HIV treatment substantially decreases hospitalization rates: evidence from rural South Africa

Abstract

The effect of HIV treatment on hospitalization for HIV-infected people has never been established. We quantified the effect of HIV treatment on hospitalization rates of HIV-infected people in a rural South African community from 2009-2013. We linked clinical data on HIV treatment start dates from more than 2,000 patients receiving care in the public sector treatment program with five years of longitudinal data on self-reported hospitalizations from a community-based population cohort of more than 100,000 adults. We estimated the effects of HIV treatment on hospitalization using fixed-effects Poisson regression. Hospitalization peaked during the first year on treatment, and was about five times higher compared to hospitalization after 4 years on treatment. Earlier treatment initiation could save more than 300,000 US$ per 1000 patients over the first 5 years of HIV treatment, freeing up scare resources. Future studies on the cost-effectiveness of HIV treatment should include these effects.

Introduction

The rapid scale-up of HIV antiretroviral treatment (ART) for HIV in sub-Saharan Africa (SSA) over the past decade is one of

the largest public health achievements in recent history. By suppressing viral replication, ART reduces disease progression (1) and infectiousness (2) of HIV-infected people. Initiation of ART at an early disease stage has resulted in a lower probability of developing AIDS defining illnesses later in life (3).

South Africa is home to the largest HIV epidemic worldwide, with about 7 million people living with HIV.(4) The rapid scale-up ART since 2004 resulted in about 3.3 million people on ART in 2016,(4) and has substantially improved general life expectancy.(5) Yet over 10 years into the ART scale-up in SSA, the economic evaluations of ART still suffer from important limitations regarding cost assumptions.(6-8) Due to limited data availability, modeling studies generally assume fixed annual costs of ART and care.(9-12) Nevertheless, per-patient costs of HIV treatment and care will likely vary substantially across several factors, and differences will to a large extent be driven by rates of inpatient hospitalization.(13-15) Additionally, hospitalizations provide an important, if crude, measure of serious morbidity. As ART becomes more widely available and eligibility criteria are expanded, it is hoped that people will initiate earlier, reducing morbidity and hospitalizations.

The causal effect of HIV treatment on hospitalization for HIV-infected people has never been established. A few empirical

studies have investigated hospitalization rates for HIV-infected patients by CD4 cell count and time on treatment,(13-15) yet these cross-sectional studies suffer from important limitations. They only compared different types of patients already receiving ART and thus could not control for important sources of unobserved confounding threatening the validity of causal inference. For example, patients with preferences for traditional over western medicine may seek HIV treatment at low CD4 counts and avoid seeking hospital care, and patients who are more risk averse may initiate ART at earlier disease stages and may also be more likely to seek hospitalization at any given health state. Furthermore, although randomized clinical trials of ART have demonstrated reduced hospitalization of people already enrolled in care, generalization of these estimates to real-life population-based hospitalization effects is likely limited. Enrollment in HIV treatment is required in order to be eligible to participate in a clinical trial and the population under observation is typically highly selected. Additionally, trial comparisons between treated and control arms may be influenced by Hawthorne effects (or observer effects) and by enhanced monitoring that departs from true standard of care (16).

With longitudinal data on the same patients, spanning the years both before and after they initiate ART in a real-life HIV treatment program, we can control for all individual-level

confounders that do not vary over time.(17, 18) Moreover, by comparing patient hospitalization rates independently from the HIV treatment program, we can gain insights into the long-term clinical impacts of HIV treatment on hospitalization, and estimate a pre-ART baseline of hospitalization that is unaffected by treatment selection effects (due to patients seeking HIV treatment as their health deteriorates) (19).

Hospitalization rates for HIV-infected patients may change substantially over the course of their treatment. Initiation of treatment in South Africa is still considered late as the CD4 cell count at initiation has not increased over the past decades(20), suggesting that patients on ART may initially require hospitalization for opportunistic infections and immune-reconstitution syndrome.(21) Hospitalization rates may therefore be relatively high prior to and during the first year of ART. We further hypothesize that the relative high hospitalization rates during the time of initiation will decline substantially with time on ART, mirroring the recovery in immune health and physical functioning,(6) reducing hospital costs and freeing up tertiary health care capacity in the long run.

Data from the population-based longitudinal cohort run by the Wellcome Trust-funded African Health Research Institute (AHRI), in the rural uMkhanyakude district in KwaZulu-Natal, South Africa, provided us with the rare opportunity to observe

hospitalization rates in HIV-infected people both before and after they enrolled in the local HIV treatment and care program (22) – our main outcome. We linked this data to longitudinal records on HIV treatment from the local ART treatment program – our main exposure. We estimated the effect of HIV treatment on hospitalization, using individual-level fixed effects analysis, thereby controlling for all time-constant confounding. We also controlled for time-varying factors age (as health care preferences me change by age) and calendar year (as health care policy my change over time). Our effect estimates thus have a causal interpretation under the assumption that there are no remaining time-varying confounders. Based on these estimates, we estimate the impact of early HIV treatment on hospitalization capacity and hospitalization expenditures among HIV patients in South Africa.

Methods

Setting and data

We used data from the AHRI population-based cohort for the period 2009-2013.(22) The cohort area covers about 438 km^2, with over 100,000 largely Zulu speaking people, of which the majority live in homesteads scattered throughout the area.(22) The area is characterized by a high HIV prevalence and high ART uptake; in 2011, HIV prevalence in adults was nearly 30%,(23) and about 18,000 people had initiated ART as of end-

2012. Over the study observation period, the local ART program, the Hlabisa HIV Treatment and Care Programme (hereafter: clinical cohort), was run by the South African Department of Health with support from AHRI through large grants from the US Presidential Emergency Fund for AIDS Relief (PEPFAR). The program covers the entire Hlabisa sub-district with a population of about 228,000 people,(24) which is located in uMkhanyakude district, the poorest among the 52 districts in South Africa. The AHRI population-based cohort covers about half of the population in the sub-district, which generates the opportunity for individual-level linkage of data from the population-based cohort and the clinical cohort.

The AHRI population-based cohort includes individual and household surveys, conducted once per year for the entire adult population in the cohort area, and every 4 months, respectively. The household surveys consist of a set of questionnaires administered to the head or key informant of the household. They contain questions on events that change the household structure, such as birth, migration, marriage, or death, as well as a wide range of economic and social exposures and outcomes. The individual surveys include an HIV sero-surveillance (since 2003/2004) and questions on a range of characteristics and behaviors. The different surveys are described in detail elsewhere.(22)

Clinical records of patients in the clinical cohort were linked at the individual level with hospitalization data on these same patients reported in the population-based longitudinal surveillance. Linkage was based on each patient's unique South African identification number, or their first name, surname, age, and sex. Ethics approval for data collection, linkage, and use was obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal.

Exposure and outcome variables

Our exposure variable is time since ART initiation. To calculate the time since ART initiation, we subtracted the date of ART initiation from the date at which the individual survey was conducted. Because we can observe hospitalization events of individuals before they appear in the ART program, we were able to include data from surveys conducted before an individual had initiated ART, and coded time since initiation as below zero for people not yet initiated. Because we do not expect a linear relationship between time on ART and hospitalization events, we categorized time on ART into: ≤-3 years; -3 to <-2 years; -2 to <-1 year; -1 to <0 years; 0 to <1 year; 1 to <2 years; 2 to <4 years; and ≥4 years.

Our outcome variable was the number of hospitalization events reported by individuals in different survey rounds of the longitudinal surveillance. Since 2009, the surveys include

questions on how often an individual was hospitalized in the 12 months prior to the survey.

Data analysis

We estimated the effects of ART on hospitalization rates in the last 12 months in HIV-infected people in individual-fixed-effects analysis. The patient fixed effects control for all observed and unobserved factors that are constant for individuals, such as sex, CD4 cell count at treatment initiation; time-invariant preferences, beliefs and attitudes; or factors that vary over time, but were likely constant during the observational period, such as educational level. In addition, we control for the important time-varying factors calendar year and age at the time of a particular survey record on hospitalization. Because the outcome variable is a count variable, we performed Poisson regression analysis. We chose Poisson over zero-inflated negative-binominal because analyses of residuals did not give rise to concerns of overdispersion as a major problem. Because the individual-fixed-effects analysis exploits co-variation in exposure and outcomes over time for causal estimation, our sample consists of those individuals with more than one observation over the observation period (2009-2013). We clustered heteroskedasticity-robust standard errors at the individual level to account for correlations in outcomes within the patient.(25)

Next, we assessed the effect of starting ART on hospital capacity and costs of hospitalization. We determined the crude hospitalization rate for people on ART for ≥4 years on ART by dividing the total number of hospitalization events by the number of observation years. We derived an average stay of 10.1 days per hospitalization event, and 170 USD per in-patient day from Meyer-Rath *et al*,(16) and calculated the hospital capacity utilization and hospitalization costs per 1,000 patients by time on ART. In addition, we explored the potential effect of earlier initiation. For this analysis, we assume that when treatment is initiated before (severe) symptoms occur, e.g. at higher CD4 cell counts, patients in the first three years of ART will experience the same hospitalization rates as the average patient in the category 2-3 years before treatment initiation.

Limitations

Our study has some limitations to take into account. Firstly, our extrapolation from hospitalization rates to inpatient days and health care costs is a simple linear extrapolation, assuming that costs and duration of inpatient days do not change with time on ART. Although simplistic, limited evidence shows that average length of a hospitalization event remains relatively constant during disease progression. (16) Secondly, our individual fixed-effects Poisson models only control for all time-constant confounding, and there is still the

possibility that time-varying factors might confound our estimates. We mitigate the threat of time-varying confounding by controlling for individuals' age (capturing factors that change with age, such as income and education), and calendar year (capturing time-varying confounding such as policy changes). Third, our data are derived from a single rural community in South Africa, and we could therefore not control for any setting specific confounding such access to different sources of care or local preferences for care. Fourth, it is unlikely that selection biases substantially distort our results. Only 1.5% of our data on hospitalization was missing and the probability of missingness did not vary with time since ART initiation. Furthermore, all patients in the clinical cohort who reside in the surveillance area could be successfully linked. Fifth, we used self-reported hospitalization, which may be inaccurate. However, the general health systems literature shows that health care utilization is usually quite accurately reported and that recall is particularly good for hospitalization (26).

Results

There were a total of 6,505 observations of 2,252 individuals (Exhibit 1). Observations were roughly evenly spread across the 5 years. The majority of individuals were female (83.9%), reflecting both the fact that more women are reached through the population-based surveillance and the fact that women

constitute a far larger proportion of ART patients in South Africa. The median CD4 cell count at treatment initiation was 163 cells/μL (interquartile range: 97; 226). The overall hospitalization rate in the sample was 103.2 per 1,000 person-years (data not shown).

Next, we calculated relative hospitalization rates by number of years on treatment from a univariate Poisson model with individual fixed effects (Exhibit 2). We chose the group with the largest number of observations as reference category (4 or more years on ART). Hospitalization rates were the highest in the first year of treatment (Adjusted Incidence Rate Ratio (AIRR) = 7.33, 95% CI: 4.89; 10.98), while hospitalization rates were lowest after 4 or more years on treatment (AIRR = 1.0). In addition, hospitalization rates in the pre-ART period were significantly higher compared to hospitalization rates after the second year of ART. Three or more years before ART initiation, HIV-infected people were almost 5 times as likely to be hospitalized compared to people on ART for 4 years or more.

After controlling for observation year and age of the patient, the observed AIRR of hospitalization by year since treatment initiation decline slightly, yet the overall trend over time remain (Exhibit 3). Due to low power, the AIRR of hospitalization 3 years or longer prior to ART initiation compared to 4 years or more on ART was no longer significantly

different from the reference category despite a point estimate that was substantially different from 1 (AIRR=2.11; 95% CI: 0.61; 7.34). Hospitalization rates 2 years (AIRR=2.82; 95% CI: 1.00; 7.93) or 1 year (AIRR=3.10; 95% CI: 1.31; 7.35) prior to ART initiation remained significant. Hospitalization rates in the first year of ART remained high (AIRR = 5.47; 95% CI: 2.72; 10.99), and declined significantly over time on ART, with AIRRs of 2.88 after 1 year on ART (95% CI: 1.63; 5.08) and 1.44 (95% CI 0.90; 2.31) after 2 or 3 years on ART, to the lowest hospitalization rate in the cohort, after 4 or more years on ART.

Baseline hospitalization in-patient days in patients on ART for 4 years or more was 67.7/1,000 person years, amounting to about 677 inpatient days and 116,000 US$ in hospitalization costs per 1,000 person-years (Exhibit 4). With a total of 3740 in-patient days, hospitalization costs peak at about 636,735 US$ per 1,000 person-years in the first year of ART (Exhibit 4). Earlier initiation of patients, which is assumed to remove the initial bump in hospitalization during initiation, would save about 1889 in-patient days and 321,515 US$ per 1,000 person-years over the first 5 years of treatment (grey area in Exhibit 4).

Discussion

We found that, in one rural South African community, ART has reduced hospitalization about 3 fold in people after 4 years of ART compared to 3 years or more before treatment initiation at baseline. Hospitalization peaked during the first year on ART, and was about five times higher compared hospitalization after 4 years on ART. We estimate that, through preventing high rates of hospitalization in the first year of ART, earlier treatment initiation could save more than 300,000 US$ per 1000 patients over the first 5 years of ART, and could free up scarce health care resources.

To our knowledge, this is the first time that the effect of ART on hospitalization of HIV-infected people has been estimated for sub-Saharan Africa in a study design that controls for all differences between patients who start ART and those who do not, and is causally-robust under the assumption of no remaining time-varying confounding. Although other observational studies have previously shown that hospitalization rates differ for HIV-infected people by time on ART and CD4 cell count at initiation,(14-16, 27, 28) all these were done from clinical cohorts or trials. The causal effect of ART on hospitalization rates can only be established if we know the no-ART care baseline, and clinical cohort studies or clinical trials endogenously introduce selection bias as the participants are all registered and entered into care. We were able to overcome this problem because of the

unique link between ART uptake data from a clinical cohort with hospitalization data from a population based cohort.

Policy Implications

Our results have important implications. Firstly, estimates of the costs-effectiveness of ART in SSA either use data on costs by number of years on treatment from clinical cohorts,(29) or assume fixed costs regardless of ART duration or CD4 cell count at initiation.(10-13) Our results show that it is essential to incorporate the effects of ART and hospitalization into cost-effectiveness and cost-benefit analysis by using both pre-ART baseline hospitalization rates and incorporating the causal effect of ART on hospitalization by time on treatment. In addition, our results highlight the importance of incorporating the effects of earlier treatment initiation on hospitalization rates and costs surrounding hospitalization, as reduced hospitalization might result in direct savings due to earlier initiation. Our results suggest that adoption of early ART initiation could save substantial financial resources, potentially making early initiation cost-saving, and challenging concerns of long-term sustainability of ART programs in South Africa and other countries (13). For instance, in South Africa, roughly about 2.5 million people still need to be initiated on ART in order to achieve the 90-90-90 targets (i.e. having 90% of all HIV infected people

tested; 90% of those tested initiated on ART; and 90% of those on ART virally suppressed by 2020). Here, early initiation compared to late initiation could save roughly about 4.5 million inpatient days and 800 million US$ in the first 5 years of treatment, provided all these people would initiate before severe symptoms occur.

Secondly, our results of reduced hospitalization add on to the growing list of benefits of ART – i.e. improved survival,(6) reduced risk of onward transmission,(30) improved employment,(31) and health-system strengthening(32) – and provide further arguments in favor of earlier initiation and treatment as prevention. Our results show that expanding guidelines and initiate HIV-infected people at an earlier stage will reduce hospitalization and will free-up scarce resources such as hospital beds and human resources in two ways. Firstly, as ART reduces hospitalization rates to below the baseline hospitalization before treatment initiation, earlier initiation will ensure that these benefits are reaped at an earlier stage of the infection. Secondly, the peak of hospitalization surrounding initiation can likely be avoided if patients were to initiate ART at an earlier stage, as early initiation is associated with fewer sever symptoms requiring hospitalization.(3) Nevertheless, this not only requires changes on the supply-side through more flexible eligibility criteria, but also on the demand-side through improved health

seeking. In addition, it is not immediately clear whether gains in hospital capacity through earlier initiation will translate into net cost and resource savings in the entire health system, as earlier initiation requires more investments into ART delivery at the primary care level. Cost-benefit analyses are needed in order to quantify these trade-offs.

The South African health system is currently overburdened.(33) As well as facing one of the world's most severe HIV epidemics, South Africa also faces a high burden of non-communicable diseases,(34) which is expected to further increase as the HIV epidemic ages.(35) Freeing-up hospital capacity is essential to meet the challenges of this complicated epidemiological transition.

Conclusions

In conclusion, we delivered the first causal evidence that ART substantially reduces hospitalization rates in HIV-infected people. ART effectively reduces hospitalization in HIV-infected people to levels below the hospitalization years before treatment initiation. In addition, earlier initiation, for instance under 'treatment as prevention', would further reduce hospitalization costs and would free-up non-financial resources. Future modeling studies on the cost-effectiveness and economic benefits of ART should include the ART effects on hospitalization rates and costs.

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List of Exhibits

Exhibit 1 (Table) – Baseline characteristics of participants in the study.

SOURCE: Authors' analysis of data from the Africa Health Research Center; 2009-2013

NOTES: Hospitalization rates were determined using univariate Poisson regression models. SE=standard error.

Exhibit 2 (Figure) - Hospitalization rate ratio for HIV-infected people by ART treatment year.

Source: authors' own analysis of data from the Africa Health Research Center (2009 – 2013).

NOTES: Hospitalization rate ratios were determined though Poisson regression models with individual fixed effects. Absolute hospitalization rates for the different categories with 95% CIs (events per 1,000 person-years): 80.7 (59.2; 110.0); 100.4 (75.7; 133.0); 107.6 (85.7; 135.2); 218.7 (182.5; 251.8); 123.9 (102.2; 150.3); 81.0 (67.5; 97.3); and 67.7 (54.6; 83.9) respectively.

Exhibit 3 (Table) - Patient-fixed-effects regression of time since treatment initiation on hospitalization rates in HIV-infected people in rural KwaZulu-Natal, South Africa.

SOURCE: Authors' analysis of data from the Africa Health Research Center; 2009-2013

NOTES: N = Total number of observations. AIC = Akaike Information Criterion. BIC = Bayesian Information Criterion. DF = degrees of freedom *p < 0.10, **p < 0.05, ***p < 0.01, ****p < 0.001.

Exhibit 4 (Figure) - Estimated benefits of early ART initiation on in-patient days and hospitalization costs incurred per year for 1,000 HIV-infected people by time on ART.

Source: authors' own analysis of data from the Africa Health Research Center (2009 – 2013) and data published by Meyer-Rath et al.(17)

Exhibit 1. Baseline characteristics of participants in the study.

	N	%	Hospitalization rate per 1000 person year	
			Estimate	SE
Total number of observations	6,505		103.1	5.4
Number of unique individuals	2,252		-	
Sex				
Male	1,055	16.2	109.3	12.6
Female	5.450	83.9	101.9	5.9
Observation year				
2009	1,128	17.3	168.0	13.4
2010	1,298	20.0	102.7	9.3
2011	1,395	21.5	105.3	8.9
2012	1,351	20.8	82.0	7.7
2013	1,333	20.5	66.4	6.9
Time since treatment initiation during survey				
Less than -3 years	572	8.8	80.7	11.0
<- 2 years to -3 years	571	8.8	100.4	12.6
< 0 years to -1 years	748	11.5	107.6	11.2
0 to < 1 years	910	14.0	218.7	18.4
1 to < 2 years	902	13.9	123.9	11.1
2 to < 4 years	1,470	22.6	81.0	6.9
4 years or more	1,332	20.5	67.7	6.7
Age at survey visit				
15-19 years	220	3.4	139.6	28.3
20-24 years	477	7.3	115.4	16.7
25-29 years	797	12.3	101.3	12.3
30-34 years	1,010	15.5	106.7	0.6
35-39 years	1,071	16.5	114.6	12.5
40-44 years	867	13.3	132.3	14.9
45-49 years	768	11.8	88.2	11.2
> 50 years	1,295	19.9	72.1	8.6
CD4 cell count at initiation (cells/µL)				
0 to 49	622	10.2	113.7	16.3
50 to 99	966	15.8	112.1	13.6
100 to 149	1,121	18.4	118.4	13.2
150 to 199	1,491	24.4	88.2	9.3
200 to 349	1,533	25.1	85.3	9.2
>350	370	6.1	101.1	18.4

SOURCE: Authors' analysis of data from the Africa Health Research Center; 2009-2013

NOTES: Hospitalization rates were determined using univariate Poisson regression models. SE=standard error.

Exhibit 3. Patient-fixed-effects regression of time since treatment initiation on hospitalization rates in HIV-infected people in rural KwaZulu-Natal, South Africa.

	Incidence rate ratio of hospitalization
Time since treatment initiation during survey (%)	
- 3 years or less	2.11
- 2 years	2.82**
- 1 year	3.10***
0 years	5.47****
1 year	2.88****
2 & 3 years	1.44
4 years or more	1
Calendar year	
2009	1
2010	0.60**
2011	0.55
2012	0.40
2013	0.34
Age (continuous per year)	1.20
Model summary	
N	1297
AIC	1202.7
BIC	1258.9
Log likelihood	-590.0
DF	11

SOURCE: Authors' analysis of data from the Africa Health Research Center; 2009-2013

NOTES: N = Total number of observations. AIC = Akaike Information Criterion. BIC = Bayesian Information Criterion. DF = degrees of freedom *p < 0.10, **p < 0.05, ***p < 0.01, ****p < 0.001.