Published in final edited form as:

Health Aff (Millwood). 2018 June ; 37(6): 997–1004. doi:10.1377/hlthaff.2017.0820.

HIV Treatment Substantially Decreases Hospitalization Rates: Evidence From Rural South Africa

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Abstract

The effect of HIV treatment on hospitalization rates for HIV-infected people has never been established. We quantified this effect in a rural South African community for the period 2009–13. We linked clinical data on HIV treatment start dates for 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. Hospitalization rates peaked during the first year of treatment and were about five times higher, compared to hospitalization rates after four years on treatment. Earlier treatment initiation could save more than US \$300,000 per 1,000 patients over the first four years of HIV treatment, freeing up scarce resources. Future studies on the cost-effectiveness of HIV treatment should include these effects.

The rapid scale-up of antiretroviral treatment (ART) for HIV in sub-Saharan Africa, which started in the mid-2000s, is one of the largest public health achievements in recent history. By suppressing viral replication, ART reduces disease progression¹ in HIV-infected people and the infectiousness of their conditions.² 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 in the world: About seven million people are living with HIV.⁴ The rapid scale-up of ART since 2004 resulted in about 3.3 million people on ART in 2016⁴ and has greatly improved general life expectancy in the country.⁵ Yet over ten years into the ART scale-up in sub-Saharan Africa, economic evaluations of ART still suffer from important limitations regarding cost assumptions.^{6–8} Because data availability is limited, modeling studies generally assume fixed annual costs of ART and care.^{9–12} Nevertheless, per patient costs of HIV treatment and care likely vary substantially across several factors, and differences are driven to a large extent by rates of inpatient hospitalization.^{13–15} Additionally, hospitalization provides 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 treatment earlier, reducing morbidity and hospitalization rates.

The causal effect of HIV treatment on rates of hospitalization for HIV-infected people has never been established. A few empirical studies have investigated hospitalization rates for HIV-infected patients by CD4 T lymphocyte cell (CD4) count and time receiving treatment.^{13–15} However, these cross-sectional studies suffer from important limitations. They compared only different types of patients already receiving ART and thus could not control for important sources of unobserved confounding that might threaten 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 rates among people already enrolled in care, these estimates have only limited generalizability to real-life population-based hospitalization effects. Enrollment in HIV treatment is required 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 (when people change their behavior if they know they are being observed) and by enhanced monitoring that departs from the 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, it is possible to control for all individual-level confounders that do not vary over time.^{17,18} Moreover, a comparison of patient hospitalization rates from data that were collected independently from the HIV treatment program allows for gaining insights into the long-term clinical impacts of HIV treatment on hospitalization rates and estimating a pre-ART baseline for these rates that is unaffected by treatment selection effects (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 average CD4 cell count at initiation has not increased over the past decades. One recent study found that average initiation remained relatively stable at CD4 counts of 152, despite the recommended guideline for initiation of ART expanding from CD4 counts of 200 to 350 and 500 subsequently.²⁰ This suggests that patients on ART in South Africa may initially require hospitalization for opportunistic infections and immune-reconstitution syndrome because of their low CD4 counts.²¹ Hospitalization rates may therefore be relatively high before and during the first year of ART. We further hypothesized that the relatively high hospitalization rates during the time of initiation would decline substantially with time on ART, mirroring the recovery in immune system and physical functioning,⁶ and would thus reduce hospital costs and free 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 in the rural uMkhanyakude district in KwaZulu-Natal, South Africa, provided us with the rare opportunity to observe hospitalization rates among HIV-infected people both before and after they enrolled in the local HIV treatment and care program²² (our main outcome). We linked these data to information in 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 the time-varying factors of age (as health care preferences can change by age) and calendar year (as health care policy can change over time). Our effect estimates thus have a causal interpretation if one assumes that there are no remaining time-varying confounders. Based on these estimates, we estimated the impact of early HIV treatment on inpatient days and hospitalization spending among HIV patients in South Africa.

Study Data And Methods

SETTING AND DATA

We used data for the period 2009–13 from the Africa Health Research Institute (AHRI) population-based cohort.²² The cohort area covers about 438 square kilometers and is home to over 100,000 largely Zulu-speaking people, the majority of whom live in homesteads scattered throughout the area.²² The area is characterized by high HIV prevalence and high ART uptake: In 2011, HIV prevalence in adults was nearly 30 percent, and about 18,000 people had initiated ART as of the end of 2012.²³ Over the study period, the local ART program—the Hlabisa HIV Treatment and Care Programme (hereafter, the clinical cohort)—was run by the South Africa Department of Health with support from the Africa Health Research Institute through large grants from the US President’s Emergency Plan for AIDS Relief (PEPFAR). The program covers the entire Hlabisa subdistrict, which has a population of about 228,000 people²⁴ and is located in uMkhanyakude District, the poorest of South Africa’s fifty-two districts. The AHRI population-based cohort covers about half of the population in the subdistrict. This makes it possible to link data at the individual level from the population-based cohort with data from the clinical cohort.

The AHRI population-based cohort includes individual and household surveys that are conducted once a year for the entire adult population in the cohort area and every four months, respectively. The household surveys consist of a set of questionnaires administered to the head of or key informant in the household. They contain questions on events that change the household structure such as birth, migration, marriage, and death, as well as on a wide range of economic and social exposures and outcomes. Since 2003–04 the individual surveys have included HIV sero-surveillance and questions on a range of characteristics and behaviors. The different surveys have been described in detail elsewhere.²²

Clinical records of patients in the clinical cohort were linked at the individual level with hospitalization data on the same patients reported in the population-based longitudinal cohort. 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 was time since ART initiation. To calculate this, we subtracted the date of ART initiation from the date at which the individual survey was conducted. Because we could observe hospitalization events of people before they appeared in the ART program, we were able to include data from surveys conducted before people had initiated ART, and we coded time since initiation as below 0 for people who had not yet initiated ART. Because we did not expect to find a linear relationship between time on ART and hospitalization events, we categorized time on ART as –3rd year or less; –2nd year; –1st year; 1st year; 2nd year; 3rd and 4th years; and 5th year or more.

Our outcome variable was the number of hospitalization events reported by people in different survey rounds of the longitudinal cohort. Since 2009 the surveys have included questions on how often a person was hospitalized in the twelve months before the survey.

DATA ANALYSIS

As noted above, we estimated the effects of ART on hospitalization rates in the past twelve months in HIV-infected people using individual-level fixed effects analysis. This analysis controlled for all observed and unobserved factors that were constant for people, such as sex and CD4 cell count at treatment initiation; time-invariant preferences, beliefs, and attitudes; and factors that vary over time but were likely constant during the observational period, such as educational level. In addition, we controlled for the important time-varying factors of calendar year and age at the time of a conducted survey in the population-based cohort. Because the outcome variable was a count variable, we performed Poisson regression analysis, choosing it over zero-inflated negative-binomial because analyses of residuals did not give rise to concerns of overdispersion as a major problem. Because the individual-level fixed effects analysis exploited covariation in exposure and outcomes over time for causal estimation, our sample consisted of people with more than one observation over the observation period (2009–13). We clustered heteroskedasticity-robust standard errors at the individual level to account for correlations in outcomes within a patient.²⁵

Next, we assessed the effect of starting ART on inpatient days and costs of hospitalization. We determined the crude hospitalization rate for people on ART for four or more years by dividing the number of hospitalization events by the number of observation years. We derived an average stay of 10.1 days per hospitalization event, and \$US170 per inpatient day from the work of Gesine Meyer-Rath and colleagues,¹⁵ and we calculated the hospital capacity utilization (defined as inpatient days) 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 assumed that when treatment was initiated before (severe) symptoms occur—for example, at higher CD4 cell counts—patients in the first three years of ART would experience the same hospitalization rates as the average patient in the category of 2–3 years before treatment initiation.

LIMITATIONS

Our study had some limitations that should be taken into account. First, our extrapolation from hospitalization rates to inpatient days and health care costs was a simple linear extrapolation and assumed that costs and duration of inpatient days did not change with time on ART. Although this assumption is relatively simplistic, limited evidence shows that the average length of a hospitalization event remains relatively constant during disease progression.¹⁶

Second, our individual-level fixed effects Poisson models controlled only for all time-constant confounding, and it is still possible that time-varying factors confounded our estimates. We mitigated the threat of time-varying confounding by controlling for people's age (capturing factors that change with age, such as income and education) and calendar year (capturing time-varying confounding factors such as policy changes).

Third, our data were derived from a single rural community in South Africa, and we therefore could not control for any setting-specific confounding, such as access to different sources of care or local preferences for care.

Fourth, while selection bias is a possibility, it is unlikely that it substantially distorted our results. Only 1.5 percent of our data on hospitalization were missing, and the probability of missingness did not vary with time since ART initiation. Furthermore, all patients in the clinical cohort who resided 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 use is usually quite accurately reported and that recall is particularly good for hospitalization.²⁶

Study Results

There were 6,505 observations of 2,252 unique participants in the Africa Health Research Institute cohort (exhibit 1). Numbers of observations were roughly evenly spread across the five years. Eighty-four percent of participants were female, which reflects the fact that more women than men are reached through population-based surveillance and that women constitute a far larger proportion of ART patients in South Africa. The median CD4 cell

count at treatment initiation was 163 cells/ μ L (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 regression model with individual-level fixed effects. Exhibit 2 shows the hospitalization rate ratios, which are calculated as the ratios of rates for each category of time since initiation to the category “5th year or more.” We chose the group with the largest number of observations (people in the fifth year or more on ART) as the reference category. Hospitalization rates were the highest in the first year of treatment (adjusted incidence rate ratio: 8.97), while they were lowest in the fifth year or more on treatment (AIRR: 1.0). In addition, rates in the period before initiating ART were higher than rates after the second year of ART. HIV-infected people three or more years before ART initiation were almost five times as likely to be hospitalized, compared to people on ART for four years or more.

After we controlled for observation year and age of the patient, we found that the observed adjusted incidence rate ratio of hospitalization by year since treatment initiation declined slightly, yet the overall trend over time remained (exhibit 3). Because of low statistical power, the ratio of hospitalization for people three or more years before ART initiation was no longer significantly different from the reference category (those with four years or more since ART initiation), despite a point estimate that was substantially different from 1 (AIRR: 2.11; 95% CI: 0.61, 7.34). Differences between hospitalization rates for people on ART for four or more years and those two years (AIRR: 2.82; 95% CI: 1.00, 7.93) or one year (AIRR: 3.10; 95% CI: 1.31, 7.35) before 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 (AIRR for one year since ART initiation: 2.88; 95% CI: 1.63, 5.08; AIRR for two or three years since ART initiation: 1.44 (95% CI: 0.90, 2.31), compared to the reference category.

Exhibit 4 shows two measures each for both early and late ART initiation, with inpatient days shown on the left axis and hospitalization costs on the right axis. The shaded area is an estimate of the benefit of early initiation. For patients who had been on ART for four years or more, there were 677 inpatient days per 1,000 person years, at a hospitalization cost per 1,000 person-years of US\$116,403 (exhibit 4). Hospitalization costs peaked at about US\$636,735 per 1,000 person years in the first year of ART. Earlier ART initiation (that is, before severe symptoms occur), which is assumed to remove the initial bump in hospitalization during initiation, would save about 1,889 inpatient days and US\$321,515 per 1,000 person-years over the first four years of treatment.

Discussion

We found that in one rural South African community, ART reduced hospitalization rates about threefold in people four years after ART initiation, compared to those three years or more before treatment initiation. Hospitalization rates peaked during the first year since ART initiation and were about five times higher compared to hospitalization rates at four years since ART initiation. We estimated that, through preventing high rates of hospitalization in the first year of ART, earlier treatment initiation could save more than US

\$300,000 per 1,000 person-years over the first four 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 that both controlled for all differences between patients who start ART and those who do not and was causally robust under the assumption of no remaining time-varying confounding. Although other observational studies have shown that hospitalization rates differ for HIV-infected people by time on ART and CD4 cell count at initiation,^{14–16,27,28} all of these used clinical cohorts or trials. The causal effect of ART on hospitalization rates can be established only when the no-ART care baseline is known, 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 our study's unique linkage of ART uptake data from a clinical cohort and hospitalization data from a population-based cohort.

Policy Implications

Our results have important implications. First, estimates of the cost-effectiveness of ART in sub-Saharan Africa either use data on costs by number of years on treatment from clinical cohorts²⁹ 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 both using 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 as a result of earlier initiation. Our results suggest that the adoption of early ART initiation could save substantial financial resources, potentially making early initiation cost-saving and challenging concerns about the 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 initiate ART to achieve the 90–90–90 targets established by UNAIDS³⁰ (that is, having 90 percent of all HIV-infected people tested, having 90 percent of those tested initiate ART, and having 90 percent of those on ART virally suppressed by 2020). According to our findings, early initiation compared to late initiation could save roughly about 4.5 million inpatient days and US\$800 million in the first four years of treatment, provided all of these people would initiate treatment before severe symptoms occur.

Second, our results of reduced hospitalization add to the growing list of benefits of ART—which already includes improved survival,⁶ reduced risk of onward transmission,³¹ better employment rates,³² and health system strengthening³³—and provide further arguments in favor of earlier initiation and treatment as prevention. Our results show that expanding guidelines and initiating treatment of HIV-infected people at an earlier stage would reduce hospitalization and free up scarce resources such as hospital beds and human resources in two ways. First, since ART reduces hospitalization rates to below the baseline rates before treatment initiation, earlier initiation would ensure that these benefits were reaped at an earlier stage of the infection. Second, the peak of hospitalization surrounding initiation could

likely be avoided if patients were to initiate ART at an earlier stage, as early initiation is associated with fewer severe symptoms requiring hospitalization.³ Nevertheless, this would require changes not only 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 would translate into net cost and resource savings in the entire health system, as earlier initiation would require more investment in ART delivery at the primary care level. Cost-benefit analyses are needed to quantify these trade-offs.

The South African health system is currently overburdened.³⁴ As well as facing one of the world's most severe HIV epidemics, South Africa also faces a high burden of noncommunicable disease,³⁵ which is expected to further increase as the HIV epidemic matures.³⁶ Freeing up hospital capacity is essential to meeting the challenges of this complicated epidemiological transition.

Conclusion

We have provided 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 free up nonfinancial resources. Future modeling studies on the cost-effectiveness and economic benefits of ART should include the effects of ART on hospitalization rates and costs. ■

Acknowledgments

Core funding supporting the Africa Health Research Institute population health surveillance system and Hlabisa HIV Treatment and Care Programme was primarily provided by the Wellcome Trust and the US President's Emergency Plan for AIDS Relief. Frank Tanser and Till Bärnighausen received funding from the Wellcome Trust and from the National Institutes of Health (NIH; Grant Nos. NICHD R01-HD084233 and NIAID R01-AI124389). Jan Hontelez is supported by the Talent Scheme Veni research program, which is financed by the Netherlands Organisation for Scientific Research. Bärnighausen also received funding from the Alexander von Humboldt Foundation through the Alexander von Humboldt Professor award; the European Commission; the Clinton Health Access Initiative; and the NIH's National Institute on Aging (Grant No. P01-AG041710), National Institute of Allergy and Infectious Diseases (Grant Nos. R01-AI124389 and R01-AI112339), and John E. Fogarty International Center (Grant No. D43-TW009775). Tanser received additional funding from the South African Medical Research Council Flagship (Grant No. MRC-RFA-UFSP-01-2013/UKZN HIVEPI) and a UK Academy of Medical Sciences Newton Advanced Fellowship (Grant No. NA150161). Jacob Bor received funding from the NIH (Grant No. NIH KO1MH105320). Mosa Moshabela holds a Wellcome Trust fellowship. The contents of this article are the responsibility of the authors and do not necessarily reflect the views of any of the funders or the US government.

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EXHIBIT 2. Hospitalization rate ratios for HIV-infected people in KwaZulu-Natal, South Africa, by time on antiretroviral treatment (ART)

SOURCE Authors' analysis of data for 2009–13 from the Africa Health Research Institute.

NOTES Adjusted for all unobserved, individual-level time-constant confounding.

Hospitalization rate ratios, calculated as the ratios of rates for each category of time since initiation to the category 4 years or more, were determined using a univariate Poisson regression model with individual fixed effects. The group with the largest number of observations (people with four or more years on ART) is the reference category (set to a rate ratio of 1). The error bars indicate 95% confidence intervals (CIs). Absolute hospitalization rates per 1,000 person-years were as follows. ^a80.7 (95% CI: 59.2, 110.0). ^b100.4 (95% CI: 75.7, 133.0). ^c107.6 (95% CI: 85.7, 135.2). ^d218.7 (95% CI: 182.5, 251.8). ^e123.9 (95% CI: 102.2, 150.3). ^f81.0 (95% CI: 67.5, 97.3). ^g67.7 (95% CI: 54.6, 83.9).

EXHIBIT 4. Estimated benefits of earlier initiation of antiretroviral treatment (ART) on inpatient days and hospitalization costs per 1,000 HIV-infected person-years in KwaZulu-Natal, South Africa, by time on ART

SOURCE Authors' analysis of data for 2009–13 from the Africa Health Research Institute and of data in Meyer-Rath G, et al. Rates and cost of hospitalization before and after initiation of antiretroviral therapy in urban and rural settings in South Africa (see note 15 in text). **NOTES** Earlier ART initiation is before severe symptoms occur.

EXHIBIT 1

Baseline characteristics of participants in the study, KwaZulu-Natal, South Africa

Hospitalization rate per 1,000 person-years			
	Number^a	Percent^a	Estimate SE
Observations	6,505	100.0	103.1 5.4
Unique participants	2,252	100.0	<i>b</i> <i>b</i>
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 ON ANTIRETROVIRAL TREATMENT (YEARS)			
–3rd year or less	572	8.8	80.7 11.0
–2nd year	571	8.8	100.4 12.6
–1st year	748	11.5	107.6 11.2
1st year	910	14.0	218.7 18.4
2nd year	902	13.9	123.9 11.1
3rd and 4th years	1,470	22.6	81.0 6.9
5th year or more	1,332	20.5	67.7 6.7
AGE AT SURVEY VISIT (YEARS)			
15–19	220	3.4	139.6 28.3
20–24	477	7.3	115.4 16.7
25–29	797	12.3	101.3 12.3
30–34	1,010	15.5	106.7 0.6
35–39	1,071	16.5	114.6 12.5
40–44	867	13.3	132.3 14.9
45–49	768	11.8	88.2 11.2

Hospitalization rate per 1,000 person-years				
	Number ^a	Percent ^a	Estimate	SE
50 or older	1,295	19.9	72.1	8.6
CD4 CELL COUNT AT INITIATION (CELLS/μL)				
0–49	622	10.2	113.7	16.3
50–99	966	15.8	112.1	13.6
100–149	1,121	18.4	118.4	13.2
150–199	1,491	24.4	88.2	9.3
200–349	1,533	25.1	85.3	9.2
350 or more	370	6.1	101.1	18.4

SOURCE Authors' analysis of data for 2009–13 from the Africa Health Research Institute. **NOTES** Time on antiretroviral treatment (ART) was calculated by subtracting the date of ART initiation from the date at which the individual survey was conducted. Hospitalization rates were determined using univariate Poisson regression models. Percentages might not sum to 100 because of rounding. SE is standard error. CD4 is CD4 T lymphocyte cell count.

^a All findings relate to number of observations (except the row for number of unique participants).

^b Not applicable, as individuals had multiple observations over time.

EXHIBIT 3

Multivariate patient-fixed-effects regression of time on antiretroviral treatment on hospitalization rates in HIV-infected people in KwaZulu-Natal, South Africa

	Adjusted incidence rate ratio of hospitalization
TIME ON ANTIRETROVIRAL TREATMENT	
–3rd year or less	2.11
–2nd year	2.82**
–1st year	3.10***
1st year	5.47****
2nd year	2.88*****
3rd and 4th years	1.44
5th year or more	1.00 ^a
OBSERVATION YEAR	
2009	1.00
2010	0.60**
2011	0.55
2012	0.40
2013	0.34
AGE	
Continuous per year	1.20
MODEL SUMMARY	
Observations	1,297
AIC	1,202.7
BIC	1,258.9
Log likelihood	–590.0
DF	11

SOURCE Authors' analysis of data for 2009–13 from the Africa Health Research Institute. **NOTES** AIC is Akaike Information Criterion. BIC is Bayesian Information Criterion. DF is degrees of freedom.

^aReference category.

**
* $p < 0.05$

100:0>*d*

10:0>*d*

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