

# Effect of antiretroviral therapy on patients' economic well being: five-year follow-up

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**Objective:** Evaluate the effect of antiretroviral therapy (ART) on South African HIV patients' economic well being, as indicated by symptoms, normal activities, employment, and external support, during the first 5 years on treatment.

**Methods:** Prospective cohort study of 879 adult patients at public or nongovernmental clinics enrolled before ART initiation or on ART less than 6 months and followed for 5.5 years or less. Patients were interviewed during routine clinic visits. Outcomes were estimated using population-averaged logistic regression and reported as proportions of the cohort experiencing outcomes by duration on ART.

**Results:** For patients remaining in care, outcomes improved continuously and substantially, with all differences between baseline and 5 years statistically significant ( $P < 0.05$ ) and continued significant improvement between year 3 and year 5. The probability of reporting pain last week fell from 69% during the three months before starting ART to 17% after 5 years on ART and fatigue from 62 to 7%. The probability of not being able to perform normal activities in the previous week fell from 47 to 5% and of being employed increased from 32 to 44%; difficulty with job performance among those employed fell from 56 to 6%. As health improved, the probability of relying on a caretaker declined from 81 to less than 1%, and receipt of a disability grant, which initially increased, fell slightly over time on ART.

**Conclusion:** Results from one of the longest prospective cohorts tracking economic outcomes of HIV treatment in Africa suggest continuous improvement during the first 5 years on treatment, confirming the sustained economic benefits of providing large-scale treatment.

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## Introduction

With the rapid expansion of antiretroviral therapy (ART) programs in lower-income and middle-income countries in the middle of the last decade, large numbers of patients are now reaching 5 or more years on ART. The biomedical outcomes of ART over the first 5 years on treatment have been well documented in many sub-

Saharan African countries [1,2], where antiretroviral provision has been associated with reductions in HIV-associated mortality at a population scale [3–5].

There is a far less robust evidence base regarding the 'nonbiomedical' outcomes of treatment in Africa. A handful of studies have considered the implications of ART for a limited set of quality of life, employment, and

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other economic and social indicators, but these studies, which have been reviewed twice in recent years [6,7], have largely been limited to the 1–2 years after initiation of treatment. They have generally reported substantial improvements in the indicators they measured in the first 6–24 months after treatment initiation. In view of the lifelong commitment that ART requires, however, it is important to know whether these improvements persist, increase, or deteriorate in the ensuing years on treatment.

We report the effect of ART over the 5 years after treatment initiation on South African adults' economic well being, using a set of indicators pertaining to symptom prevalence, ability to perform normal activities, employment and job performance, and reliance on external support. Each of these outcomes reflects the ability of ART patients to contribute to their own, their households', or society's economic activity. Our results expand upon and extend a previous, 3-year analysis [8] of one of the longest-running prospective cohorts in Africa for nonbiomedical outcomes of treatment. New results reported here include both a longer duration of follow-up (the fourth and fifth years after treatment initiation) and additional outcomes related to employment and reliance on external support. The present evaluation aims to characterize the long-term effect of ART on quality of life and economic activity.

## Methods

### Study sites and data collection

A detailed description of the study sites, sample selection, and data collection has been published elsewhere [8]. Patients were enrolled in the study from three ART clinics in South Africa: the Themba Lethu Clinic at Helen Joseph Hospital in Gauteng Province, a large, urban, public referral hospital, and two nongovernmental clinics, the Witkoppen Health and Welfare Center, a full service primary care clinic serving informal settlements in Gauteng Province, and ACTS Clinic, an HIV/AIDS clinic in rural Mpumalanga Province. All study sites followed national guidelines for HIV/AIDS care and treatment.

Between June 2005 and June 2006, patients were identified from each site at random from patients present at the clinic each day. HIV-positive adult patients who were not on ART or had initiated ART less than 6 months prior to recruitment were eligible for enrollment. Patients who provided written consent were enrolled and administered a baseline questionnaire. Follow-up interviews were administered as often as possible, when participants returned for routine clinic visits for medical consultation or to pick up medication. Interviews at all sites ended by June 2011. Patients' medical records provided information about the date of ART initiation, clinic attendance, and CD4<sup>+</sup> cell counts.

The questionnaire designed for this study focused on self-reported health condition and engagement in economic activities. Outcomes reported here include two specific symptom indicators, four outcomes relating to employment and normal activities, and two outcomes related to reliance on external assistance in daily life. The symptoms were any bodily pain or headache and feeling tired or fatigued last week. We asked if participants were able to perform their normal primary activity during the last 5-day work week, and, if not able to perform that activity, for how many days in the previous week they were unable to do so. Patients were also asked about their employment status and, if employed, performance at work. The first measure of external assistance was receipt of the South African Government's disability grant. Disability grants are typically approved for HIV patients who are judged too sick to work and/or have a CD4<sup>+</sup> cell count below the threshold for starting ART. Successful ART should thus reduce the proportion of HIV patients who are eligible for grants. Finally, patients were asked whether they relied on someone else to take care of them, an indicator of the multiplier effect of illness on patients' families.

The study was approved by the ethics committees of Boston University and the University of the Witwatersrand. Written informed consent was provided by all study patients.

### Statistical analysis

Interviews conducted between 3 months prior to ART initiation and 63 months after ART initiation were included in the analysis. Time on ART at each interview was calculated from the date of ART initiation provided by the patients' medical records. Time on ART extended from 90 days (3 months) pre-initiation to 1980 days (5.5 years) post-ART initiation. Time intervals were categorized as 90 days pre-ART, 0–30 days on ART, 31–90 days on ART, and 90-day intervals during the rest of the first year on ART, followed by 180-day intervals through 5.5 years. The shorter time periods around ART initiation are intended to detect any rapid changes immediately after initiation.

All outcome variables other than the number of days unable to perform normal activities in the previous week were dichotomous and modeled with a logistic regression; number of days unable to perform usual activities was modeled with a linear regression. Regression models included dummy variables for time category on ART, sex, age group (18–29 years, 30–39 years, 40–49 years and 50 years old or more), CD4<sup>+</sup> cell count category at ART initiation, and CD4<sup>+</sup> cell count category closest to interview date. For the employment status and disability grant outcomes, a 6-month lagged estimate of CD4<sup>+</sup> cell count was used rather than the CD4<sup>+</sup> cell count closest to interview. CD4<sup>+</sup> cell counts were categorized as 0–49 cells/ $\mu$ l, 50–99 cells/ $\mu$ l, 100–199 cells/ $\mu$ l, and 200 cells/ $\mu$ l or greater. All regression

analyses were implemented using generalized estimating equation methods [in SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) and STATA version 11.2 (STATA Corp., College Station, Texas, USA)], with population-averaged models with robust standard errors accounting for the individual correlation across multiple observations over time. Odds ratios and associated probabilities for the logistic regression models are reported, with the probabilities and confidence intervals estimated using the margins command in STATA. For all outcomes, the reference case reported is for a female age 30–39 years, at 0–30 days on ART, with a CD4<sup>+</sup> cell count category of 100–199 cells/ $\mu$ l. To highlight long-term changes during the fourth and fifth years on treatment, a secondary analysis estimates the change in the probability of experiencing each outcome between month 36 and month 63, with months 33–36 as the reference case.

Because many patients in our cohort stopped receiving treatment at the study clinics over our 5-year period of observation, we assessed the extent to which clinic attrition affected the generalizability of our findings. Clinic attrition included death, transferring to another treatment facility, and site loss to follow-up (>3 months late for last scheduled appointment). We distinguish clinic attrition from study loss to follow-up, defined as making a visit to the clinic at least 6 months after the last completed interview. Average CD4<sup>+</sup> cell counts and clinic attrition from the study cohort and from the full population of patients initiating ART at Themba Lethu Clinic, our largest study site, were compared to determine if attrition led to differences between the study sample and the overall population of ART patients.

## Results

### Cohort characteristics and attrition

A total of 1065 patients were enrolled in the study in 2005–2006. Of these, 174 patients had no record of

beginning ART before June 2011 and 12 patients only had interviews more than 90 days prior to ART initiation. The remaining 879 patients were included in the cohort for analysis of outcomes. Baseline and 48-month characteristics of these patients are presented in Table 1, with further details available in an earlier publication [8]. Each of the 879 patients included in the analysis was interviewed a mean of 7.6 times over the course of the study, with a median interval between interviews of 185 days.

Clinic attrition over the course of the 5 years of study follow-up was 47% of the original cohort of 1065 patients. The study cohort and the overall treated population at our largest study site, Themba Lethu Clinic, experienced a steady and similar increase in CD4<sup>+</sup> cell count over time on ART, with overlapping 95% confidence intervals (not shown). Similarly, clinic attrition from our cohort was not greater than overall attrition at Themba Lethu Clinic, where a separate analysis found that average attrition among all patients initiated on treatment between 2004 and 2010 was 47% [9]. Neither the immunological status nor retention in care of our study cohort thus differed from that of all patients remaining in care, either at baseline or after 5 years on treatment.

Due to missing data on CD4<sup>+</sup> cell count values, 19% of interviews were excluded from the adjusted models. Model estimates were unchanged when missing CD4<sup>+</sup> values were imputed using multiple imputation.

### Symptom outcomes

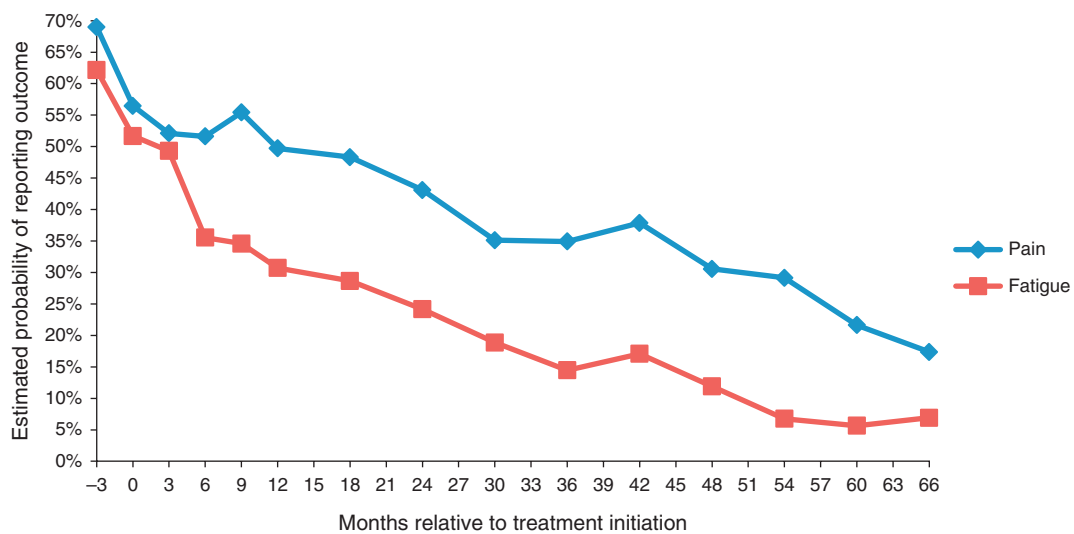
As illustrated in Fig. 1 and detailed in Table S1, <http://links.lww.com/QAD/A407>, reported pain and fatigue in the previous week decreased continuously over the full 5-year period after ART initiation. Nausea and skin problems showed a similar pattern of decline (not shown).

All decreases in symptoms at the end of year 5 on ART were statistically significant compared to the first month

**Table 1. Characteristics of study patients at 0 and 48 months after antiretroviral therapy initiation.**

Variable	Value at 0 months (baseline) ( <i>n</i> = 879)	Value at 48 months ( <i>n</i> = 547)
Female (%)	683 (78%)	443 (81%)
Age in years (%)		
18–29	250 (28%)	144 (26%)
30–39	411 (47%)	280 (51%)
40–49	165 (19%)	95 (17%)
>49	52 (6%)	27 (5%)
Missing	1 (0%)	1 (0%)
Median CD4 <sup>+</sup> cell count (cells/ $\mu$ l) [IQR] <sup>a</sup>	104 [35–159]	472 [353–639]
Primary activity when feeling well enough to perform normal activities ( <i>n</i> (%))		
Employed in formal sector	224 (26%)	196 (36%)
Work in informal sector or self employed	172 (20%)	112 (20%)
Unemployed, seeking work	207 (24%)	130 (24%)
Housework or family care (unpaid)	229 (26%)	91 (17%)
Other (studying, retired, leisure, service, missing)	47 (5%)	18 (3%)

<sup>a</sup>CD4<sup>+</sup> cell count test result closest in time to specified period (0 or 48 months after initiation).



**Fig. 1. Probability of experiencing pain or fatigue last week, by time on antiretroviral therapy (ART). Results shown are for a female patient age 30–39.**

on ART. Notably, the decline in symptom prevalence between the end of year 3 and the end of year 5 was also significant, confirming that while the sharpest drop in symptoms occurs during the first 2 years, patient condition continues to improve even in the fourth and fifth years, even when controlling for CD4<sup>+</sup> cell count. Patients' reports of experiencing pain in the previous week, for example, decreased from 69% in the months preceding ART initiation to 35% ( $P < 0.001$ ) after 3 years on ART and then fell further, to 17% ( $P < 0.001$ ), after 5 years on ART. Sixty-two percent of patients reported experiencing fatigue in the previous week before starting ART; by the end of year 5 on ART, only 7% ( $P < 0.001$ ) of patients reported it. Men were less likely to report bodily pain or fatigue than women, and older patients were more likely to report bodily pain than younger patients. Lower current CD4<sup>+</sup> cell count was associated with increased odds of reporting bodily pain and fatigue, although the effect was not statistically significant for fatigue.

### Normal activities and employment

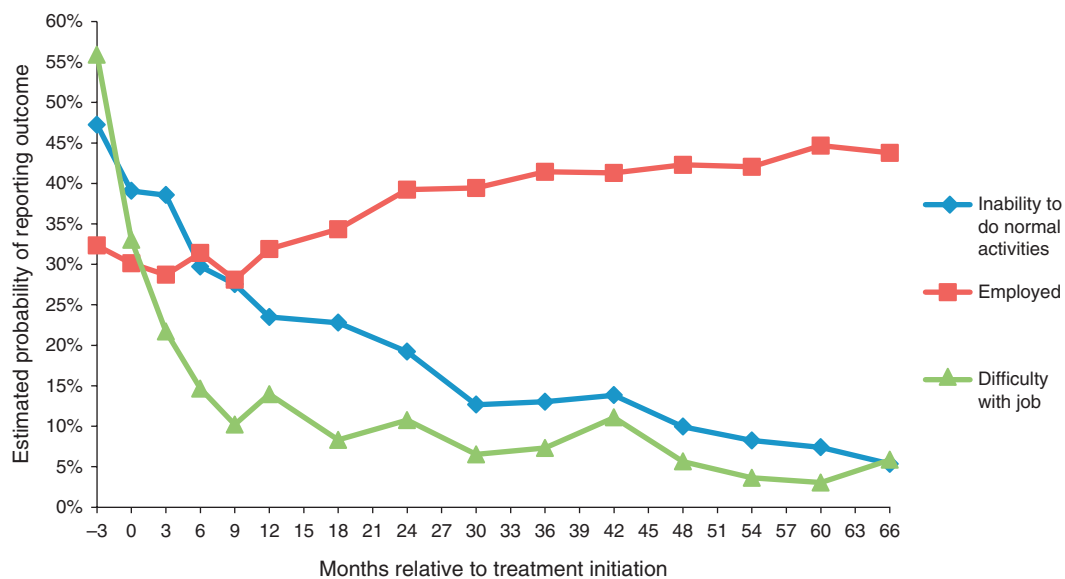
Figure 2 and Supplemental Table S2, <http://links.lww.com/QAD/A407> report results for having a job at the time of the interview, difficulty with job performance, ability to perform normal activities during the previous 5-day workweek, and number of days unable to perform normal activities over the previous 5-day workweek, among those who reported inability. The probability of being unable to perform normal activities in the previous week diminished continuously throughout the 5 years of follow-up, from 47% in the 3 months prior to initiation, to 13% ( $P < 0.001$ ) after 3 years on ART, to just 5% by the end of 5 years. Among those who reported impairment, the number of days unable to perform normal activities in the last 5-day workweek decreased from 3.7 days in the

month prior to ART initiation to 1.9 days after 5 years on ART ( $P = 0.03$ ). Both the ability to perform normal activities and the number of days unable showed statistically significant improvements from year 3 to year 5 on ART.

The probability of having a job at the time of the interview (current employment) increased most sharply between 6 and 24 months on ART but showed continued steady improvement through year 5. After 5 years on ART, 44% of patients reported being currently employed, a substantial increase from the 32% reporting employment during the first month on ART ( $P < 0.000$ ). Although the percentage of patients with a job increased between year 3 (41%) and year 5 (44%), the difference was not statistically significant. Patients with a CD4<sup>+</sup> cell count at least 200 cells/ $\mu$ l 6 months prior to the interview were significantly more likely to be employed at the time of the interview.

Among patients who were employed at the time of interview, difficulty with job performance decreased significantly with duration on ART. During the 3 months prior to ART initiation, job difficulty was reported among 56% of respondents. Job difficulty dropped precipitously during the first year on ART. By the end of 3 years on ART, difficulty with job performance was reported among 7% of respondents ( $P < 0.001$ ), falling further to 6% by the end of year 5 (difference not statistically significant).

To explore further the observed increase in employment, we examined employment outcomes among study patients who had at least 4 years of follow-up. As would be expected, much of the improvement in overall employment came from patients who said they were

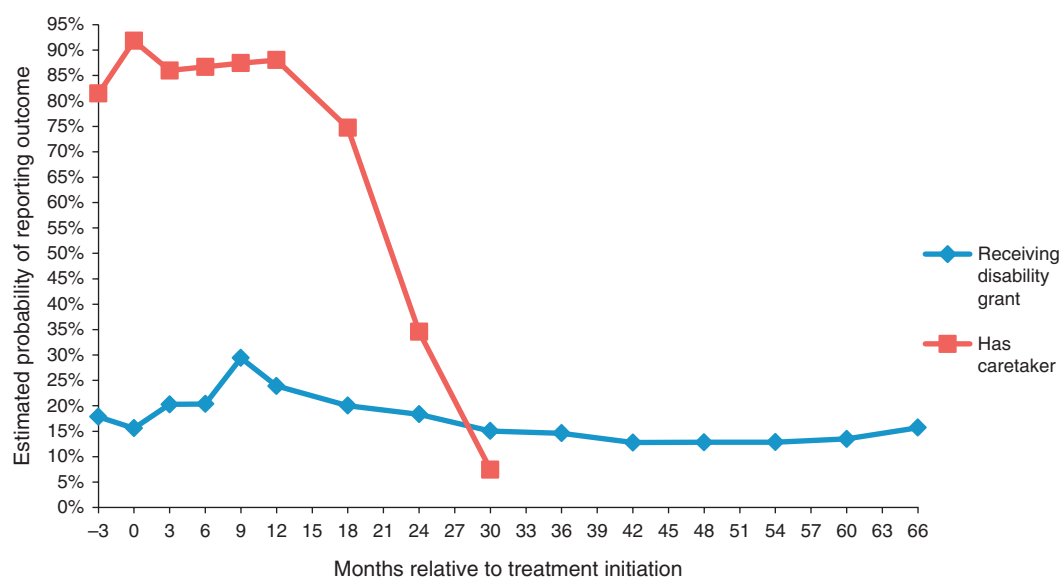


**Fig. 2. Probability of being unable to perform normal activities, having a job, and having difficulty performing the job, by time on antiretroviral therapy (ART). Results shown are for a female patient age 30–39.**

unemployed and looking for work at baseline ( $n=248$ ) and had found jobs by the time of their last interview ( $n=96$ , 39% of those looking for work at baseline). There was also substantial improvement, however, among those who said they were unemployed but not looking for work at baseline ( $n=96$ ). By their last interview, 30% ( $n=29$ ) of these patients had found jobs and 53% ( $n=51$ ) were now looking for work. It thus appears that many of those who had not previously been seeking employment joined the active labor force within 5 years of initiating ART.

### Reliance on external support

Patients were asked whether they were currently receiving a disability grant from the government and whether they relied on another person to take care of them (Fig. 3 and Table S3, <http://links.lww.com/QAD/A407>). Prior to treatment initiation, 18% of patients reported receiving a grant. This proportion then increased over the first year on treatment to a high of 29%, before gradually declining again back to a low of roughly 13% after 4–5 years. The increase in grant receipt in the first year may reflect the fact that new ART patients



**Fig. 3. Probability of receiving a disability grant and of relying on a caretaker, by time on antiretroviral therapy (ART). Results shown are for a female patient age 30–39.**

are offered access to social services such as the disability grant when they enroll in the treatment program, while the decrease in later years is likely to reflect improving health over time on treatment.

A large proportion of patients reported having a caretaker in the 3 months prior to ART initiation (81%) and in the year following the beginning of treatment. After 1.5 years on ART the need for caretakers declined significantly. After 2.5 years on ART less than 1% of patients reported having a caretaker, and as a result the model could not be estimated past 2.5 years on ART. An increased CD4<sup>+</sup> cell count at both ART initiation and over time was significantly associated with decreased odds of needing a caretaker. Caretakers were most commonly the patient's spouse or partner (33.4%), mother or father (23.3%), or sister or brother (17.9%).

All model estimates were also estimated using inverse probability weighting to adjust for study loss to follow-up, defined as making a visit to the clinic at least 6 months after the last completed interview. Study loss to follow up was just 3.8% of the original cohort, and the analyses (not shown) indicated that it did not affect results significantly.

## Discussion

In high HIV prevalence countries that are aiming for universal access to ART, a substantial proportion of working-aged adults will ultimately be dependent on lifelong treatment. In South Africa, where adult HIV prevalence is estimated at 16.6% and ART coverage at 52% of those eligible – almost 2 million people – nearly 5% of all adults are already on ART, based on published population and treatment coverage estimates [10,11]. In view of the effectiveness of ART in prolonging survival, new ART initiation guidelines that expand the treatment-eligible population, and the national goal of treating at least 80% of those eligible, this proportion can be expected to rise steadily over the coming years, as will the share of ART patients who have been on treatment for more than just 1 or 2 years. It is thus of critical importance to patients, their households, their employers, and society as a whole that ART do more than simply delay mortality: it must produce people who feel healthy enough to lead normal lives, support their families, and participate in the economic and social life of their communities.

The data presented here suggest that, for HIV-infected adults who remain on ART, the benefits of treatment for economic engagement are large and sustained and continue to increase steadily over at least the first 5 years on treatment. Equally important, and reflecting the value of long-term follow-up, almost all outcomes assessed continued to improve even in the fourth and fifth year

after starting treatment, with significant differences between year 3 and year 5. We found, for example, that pain and headache, which nearly three-quarters of the study cohort reported during the period just before and after starting ART, was experienced by only about 17% after 5 years on treatment, with steady decline from ART initiation all the way to the end of our period of observation at month 66. Similarly, inability to perform normal activities – arguably the most important indicator of the effect of illness on patients' lives – fell from 47% of the cohort before starting treatment to a nearly negligible 5% by 5 years later. Employment, in turn, climbed from 32 to 44%. The official unemployment rate in South Africa remained roughly stable throughout the study period, varying only slightly from an average of 24% [12]. We thus do not attribute our patients' reported increase in employment to a secular reduction in unemployment rates during the study period, but rather to changes in the patients' own circumstances. Patients who had jobs reported substantially less difficulty performing their jobs as their duration on ART lengthened. Reliance on external support also fell steadily after the first year on ART, with fewer patients receiving disability grants or needing caretakers as time progressed.

Our findings are consistent with those reported by the shorter studies cited earlier, which generally found large improvements up to the first 24 months after treatment initiation. Of the four other studies we found that report beyond 2 years, all observed large improvements in their chosen outcomes: activities of daily living in South Africa [13], physical health status in Uganda [14], workplace absenteeism in Botswana [15], and labor force participation and hours worked in Kenya [16]. Differences in survey instruments and reporting formats make it difficult to compare their results to ours directly, but taken together these studies suggest that the improvements we observed are not unique to our study population or the specific outcomes we assessed.

Although our enrolled cohort was a representative sample of patients at our study sites, the results we report are for patients retained in care at the study clinics, attending clinic visits, and presumably remaining adherent to therapy. Achieving the benefits we show is thus conditional on staying in care. A large proportion of our original cohort did not remain in care at the study sites for the full 5-year duration of follow up, and it is likely that for at least some individuals, reasons for attrition and study outcomes were related. This may include patients who responded poorly or were nonadherent to treatment, and thus would probably have reported less improvement than did those remaining in the study. Clinic attrition may also include some subjects who responded well to treatment and stopped attending the clinic because they no longer felt sick, got jobs and could not keep appointments during working hours, or relocated for work; these subjects may have

reported better outcomes than did those who remained in the study, at least in the near term. Regardless of the reasons for attrition, it is important to interpret our findings as conditional on staying on ART.

The other main limitations of this study are those that are common to observational research in routine clinical settings everywhere. In particular, because patients visited the study clinics on irregular schedules and did not participate in interviews at every visit – either by patient preference or because they were not found by a study interviewer before the end of the visit – we often had long and irregular gaps between interviews, resulting in an unbalanced data set with different numbers of observations among patients. In addition, our results are based on self-reported data and likely reflect some recall error and/or strategic answering of questions.

Although the limitations mentioned above should be kept in mind in interpreting our results, none seems sufficient to call into doubt the core finding of our study: patients who remain on ART experience large benefits in their ability to engage in economic activities, and these benefits are sustained and increase over at least the first 5 years on treatment. By the end of the fifth year, the proportion of patients reporting negative outcomes such as an inability to perform normal activities is sufficiently low that it is reasonable to conclude that ART patients may be indistinguishable from the general HIV-negative population. Some negative outcomes persist – the probability of experiencing pain last week remained around 17% even after 5 years – and even the patients with the most positive responses continue to be burdened by daily adherence to medications, regular clinic visits, and all of the other practical, emotional, and financial consequences of HIV infection. The results of this study suggest, however, that for most patients, ART offers the possibility of a normal, healthy life over a number of years. Through their effect on productivity and employment, the benefits to individual patients will translate, in turn, into social and economic development gains for societies as a whole.

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Authors' contributions: S.R. and I.S. conceived of the study and designed the protocol. B.L., J.R., and O.G. designed and conducted the analysis. C.M. and A.B. contributed to the analysis. All authors contributed to interpreting the results. J.R. and S.R. drafted the article. All authors edited the article and approved the final article.

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## Conflicts of interest

The authors report no conflicts of interest pertaining to this manuscript. I.S. is the Managing Director of Right to Care, a South African nongovernmental organization that supports the delivery of HIV treatment at the study sites.

Partial results of the current analysis were presented at the XIX International AIDS Conference, Washington DC, July 22–27, 2012 (Poster MOPE760).

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