*

*Each stage in the treatment cascade is defined as *number of people in cascade stage divided by the total number of people who tested for HIV, by gender.*

Table 1.

Definitions of key stages of the HIV treatment cascade and status at the end of the study period

Stage	Definition
1. First positive HIV Test	Patient HIV status confirmed through logging of a first CD4 cell count test result in the laboratory database
2. Linkage to Care	Patient engages with formal health-care sector for HIV-related health care through at least one clinic visit involving an encounter with clinical, laboratory or pharmacy providers that takes place after the visit in which an HIV test was performed
3a. ART Eligibility at Enrollment 3b. ART Eligibility at any time during follow-up	On date of enrollment/linkage, patient qualifies for ART, according to South African national treatment guidelines at the time* Patient qualified for ART at any point during follow-up according to the South African national treatment guidelines at the time*
4. ART Initiation	Date of first ART prescribing or dispensing
5. Therapeutic Response	Date of first occurrence of CD4 cell count >500 cells per μ L or undetectable viral load (below 1,000 viral copies per mL)
Status at the end of Follow-up Period	Still in care: in database at least once after Dec 31, 2015; Transferred: documentation of transfer to another site for HIV care within the Western Cape; Died: Documented death at any time; Lost to follow-up: not in database after Dec 31, 2015, no documentation of death or transfer within the Western Cape.

* ART eligibility guidelines over time:

August 2004 – March 2010: CD4 cell count < 200 cells/ μ L;

April 2010 to July 2011: CD4 cell count 200 cells per μ L and 350 cells per μ L for patients who were pregnant or patients diagnosed with active tuberculosis;

After July 2011: CD4 cell count 350 cells per μ L for all individuals and no threshold for those who were pregnant or diagnosed with active tuberculosis;

January 2015: CD4 cell count 500 cells per μ L; universal treatment for patients with Hepatitis B, Tuberculosis and those pregnant, breastfeeding or within 1-year post-partum;

September 2016: universal treatment for everyone (20–22).

Table 2.

Patient characteristics by age* and year of initial HIV-positive test

Characteristic	All (N=8,382)		Tested in 2012 (n=4,731)		Tested in 2013 (n=3,651)	
	Male n=2,736	Female n=5,646	Male n=1,560	Female n=3,171	Male n=1,176	Female n=2,475
Age, mean (SD), years	36.5 (10.1)	31.3 (9.9)	36.6 (10.1)	31.5 (10.1)	36.5 (10.1)	31.0 (9.8)
First CD4 cell count, mean (SD), per μL						
All	298 (233)	404 (263)	298 (234)	394 (259)	297 (231)	416 (268)
15–24 years	339 (188)	454 (250)	328 (186)	440 (238)	353 (190)	471 (262)
25–34 years	306 (222)	391 (248)	304 (221)	380 (246)	404 (251)	404 (251)
35–44 years	267 (227)	360 (258)	266 (223)	363 (262)	357 (254)	357 (254)
45 or older	314 (271)	402 (336)	328 (284)	393 (332)	414 (340)	414 (340)
First CD4 cell count, median (IQR), per μL						
All	245 (124–413)	361 (215–542)	241 (125–412)	350 (205–532)	250 (123–413)	377 (226–556)
15–24 years	323 (208–446)	415 (284–586)	297 (189–435)	401 (274–581)	352 (227–465)	432 (293–591)
25–34 years	266 (136–423)	352 (210–528)	263 (139–425)	337 (200–517)	368 (228–547)	368 (228–547)
35–44 years	206 (101–377)	317 (163–494)	205 (104–362)	321 (169–487)	310 (156–504)	310 (156–504)
45 or older	239 (118–423)	315 (169–542)	248 (120–445)	315 (169–514)	326 (159–582)	326 (159–582)
Follow-up duration, median (IQR), days						
All	903 (115–1,286)	1,008 (212–1,317)	1,076 (168–1,448)	1,173 (211–1,474)	784 (66–1,074)	894 (212–1,127)
15–24 years	698 (25–1,186)	1,002 (210–1,306)	831 (49–1,399)	1,203 (283–1,462)	615 (25–1,050)	848 (159–1,100)
25–34 years	904 (122–1,297)	1,024 (264–1,332)	1,116 (165–1,448)	1,212 (248–1,487)	765 (73–1,049)	902 (289–1,130)
35–44 years	950 (132–1,297)	991 (165–1,291)	1,074 (230–1,437)	1,086 (150–1,445)	818 (61–1,114)	961 (185–1,144)
45 or older	890 (95–1,284)	980 (165–1,318)	1,050 (121–1,437)	1,127 (142–1,483)	804 (81–1,084)	919 (175–1,148)

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SD = Standard Deviation; IQR = Interquartile Range

*

The number of participants in the 15–24, 25–34, 35–44 and >45 year age-groups, respectively, were as follows: 1) Male: 231, 1,086, 875 and 544; 2) Female: 1,492, 2,478, 1,084, 622.

Of the 8,382 people who had an initial HIV positive test during 2012 or 2013 (Figure 1), 89.7% linked to care, 58.8% were ART eligible, 48.9% started ART, 44.6% experienced a therapeutic response to treatment and 3.7% died.

Figure 2 stratifies the treatment cascade data by gender, and Table 3 presents p values for comparison by gender for each step of the treatment cascade. Women were more likely to link to care, to start ART and to have a therapeutic treatment response, while men were more likely to be eligible for ART. Men were nearly twice as likely to die during the study period. In total 2,804 women (50% of total sample) and 1,427 (52%) men were lost without confirmation of death or transfer to other care sites.

Table 3.

Hazard ratios and 95% confidence intervals comparing female to male probabilities of reaching a stage of the HIV care continuum given they reached the previous stage.*

Stage	Age-group	Hazard ratio (95% CI)	p value
Tested**	-	-	-
Linked to care	All	1.26 (1.11, 1.44)	< 0.001
	15–24 years	1.56 (1.14, 2.14)	0.009
	25–34 years	1.53 (1.26, 1.86)	< 0.001
	35–44 years	1.18 (0.90, 1.56)	0.246
	45 or older	0.98 (0.68, 1.42)	0.992
ART eligible	All	0.59 (0.54, 0.64)	< 0.001
	15–24 years	0.63 (0.50, 0.79)	< 0.001
	25–34 years	0.66 (0.58, 0.74)	< 0.001
	35–44 years	0.58 (0.49, 0.68)	< 0.001
	45 or older	0.64 (0.53, 0.77)	< 0.001
Started ART	All	2.97 (2.61, 3.38)	< 0.001
	15–24 years	3.55 (2.63, 4.81)	< 0.001
	25–34 years	3.16 (2.56, 3.88)	< 0.001
	35–44 years	1.41 (1.14, 1.73)	0.001
	45 or older	1.24 (0.98, 1.56)	0.072
Therapeutic Response	All	1.60 (1.31, 1.95)	< 0.001
	15–24 years	1.54 (1.06, 2.23)	0.041
	25–34 years	1.64 (1.34, 2.02)	< 0.001
	35–44 years	1.25 (0.92, 1.69)	0.173
	45 or older	1.07 (0.72, 1.60)	0.808
Died	All	0.95 (0.92, 0.97)	< 0.001
	15–24 years	0.91 (0.83, 0.99)	0.004
	25–34 years	0.95% (0.92, 0.99)	0.004
	35–44 years	0.96% (0.92, 1.01)	0.152
	45 or older	1.07 (0.97, 1.18)	0.210

* Adjusted for baseline CD4 count and year of first HIV test

** All study participants received an HIV test