Life expectancy among HIV-positive patients in Rwanda: a retrospective observational cohort study

Sabin Nsanzimana, Eric Remera, Steve Kanters, Keith Chan, Jamie I Forrest, Nathan Ford, Jeanine Condo, Agnes Binagwaho, Edward J Mills

Summary

Background **Rwanda has achieved substantial progress in scaling up of antiretroviral therapy. We aimed to assess the effect of increased access to antiretroviral therapy on life expectancy among HIV-positive patients in two distinct periods of lower and higher antiretroviral therapy coverage (1997–2007 and 2008–11).**

Methods **In a retrospective observational cohort study, we collected clinical and demographic data for all HIV-positive patients enrolled in care at 110 health facilities across all five provinces of Rwanda. We included patients aged 15 years or older with a known enrolment date between 1997 and 2014. We constructed abridged life tables from age-specific mortality rates and life expectancy stratified by sex, CD4 cell count, and WHO disease stage at enrolment in care and initiation of antiretroviral therapy.**

Findings **We included 72 061 patients in this study, contributing 213 983 person-years of follow-up. The crude mortality rate was 33·4 deaths per 1000 person-years (95% CI 32·7–34·2). Life expectancy for the overall cohort was 25·6 additional years (95% CI 25·1–26·1) at 20 years of age and 23·3 additional years (95% CI 22·9–23·7) at 35 years of age. Life expectancy at 20 years of age in the period of 1997–2007 was 20·4 additional years (95% CI 19·5–21·3); for the period of 2008–11, life expectancy had increased to 25·6 additional years (95% CI 24·8–26·4). Individuals enrolling in care with CD4 cell counts of 500 cells per μL or more, and with WHO disease stage I, had the highest life expectancies.**

Interpretation **This study adds to the growing body of evidence showing the benefit to HIV-positive patients of early enrolment in care and initiation of antiretroviral therapy.**

Funding **Bill & Melinda Gates Foundation.**

Lancet Glob Health 2015; 3: e169–77

See **Comment** page e122

Institute of HIV Disease Prevention and Control, Rwanda Biomedical Centre, Kigali, Rwanda (S Nsanzimana MD, E Remera MSc); **Global Evaluative Sciences, Vancouver, BC, Canada** (S Kanters MSc, K Chan MSc, J I Forrest MPH, E J Mills PhD); **School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada** (S Kanters, J I Forrest); **Centre for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa** (N Ford PhD); **School of Public Health, College of Medicine & Health Sciences, University of Rwanda, Kigali, Rwanda** (E J Mills, J Condo MD); **Ministry of Health, Government of Rwanda, Kigali, Rwanda** (A Binagwaho MD); **and Harvard Medical School, Boston, MA, USA** (A Binagwaho)

Correspondence to: Dr Edward J Mills, Global Evaluative Sciences, Vancouver, BC, V6H 3Y4, Canada **emills@geshealth.com**

Introduction

Before the global scale-up of antiretroviral therapy, data from many regions of the world consistently showed a strong negative association between adult HIV prevalence and life expectancy.[1] Because access to antiretroviral therapy has greatly improved in many regions of the world, this negative association is dwindling. Reductions in morbidity and mortality associated with antiretroviral therapy have translated into increased life expectancy and decreased years of life lost.[2,3] A collaborative cohort analysis by the Antiretroviral Therapy Cohort Collaboration[2] showed that patients in Europe and North America who started antiretroviral therapy at age 20 years between 2003 and 2005 could expect to live an additional 49 years after initiation of antiretroviral therapy, an overall increase in life expectancy of 81% since 1996. Findings from a similar analysis of data from Uganda showed that a 20-year-old individual starting antiretroviral therapy was projected an additional 26 years, increasing according to CD4 status at antiretroviral therapy initiation.[3]

Rwanda has recently made remarkable progress in expansion of access to antiretroviral therapy.[4] The country was recently singled out by the UN as one of the few to have achieved near-universal access to treatment in 2012, according to previous eligibility criteria for antiretroviral therapy (ie, 350 CD4 cells per μL or less).[5] Rwanda first achieved universal coverage in 2008, with 80% of HIV-positive patients receiving antiretroviral therapy under a CD4 eligibility criterion of 200 cells per μL or less, and then again in 2010, a year after the guidelines changed the eligibility criteria to 350 cells per μL or less. The government is now working to implement a new strategy to both raise the CD4 threshold for antiretroviral therapy initiation to 500 cells per μL or less and provide immediate antiretroviral therapy for key populations, including pregnant women through option B+ (in which all pregnant and breastfeeding women are eligible for lifelong antiretroviral therapy irrespective of CD4 cell count), HIV-positive patients with comorbidities, men who have sex with men, and female sex workers.[6,7]

This achievement makes the investigation of the effect of HIV treatment scale-up on life expectancy among HIV-positive patients in Rwanda particularly interesting. Two distinct periods of antiretroviral therapy coverage can be retrospectively assessed: lower coverage (1997–2007), and higher coverage (2008 onwards). In an observational cohort study we aimed to evaluate life expectancy of HIV-positive people in Rwanda, first by constructing life tables among HIV-positive Rwandans

enrolled in care, and second by comparing these results across the two periods of lower and higher coverage of antiretroviral therapy.

	Overall	1997–2007	2008–11
Number of patients	72 061	38 546	33 515
Age, years	35 (28–42)	36 (29–43)	34 (27–42)
15–19	2028 (2·8%)	808 (2·1%)	1220 (3·6%)
20–24	7173 (10·0%)	2925 (7·6%)	4248 (12·7%)
25–29	12 146 (16·9%)	5909 (15·3%)	6237 (18·6%)
30–34	13 898 (19·3%)	7767 (20·1%)	6131 (18·3%)
35–39	12 939 (18·0%)	7537 (19·6%)	5402 (16·1%)
40–44	9559 (13·3%)	5788 (15·0%)	3771 (11·3%)
45–49	6763 (9·4%)	3920 (10·2%)	2843 (8·5%)
50–54	3892 (5·4%)	2072 (5·4%)	1820 (5·4%)
55–59	1908 (2·6%)	969 (2·5%)	939 (2·8%)
60–64	874 (1·2%)	429 (1·1%)	445 (1·3%)
≥65	881 (1·2%)	422 (1·1%)	459 (1·4%)
Sex			
Men	26 055 (36·2%)	12 953 (33·6%)	13 102 (39·1%)
Women	46 006 (63·8%)	25 593 (66·4%)	20 413 (60·9%)
Marriage status			
Married or living with partner	34 508 (47·9%)	16 547 (42·9%)	17 961 (53·6%)
Divorced or widowed	16 065 (22·3%)	9632 (25·0%)	6433 (19·2%)
Single	8021 (11·1%)	2787 (7·2%)	5234 (15·6%)
Other or unknown	13 467 (18·7%)	9580 (24·9%)	3887 (11·6%)
Mode of diagnosis			
Voluntary counselling and testing	45 897 (63·7%)	25 508 (66·2%)	20 389 (60·8%)
Prevention of mother-to-child transmission	12 880 (17·9%)	6557 (17·0%)	6323 (18·9%)
Provider-initiated testing or other	13 284 (18·4%)	6481 (16·8%)	6803 (20·3%)
CD4 cell count at linkage	394 (210–636)	348 (183–606)	436 (253–663)
<50 cells per μL	3181 (4·4%)	1979 (5·1%)	1202 (3·6%)
50–99 cells per μL	3987 (5·5%)	2510 (6·5%)	1477 (4·4%)
100–199 cells per μL	9645 (13·4%)	6112 (15·9%)	3533 (10·5%)
200–349 cells per μL	15 170 (21·1%)	8493 (22·0%)	6677 (19·9%)
350–499 cells per μL	12 406 (17·2%)	6074 (15·8%)	6332 (18·9%)
≥500 cells per μL	27 005 (37·5%)	12 922 (33·5%)	14 083 (42·0%)
Unknown	667 (0·9%)	456 (1·2%)	211 (0·6%)
WHO disease stage			
I	34 281 (47·6%)	14 798 (38·4%)	19 483 (58·1%)
II	18 113 (25·1%)	10 514 (27·3%)	7599 (22·7%)
III	15 525 (21·5%)	10 486 (27·2%)	5039 (15·0%)
IV	1721 (2·4%)	1068 (2·8%)	653 (1·9%)
Unknown	2421 (3·4%)	1680 (4·4%)	741 (2·2%)
Tuberculosis status at baseline			
Negative	53 675 (74·5%)	26 239 (68·1%)	27 436 (81·9%)
Positive	12 265 (17·0%)	7077 (18·4%)	5188 (15·5%)
Unknown	6121 (8·5%)	5230 (13·6%)	891 (2·7%)
Cumulative loss to follow-up			
Still in follow-up	65 027 (90·2%)	34 392 (89·2%)	30 635 (91·4%)
Lost to follow-up	7034 (9·8%)	4154 (10·8%)	2880 (8·6%)

(Table 1 continues on next page)

Methods

Study design and participants

In an observational cohort study, we used data from the Rwanda Biomedical Center, which oversees surveillance of HIV/AIDS and scale-up of antiretroviral therapy within the country. The national treatment programme in Rwanda consists of monthly follow-up visits with health-care professionals for treatment pickup, CD4 measurements every 6 months, and annual viral load monitoring, beginning 1 year after antiretroviral therapy initiation. This study used data from the IQ Charts database, an electronic medical record system that captures demographic and clinical characteristics at enrolment and longitudinal HIV-specific clinical factors and vital statistics. This database began collecting data prospectively in 2004 and includes data obtained retrospectively for 1997–2003. The IQ Charts database covers 110 health facilities across all five provinces of Rwanda, providing a nationally representative sample of 25% of facilities providing antiretroviral therapy over the study period.

For this study, we included all patients within these 110 health facilities aged 15 years or older with a known enrolment date, follow-up time (ie, did not enter and exit the programme on the same day), and who enrolled in care between 1997 and 2011. We defined enrolment in care as a patient having received a positive test result and subsequently registered for the first time in the monitoring and surveillance database. At enrolment a patient could be retained in the pre-antiretroviral therapy phase or begin antiretroviral therapy if clinically indicated. The IQ Charts database includes 87 613 patients. As of 2013, roughly 176 000 Rwandans were retained in the national HIV care programme. Selection within this database is based on health facility rather than individuals. Large health facilities and rural health facilities have slightly higher probabilities of inclusion, but how this factor affects patient characteristics is unknown.

The routinely collected programme data analysed for this study are maintained by the Rwanda Biomedical Centre, Division of HIV/AIDS, STIs and Other Blood Borne Infections; the ethical procedures for the collection of these data are governed by the Medical Research Council of Rwanda. Secondary analyses of routinely collected data are exempt from ethics approval when led by the Rwanda Biomedical Centre.

Procedures

We measured follow-up time in two ways: first, as time from enrolment into care to study exit due to end of study period, death, loss to follow-up, or transfer out to facilities not participating in IQ chart surveillance; and second, as time from antiretroviral therapy initiation to study exit. Mortality data were ascertained in health facilities and through home follow-ups. For the purpose of this analysis, loss to follow-up was defined as missing three

consecutive months of health-care appointments and treatment pickups. Unsupervised treatment interruptions were not accounted for and were not classified as loss to follow-up at start of the treatment interruption. The demographic variables we used in this analysis included sex, age (categorised in 5-year categories for 15–64 years, and ≥65 years), and marital status. Clinical variables at enrolment included CD4 cell count status (<50, 50–99, 100–199, 200–349, 350–499, and ≥500 cells per μL) and WHO disease stage (I, II, III, IV, and not reported), and route of diagnosis. We chose CD4 cell count categories based on levels known to be associated with increased risk of acquiring opportunistic infections, and levels used for antiretroviral therapy guidelines during the past decade. Route of diagnosis included voluntary counselling and testing, through prevention of mother-to-child transmission services, and through other means (such as provider-initiated testing and counselling, which began in 2010, hospital admissions, and testing through comorbidities). Finally, we divided the study population into two periods, 1997–2007 and 2008–11, to account for changes in antiretroviral therapy guidelines that have taken place in Rwanda.

	Overall	1997–2007	2008–11
(Continued from previous page)			
Death after enrolment			
No	68 144 (94·6%)	35 918 (93·2%)	32 226 (96·2%)
Yes	3917 (5·4%)	2628 (6·8%)	1289 (3·8%)
Years of follow-up	2·6 (1·2–4·5)	4·4 (2·1–5·6)	1·8 (0·9–2·8)
Antiretroviral therapy initiated during follow-up			
No	30 968 (43·0%)	14 092 (36·6%)	16 876 (50·4%)
Yes	41 093 (57·0%)	24 454 (63·4%)	16 639 (49·6%)
Years since starting antiretroviral therapy	2·6 (1·2–4·3)	3·9 (1·9–5·3)	1·6 (0·8–2·5)

Data are n (%) or median (IQR).

Table 1: **Baseline characteristics of patients included in study, stratified by period of antiretroviral therapy coverage (1997–2007 and 2008–11)**

Statistical analysis

We assessed whether mortality differed between the two periods specified. Mortality rates were expressed as number of deaths per 1000 person-years and stratified by age category, sex, and baseline CD4 cell count and WHO disease stage.

We constructed abridged life tables from age-specific mortality rates using methods established by Chiang.[8] Life expectancy estimated from this type of life table is viewed as depicting the lifetime mortality experience of a single cohort of people who are subject to the mortality schedules on which the table is constructed. Therefore, life expectancy at an exact age is an indicator measuring the average number of additional years that will be lived by a person after that age, according to the age-specific mortality rates for all deaths during the study period. Because a very large population and number of deaths are needed to overcome variations in mortality when constructing a complete life table by single years, we used abridged life tables by aggregated age groups, which describe the effect of mortality on a sample of people if they were subjected to the mortality rates in the observed calendar periods.[9] Complete details about these methods are provided in the appendix. Life expectancy was reported by age group and stratified by sex, CD4 cell count, and WHO disease stage at enrolment in care.

Central to the estimation of life expectancy through life tables is the estimation of mortality rates. Loss to follow-up is known to account for a proportion of mortality among patients enrolled into care throughout sub-Saharan Africa.[10] At present, no studies tracing individuals lost to follow-up among the general HIV-positive population of Rwanda have been reported. Approaches have been put forward to adjust for misclassification of mortality as loss to follow-up, but such approaches are based on estimates derived outside of Rwanda and exclusively among patients who had started antiretroviral therapy.[11,12] By contrast, a substantial number of people lost to follow-up in our study were young and healthy. Just under half (46·2%) of all patients lost to follow-up could be classified as at high risk of mortality because they met at least one of the following conditions: CD4 count less than 200 cells per μL, positive tuberculosis screen, WHO disease stage of III or IV, age 50 years or older, or an unreported tuberculosis screen or WHO disease stage. We estimated propensity scores for mortality using logistic regression with all available demographic and clinical variables. Individuals with the highest 46·2% propensities for mortality were recorded as deaths. In this manner, we avoided equally distributing the additional 46·2% of deaths through loss to follow-up among young and old or healthy and sick individuals. These mortality corrections for loss to follow-up were done separately for both time of enrolment and time of antiretroviral therapy initiation to study exit and used throughout the analyses. A sensitivity analysis with no adjustments for loss to follow-up is included in the appendix.

We also adjusted known underestimates of mortality in the oldest age group (age ≥65 years). Occasionally, the unbounded nature of the category led to selection bias. The distribution of age among people living with HIV/AIDS and aged 65 years or older tends to be lower than the distribution of age among the general population within this age category, which in turn can lead to biased estimates of mortality. Within each stratified life expectancy analysis, we adjusted the mortality rate in the healthiest stratum with the lowest mortality rate to be equal to that of the general population for the 65 years and older age category and added the resulting constant to all other strata. No adjustments were made if the mortality rate for the 65 years and older age category was greater than in the general population.

See Online for appendix

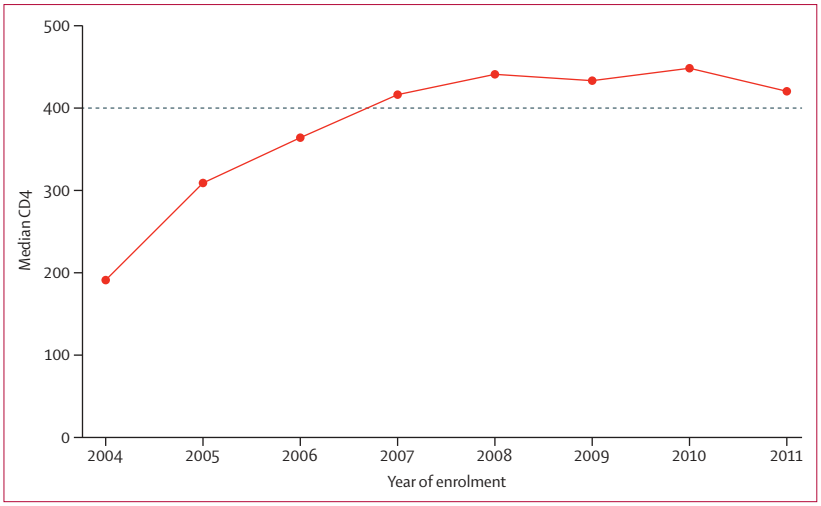

Figure 1: **Median CD4 cell count at enrolment in care by year of enrolment**
2004 contains all pre-2003 participants because of a small number of enrollees.

	Number of deaths	Person-years	Deaths per 1000 person-years (95% CI)
Overall	7153	213 983·4	33·4 (32·7–34·2)
Period of antiretroviral therapy coverage*			
1997–2007	3872	94 129·6	41·1 (39·8–42·5)
2008–11	2201	58 814·3	37·4 (35·9–39·0)
Sex			
Men	3335	72 500·0	46·0 (44·5–47·6)
Women	3818	141 483·5	27·0 (26·1–27·9)
CD4 cell count at enrolment (cells per μL)			
<50	889	8986·7	98·9 (92·5–105·6)
50–99	690	12 974·0	53·2 (49·3–57·3)
100–199	1204	32 660·6	36·9 (34·8–39·0)
200–349	1438	47 521·5	30·3 (28·7–31·9)
350–499	1063	35 193·2	30·2 (28·4–32·1)
≥500	1791	74 494·0	24·0 (22·9–25·2)
WHO Disease Stage			
I	1380	95 758·9	14·4 (13·7–15·2)
II	1562	57 876·0	27·0 (25·7–28·4)
III	2683	51 987·1	51·6 (49·7–53·6)
IV	513	5088·6	100·8 (92·3–109·9)

*In view of the difference in possible follow-up times, we restricted this variable to mortality within the first 36 months to reduce survival bias.

Table 2: **Crude mortality rates among HIV-positive patients**

Potential years of life lost up to the age of 65 years, was used to assess the effect of HIV on premature mortality. The potential years of life lost estimates the average years a person or group would have lived if they had not died prematurely. We calculated these values by multiplying the total number of deaths in each 5-year age group by the average number of years remaining in that age group, up to age 65 years. Potential years of life lost were expressed per 1000 people for ages 14–64 years.[13] We stratified values by sex, WHO disease stage, and CD4 cell count at enrolment.

All significance tests were two sided, and p values of less than 0·05 were classified as statistically significant. All analyses were done with SAS software, version 9.3, R version 3.02, and Microsoft Excel 2013.

Role of the funding source

The funders had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the report. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the final decision to submit for publication.

Results

Our analyses were based on 72 061 patients from the IQ Charts database aged 15 years or older who enrolled in care in Rwanda between 1997 and 2011, contributing a total of 213 983 person-years of follow-up. Table 1 shows baseline characteristics for patients who enrolled in care overall and in two periods of antiretroviral therapy access in Rwanda. Median CD4 cell count at enrolment increased from 348 cells per μL (IQR 183–606) in the period 1997–2007 to 436 cells per μL (IQR 253–663) in the period 2008–11, resulting from a growth in capacity to deliver better care for people living with HIV. Similarly, median CD4 cell count at time of enrolment in care by year of enrolment showed an increase between the two periods (figure 1). Cumulative loss to follow-up was low (7034 individuals, 9·8%).

For the overall cohort, the crude mortality rate was 33·4 deaths per 1000 person-years (95% CI 32·7–34·2) and the potential years of life lost was 851·2 years per 1000 people (95% CI 847·3–855·1). Mortality rates are presented in table 2. For both periods, we restricted mortality analyses to the first 3 years of follow-up to reduce survivor bias (risk of mortality decreases over time in care, so unequal follow-up would bias comparisons). The 3 year mortality rate was significantly decreased in the period of 2008–11 (37·4 deaths per 1000 person-years, *vs* 41·1 deaths per 1000 person-years in 1997–2007, p<0·0001), after national guidelines for antiretroviral therapy in Rwanda raised CD4 cell count thresholds from 200 cells per μL. Women had a lower mortality rate than men, at 27·0 deaths per 1000 person-years (95% CI 26·1–27·9) compared with 46·0 deaths per 1000 person-years (95% CI 44·5–47·6), respectively. Similarly, potential years of life lost was less for women than men (2325·4 *vs* 2884·9 years per 1000 people). The mortality rate and potential years of life lost decreased substantially with increasing baseline CD4 cell count status. For patients with a baseline CD4 cell count less than 50 cells per μL, the mortality rate was 98·9 deaths per 1000 person-years (95% CI 92·5–105·6). For patients

with CD4 cell counts of 50–99 cells per µL, it was 53·2 deaths per 1000 person-years (95% CI 49·3–57·3). Mortality consistently decreased through to patients with CD4 cell counts of 500 cells per µL or higher, with an estimated mortality rate of 24·0 deaths per 1000 person-years (95% CI 22·9–25·2) in these patients (table 2). Similarly, the potential years of life lost among patients with a baseline CD4 cell count status less than 50 cells per µL was much higher (7015·9 per 1000 people) than in those with a baseline CD4 cell count of 500 cells per µL or higher (1693·6 per 1000 people).

Table 3 presents the results of the life expectancy analyses for patients with HIV enrolled in care. Life expectancy for the overall cohort was 25·6 years of additional life (95% CI 25·1–26·1) at 20 years of age and 23·3 years of additional life (95% CI 22·9–23·7) at 35 years of age. Life expectancy greatly decreased with decreasing CD4 cell count (figure 2) at enrolment and with increasing WHO disease stage (figure 3). A patient enrolled in care with WHO disease stage I at 20 years of age could expect an additional 42·5 years of life (95% CI 41·5–43·5), by contrast with a 20-year-old patient enrolled at WHO disease stage IV who could expect 8·3 additional years (95% CI 6·6–10·0). We noted a similar trend among CD4 cell count strata at enrolment. 20-year-old patients enrolling with a CD4 cell count of 500 cells per µL or more could expect an additional 32·4 years of life (95% CI 31·5–33·3), compared with 8·1 additional years of life (95% CI 6·8–9·4) for 20-year-old patients with a CD4 cell count of less than 50 cells per µL at enrolment. Men had consistently shorter life expectancy than women. Life expectancy at 20 years of age for men was 19·4 years of additional life (95% CI 18·4–20·4), compared with women at 20 years of age who had 29·5 years of additional life (95% CI 6·8–9·4). Life expectancy at 20 years of age in the period of 1997–2007

	15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	50–54 years	55–59 years	60–64 years	≥65 years*
General Rwandan life expectancy (WHO, 2002–14)[14]	44–55	40–51	36–46	32–42	29–38	27–34	24–30	21–26	18–22	15–18	NA
Overall	26·7 (25·9–27·5)	25·6 (25·1–26·1)	25·5 (25·1–25·9)	24·5 (24·1–24·9)	23·3 (22·9–23·7)	21·7 (21·3–22·1)	20·0 (19·6–20·4)	18·1 (17·6–18·6)	16·1 (15·6–16·6)	14·2 (13·8–14·7)	12·5
Men	21·9 (20·5–23·3)	19·4 (18·4–20·4)	19·9 (19·2–20·6)	19·9 (19·3–20·5)	19·8 (19·3–20·3)	18·6 (18·1–19·1)	17·6 (17·1–18·1)	16·1 (15·5–16·7)	14·6 (14·0–15·2)	13·0 (12·4–13·6)	11·5
Women	29·8 (28·6–31·0)	29·5 (28·8–30·2)	29·6 (29·0–30·2)	28·6 (28·0–29·2)	27·2 (26·6–27·8)	25·5 (24·8–26·2)	23·6 (22·9–24·3)	21·3 (20·5–22·1)	18·8 (18·0–19·6)	16·5 (15·8–17·2)	14·8
Period of antiretroviral therapy coverage											
1997–2007	21·3 (19·9–22·7)	20·4 (19·5–21·3)	20·8 (20·2–21·4)	19·9 (19·3–20·5)	19·0 (18·4–19·6)	17·6 (16·9–18·3)	16·4 (15·7–17·1)	14·6 (13·8–15·4)	12·5 (11·6–13·4)	10·3 (9·5–11·1)	8·7
2008–11	27·2 (26·0–28·4)	25·6 (24·8–26·4)	24·2 (23·5–24·9)	22·9 (22·2–23·6)	21·5 (20·7–22·3)	19·8 (19·0–20·6)	18·7 (17·8–19·6)	17·3 (16·3–18·3)	16·2 (15·1–17·3)	15·0 (13·9–16·1)	15·4
CD4 at enrolment											
<50 cells per µL	10·4 (8·5–12·3)	8·1 (6·8–9·4)	9·2 (8·3–10·1)	9·5 (8·7–10·3)	10·6 (9·8–11·4)	10·6 (9·8–11·4)	10·5 (9·6–11·4)	9·1 (8·1–10·1)	7·7 (6·6–8·8)	5·5 (4·3–6·7)	5·0
50–99 cells per µL	15·3 (12·1–18·5)	14·5 (12·2–16·8)	17·9 (16·5–19·3)	17·6 (16·5–18·7)	17·6 (16·5–18·7)	16·2 (15·0–17·4)	14·8 (13·5–16·1)	14·0 (12·6–15·4)	11·9 (10·3–13·5)	10·3 (8·6–12·0)	10·5
100–199 cells per µL	22·8 (20·4–25·2)	20·5 (18·8–22·2)	22·2 (21·1–23·3)	22·8 (21·9–23·7)	22·0 (21·2–22·8)	20·6 (19·7–21·5)	18·4 (17·5–19·3)	16·3 (15·3–17·3)	13·9 (12·9–14·9)	11·6 (10·7–12·5)	9·8
200–349 cells per µL	27·7 (25·6–29·8)	26·7 (25·4–28·0)	26·9 (26·0–27·8)	25·9 (25·1–26·7)	24·7 (23·9–25·5)	22·8 (21·9–23·7)	20·9 (20·0–21·8)	18·5 (17·6–19·4)	16·3 (15·4–17·2)	14·4 (13·6–15·2)	12·0
350–499 cells per µL	28·3 (25·9–30·7)	27·6 (26·2–29·0)	28·1 (26·9–28·5)	27·3 (26·1–28·5)	25·5 (24·3–26·7)	23·7 (22·4–25·0)	22·3 (20·9–23·7)	20·4 (18·9–21·9)	18·7 (17·2–20·2)	17·8 (16·4–19·2)	16·7
≥500 cells per µL	33·1 (31·6–34·6)	32·4 (31·5–33·3)	31·5 (30·7–32·3)	30·1 (29·3–30·9)	28·2 (27·4–29·0)	25·9 (25·1–26·7)	23·9 (23·0–24·8)	21·6 (20·7–22·5)	19·3 (18·4–20·2)	16·9 (15·3–16·9)	14·5
WHO stage at enrolment											
I	45·5 (44·1–46·9)	42·5 (41·5–43·5)	40·7 (39·8–41·6)	38·3 (37·4–39·2)	35·7 (24·8–36·6)	32·7 (37·8–33·6)	29·9 (29·0–30·8)	27·3 (26·4–28·2)	24·3 (23·4–22·7)	22·0 (21·3–22·7)	19·0
II	32·9 (31·1–34·7)	30·6 (29·4–31·8)	29·9 (29·0–30·8)	28·5 (27·6–29·4)	27·0 (26·1–27·9)	25·0 (24·5–26·5)	23·2 (22·2–24·2)	21·0 (19·9–22·1)	19·5 (18·4–20·6)	17·6 (16·5–18·7)	16·8
III	16·8 (15·4–18·2)	15·5 (14·5–16·5)	17·3 (16·6–18·0)	18·3 (17·7–18·9)	18·2 (17·6–18·8)	17·3 (16·7–18·)	16·1 (15·5–16·7)	14·5 (13·8–15·2)	12·3 (11·6–13·0)	10·5 (9·8–11·2)	8·9
IV	9·9 (7·6–12·2)	8·3 (6·6–10·0)	9·9 (8·7–11·1)	9·6 (8·6–10·6)	9·6 (8·6–10·6)	10·0 (8·9–11·1)	10·9 (9·6–12·2)	9·7 (8·2–11·2)	8·6 (6·9–10·3)	7·6 (6·0–9·2)	5·7

Table shows additional years of life (95% CI). Life expectancy was defined as the average number of additional years that will be lived by a person after that age. General Rwandan life expectancy is presented as the range of the time period 2002–14, covering most our study period. NA=not applicable. *95% CIs not available for age ≥65 years because it is not a closed interval.

Table 3: **Life expectancy among HIV-positive patients enrolled in care, by age category**

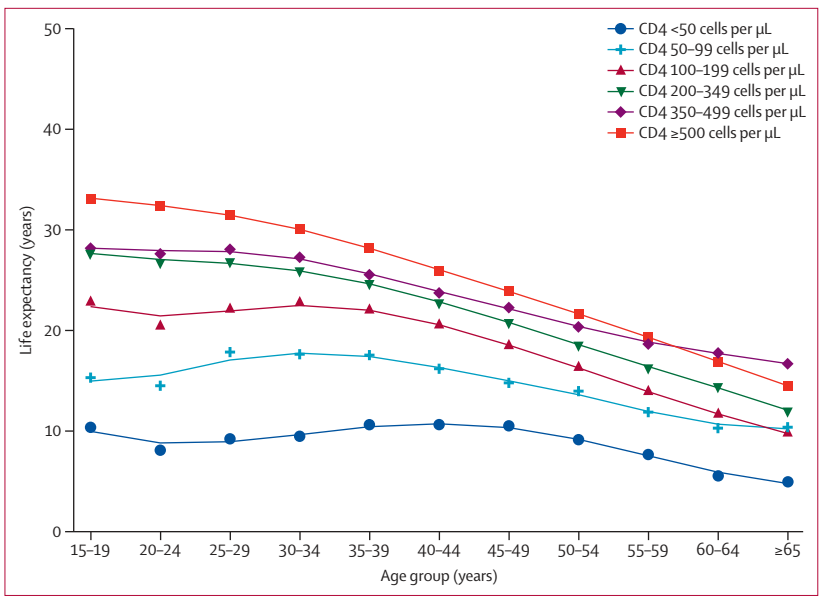

Figure 2: **Life expectancy (additional years of life) among HIV-positive individuals overall according to CD4 cell count at time of enrolment**

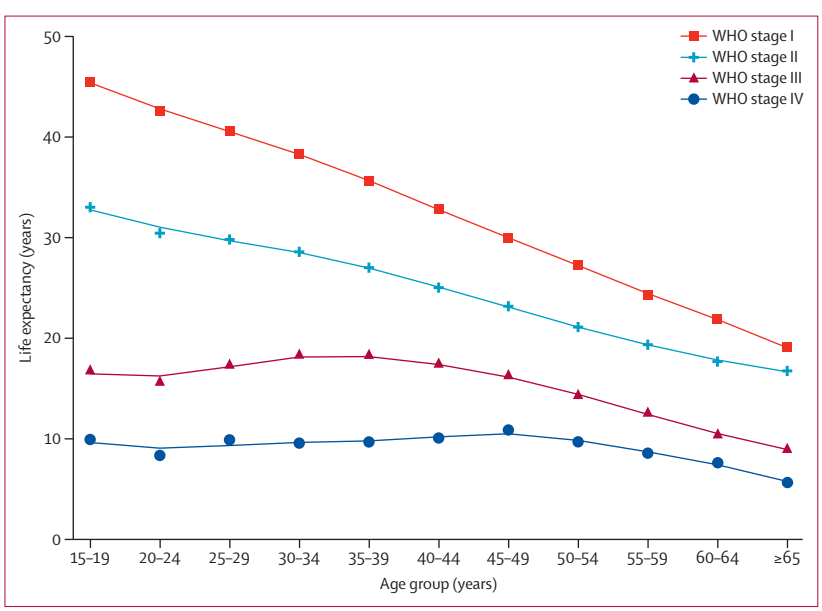

Figure 3: **Life expectancy (additional years of life) among HIV-positive individuals overall according to WHO disease stage at time of enrolment**

was 20·4 additional years (95% CI 19·5–21·3) and in the period of 2008–11 was 25·6 additional years (95% CI 24·8–26·4). The life expectancy among individuals enrolling in care with WHO disease stage I had estimated projections that fell within the range of life expectancies for the general Rwandan population during the study period, across all age categories.

Table 4 presents the results of life expectancy following patients starting from antiretroviral therapy initiation. Life expectancy for the overall cohort was 29·9 years of additional life (95% CI 29·1–30·7) at 20 years of age and 25·6 years of additional life (95% CI 25·0–26·2) at 35 years of age. The difference between life expectancy for individuals in enrolled in HIV care not yet receiving antiretroviral therapy compared with that of individuals receiving antiretroviral therapy was greatest among younger people (an additional 4·3 years among 20-year-olds) and decreased to 1·3 years among those aged 65 years or older. We noted similar patterns in this subset for sex, WHO disease stage, antiretroviral therapy coverage period, and the lower CD4 categories.

The additional life expectancy estimated in the analysis restricted to those on antiretroviral therapy was not shared equally among the CD4 strata. Among 20–24-year -olds, the jump was 4·0 years in the lowest CD4 category and 12·7 years in the 350–499 cells per µL group. Differences between the 350–499 cells per µL group and the 500 cells per µL or higher group were not statistically significant, as shown by the overlapping 95% CIs. The life expectancy estimates were slightly lower in the 500 cells per µL or higher group, due to a higher propensity of linking and initiation of antiretroviral therapy at higher CD4 for other clinical reasons, such as opportunistic infections.

The appendix shows the estimated life expectancies across CD4 categories when no adjustments were made for mortality among individuals lost to follow-up. By comparison with the main analysis, we estimated the life expectancies to be much higher in the unadjusted analysis. Moreover, life expectancies among the higher CD4 categories in the unadjusted sensitivity analysis seemed to be almost entirely accounted for by age, whereas life expectancy among younger individuals seemed to be flatter in the age categories of 15–35 years when accounting for loss to follow-up. This difference suggests that many deaths among younger patients could be undetected because of loss to follow-up.

Discussion

Our study supports life expectancy gains for enrolment of patients into HIV care at any CD4 cell count, as shown by improved life expectancy between the two periods of lower and higher coverage of antiretroviral therapy at both time of enrolment and initiation of antiretroviral therapy. We noted that life expectancy varied by sex, with women having greater gains than men, and that access to antiretroviral therapy greatly improved life expectancy, particularly among patients with high baseline CD4 status. To our knowledge, this study is the first to assess life expectancy among patients enrolling in care and those initiating antiretroviral therapy in two distinct periods, defined by antiretroviral therapy coverage and CD4 cell count at enrolment in care and antiretroviral therapy initiation (panel).

In 2014, the WHO Global Health Observatory Repository estimated life expectancy in Rwanda at age 20 years to be an additional 45 years of life, a 35% gain in just 10 years.[14] Although Rwanda had almost no provision

	15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	50–54 years	55–59 years	60–64 years	≥65 years*
General Rwandan life expectancy (WHO, 2002–14)[14]	44–55	40–51	36–46	32–42	29–38	27–34	24–30	21–26	18–22	15–18	NA
Overall	31·9 (30·6–33·2)	29·9 (29·1–30·7)	28·9 (28·3–29·5)	27·4 (26·8–28·0)	25·6 (25·0–26·2)	23·4 (22·8–24·0)	21·3 (20·7–21·9)	19·3 (18·6–20·0)	17·0 (16·3–17·7)	14·9 (14·2–15·6)	13·8
Men	24·1 (21·8–26·4)	22·2 (20·2–24·2)	23·7 (22·6–24·8)	23·3 (22·4–24·2)	22·8 (22·0–23·6)	21·2 (20·4–22·0)	19·7 (18·9–20·5)	18·1 (17·2–19·0)	16·2 (15·2· 17·2)	14·7 (13·7–15·7)	14·2
Women	35·7 (34·1–37·3)	33·2 (32·2–34·2)	31·8 (31·0–32·6)	30·1 (29·3–30·9)	28·0 (27·2–28·8	25·6 (24·7–26·5)	23·2 (22·3–24·1)	20·5 (19·6–21·4)	17·8 (16·8–18·8)	15·1 (14·2–16·0)	13·2
Period of antiretroviral therapy coverage											
1997–2007	21·7 (19·3–24·1)	21·1 (19·5–22·7)	21·4 (20·4–22·4)	20·2 (19·4–21·0)	18·9 (18·1–19·7)	17·3 (16·4–18·2)	15·4 (14·5–16·3)	13·7 (12·7–14·7)	11·2 (10·1–12·3)	8·6 (7·5–9·7)	7·2
2008–11	31·6 (29·9–33·3)	28·9 (27·8–30·0)	27·2 (26·2–28·2)	25·7 (24·7–26·7)	23·8 (22·8–24·8)	21·5 (20·5–22·5)	19·7 (18·6–20·8)	17·8 (16·6–19·0)	16·4 (15·1–17·7)	15·2 (13·9–16·5)	15·4
CD4 at enrolment											
<50 cells per μL	13·6 (11·0–16·2)	12·1 (10·3–13·9)	12·2 (10·9–13·5)	12·7 (11·6–13·8)	13·5 (12·5–14·5)	13·1 (12·0–14·2)	12·7 (11·5–13·9)	10·9 (9·6–12·2)	8·9 (7·4–10·4)	7·2 (5·6–8·8)	6·9
50–99 cells per μL	22·4 (18·3–26·5)	21·2 (18·5–23·9)	21·6 (20·0–23·2)	20·4 (19·1–21·7)	20·0 (18·7–21·3)	18·0 (16·7–19·3)	16·2 (14·8–17·6)	15·2 (13·6–16·8)	12·8 (11·1–14·5)	10·3 (8·6–12·0)	10·4
100–199 cells per μL	30·1 (27·3–32·9)	27·3 (25·2–29·4)	27·7 (26·4–29·0)	27·0 (25·9–28·1)	25·4 (24·4–26·4)	23·3 (22·3–24·3)	20·8 (19·7–21·9)	18·4 (17·3–19·5)	15·7 (14·5–16·9)	13·4 (12·3–14·5)	11·9
200–349 cells per μL	38·4 (36·0–40·8)	36·1 (34·5–37·7)	34·7 (33·5–35·9)	32·6 (31·5–33·7)	29·8 (28·7–30·9)	27·2 (26·0–28·4)	24·6 (23·4–25·8)	22·3 (21·1–23·5)	20·0 (18·8–21·2)	17·7 (16·6–18·8)	15·8
350–499 cells per μL	43·3 (39·7–46·9)	40·3 (37·9–42·7)	38·0 (36·0–40·0)	35·1 (33·2–37·0)	31·7 (29·8–33·6)	28·3 (26·3–30·3)	25·4 (23·4–27·4)	22·6 (20·5–24·7)	20·0 (18·0–22·0)	17·5 (15·7–19·3)	15·4
≥500 cells per μL	39·8 (35·5–44·1)	38·0 (35·3–40·7)	35·2 (32·7–37·7)	33·2 (30·7–35·7)	30·5 (28·0–33·0)	27·6 (25·0–30·2)	24·9 (22·3–27·5)	22·1 (19·4–24·8)	19·6 (16·9–22·3)	17·2 (14·8–19·7)	15·3
WHO stage at enrolment											
I	50·0 (48·2–51·8)	45·5 (44·0–47·0)	42·5 (41·2–43·8)	39·1 (37·8–40·4)	35·4 (34·2–36·6)	31·9 (30·6–33·2)	28·3 (27·0–29·6)	25·0 (23·7–26·3)	21·4 (20·2–22·6)	18·2 (17·1–19·3)	15·4
II	38·0 (35·7–40·3)	34·9 (33·3–36·5)	32·9 (31·8–34·0)	29·9 (28·8–31·0)	27·3 (26·3–28·3)	24·3 (23·3–25·3)	21·1 (20·0–22·2)	18·5 (17·4–19·6)	15·9 (14·8–17·0)	13·1 (12·0–14·2)	11·4
III	21·1 (19·1–23·1)	19·7 (18·2–21·2)	20·6 (19·7–21·5)	21·2 (20·5–21·9)	20·5 (19·8–21·2)	18·7 (18·0–19·4)	16·9 (16·2–17·6)	14·8 (14·1–15·5)	12·2 (11·5–12·9)	9·8 (9·1–10·5)	7·6
IV	12·2 (9·4–15·0)	10·2 (8·0–12·4)	10·8 (9·3–12·3)	11·1 (9·8–12·4)	10·8 (9·6–12·0)	11·3 (9·9–12·7)	11·8 (10·2–13·4)	10·9 (9·0–12·8)	10·2 (7·9–12·5)	9·2 (7·0–11·4)	8·2

Table shows additional years of life (95% CI). Life expectancy was defined as the average number of additional years that will be lived by a person after that age. General Rwandan life expectancy is presented as the range of the time period 2002–14, covering most our study period. NA=not applicable. *95% CIs not available for age ≥65 years because it is not a closed interval.

Table 4: **Life expectancy among HIV-positive patients enrolled in HIV care after initiating antiretroviral therapy, by age category**

for antiretroviral therapy before the financial assistance provided by the US President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria, the government made a specific target of antiretroviral therapy initiation in rural settings and among individuals infected with HIV during the Rwandan genocide of 1994.[4] This early response is, partly, responsible for the impressive coverage of antiretroviral therapy across Rwanda, and ability of the government to reach targets for universal access to antiretroviral therapy (defined as >80% coverage at a CD4 cell count of >200 cells per μL before 2009 and >350 cells per μL afterwards). Now, with assistance from the US President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria, as of July, 2014, the Rwanda Ministry of Health now advises the initiation of antiretroviral therapy at a CD4 threshold of 500 cells per μL or immediate therapy to specific populations including men who have sex with men, female sex workers, and other high-risk populations, with the objective to reduce mortality, reduce HIV transmission, and increase coverage of antiretroviral therapy.[7]

There are several strengths and limitations to this study. Strengths include the large sample size (roughly 21% of all Rwandans infected by HIV) that was nationally representative and included a diverse population of patients with varying levels of health. This aspect provided precise estimates throughout the analyses, and allowed for granular categorisation of age. We also had a very large number of early enrollers (enrolling at CD4 cell counts >350 cells per μL) that allowed us to project the life expectancy gains for people enrolling in care

Panel: **Research in context**

Systematic Review

We searched Medline with the terms "HIV", "life expectancy", and "antiretroviral therapy" for articles published in English up to March 31, 2014. We found several observational studies from both low-income and middle-income countries,[3,15,16] and cohort collaborations from high-income countries.[2,17] We also reviewed the 2013 WHO treatment guidelines[6] and the WHO Global Health Observatory Repository for Rwanda life expectancy. The largest assessment of life expectancy in a developed setting was the Antiretroviral Therapy Cohort Collaboration.[2] The study included 18 587 patients across 14 high-income country cohorts and its findings showed that, for the period 1996–99 (when less efficacious drug formulations were available, compared with those used nowadays), a 20-year-old patient could expect to survive an additional 36·1 years; by 2003–05, when drug formulations had improved, additional life-years at 20 years of age had risen to 49·4 years. Another assessment using US and Canadian data showed that, among patients initiating antiretroviral therapy in 2007, a 20-year-old could expect a further 51 years of life.[17] Three studies have reported on life expectancy in Africa.[3,15,16] An evaluation among antiretroviral therapy recipients in Uganda showed that a patient initiating first-line regimens at the age of 20 years was projected to have an additional 26 years of life.[3] Findings from a study in South Africa showed that life expectancies of patients with baseline CD4 counts of 200 cells per μL or more were between 70% and 86% of those in HIV-negative adults of the same age and sex, with men having a shorter life expectancy than women.[15] Finally, investigators of a community-level evaluation in rural South Africa reported that, in 2003 (the year before antiretroviral therapy became available in the public-sector health system), adult life expectancy was 49·2 years; by 2011, adult life expectancy had increased to 60·5 years: an 11·3-year gain.[16]

Interpretation

The scale-up of antiretroviral therapy has improved life expectancy for HIV-positive patients in both low-income and high-income countries. Our results from Rwanda lend support to life expectancy gains for patients enrolled into HIV care at any CD4 cell count, and show near-normal life expectancy among individuals enrolled in care with high CD4 cell counts. We noted that life expectancy varied by sex, with women having greater gains than men, and that access to antiretroviral therapy greatly improved life expectancy, particularly among patients with high baseline CD4 cell count.

early. Moreover, our study assessed both time in HIV care and time on antiretroviral therapy, recognising the importance of the pre-antiretroviral therapy period in which loss to follow-up is increased. Nonetheless, loss to follow-up was low in this study, consistent with other studies that have shown Rwanda to have among the highest retention rates in sub-Saharan Africa,[18] and serving to reduce the potential for misclassification bias in this study. Finally, through adjustments to mortality for loss to follow-up, including loss to follow-up in the pre-antiretroviral therapy period, our study underscores the additional strain on life expectancy experienced by younger HIV-positive patients.

Limitations include first the absence of important baseline variables, notably viral load, which serves as a marker of treatment adherence but which remains limited in Rwanda to HIV-positive patients on antiretroviral therapy. Second, we adjusted for mortality among loss to follow-up through propensity adjustments using a conservative proportion of mortality (ie, a proportion that was probably too high), which could lead to underestimation of life expectancy. By contrast with a recent study from South Africa,[15] we could not link our HIV cohort data with the national death register in Rwanda. Third, we only considered one clinical marker at a time, which would not include individuals initiating antiretroviral therapy with high CD4 cell counts due to opportunistic infections and patients not initiating antiretroviral therapy despite low CD4 cell counts. Finally, missing values for WHO disease stage (2421 individuals, 3·4%) might have affected the mortality rates and life expectancy for both these variables.

Within the international community for AIDS research and implementation there is substantial debate about the value of CD4 cell count as a threshold for initiation of antiretroviral therapy.[19–21] In our study we noted that higher CD4 status at initiation of therapy increased life expectancy. Other study findings have shown that early initiation of antiretroviral therapy reduces clinical events and infectiousness, the likelihood transmission of disease to a sexual partner, and the acquisition of tuberculosis,[19,22–24] raising the question of whether CD4 thresholds for initiation have any value to the health of the population. Understanding of baseline disease risk is valuable to physicians, but in view of the substantial challenges involved with retention of patients in pre-antiretroviral therapy, there is growing support for a simplified system in which patients are placed on treatment immediately after enrolment in care.[25]

In summary, our study findings add to the growing body of evidence that early enrolment and antiretroviral therapy have several benefits that extend well beyond immediate reductions in mortality. These findings strongly support the Rwandan Government's policy change to provide antiretroviral therapy at an increased CD4 threshold and their continued efforts to improve retention and testing.

Contributors

SN, SK, KC, JIF, NF, JC, AB, and EJM contributed to study concept and design. SN, ER, SK, KC, JC, AB, and EJM contributed to acquisition, analysis, or interpretation of data. SN, SK, JIF, and EJM drafted the report. SN, ER, SK, KC, JIF, NF, JC, AB, and EJM contributed to critical revision of the report for important intellectual content. ER, SK, and KC did the statistical analysis. SN, JC, AB, and EJM obtained funding. SN, ER, JIF, JC, and EJM provided administrative, technical, or material support. SN, AB, and EJM supervised the study.

Declaration of interests

We declare no competing interests. AB is the Minister of Health for Rwanda.

Acknowledgments

Analysis of these data was supported by the Bill & Melinda Gates Foundation. Programme partners that assist in the delivery and implementation of HIV services in Rwanda include the Global Fund to Fight HIV/AIDS, TB, and Malaria, the US President's Emergency Plan for AIDS Relief, and the Government of Rwanda.

References

1 McGuire AL, Barer JM, Montaner JS, Hogg RS. There and back again: the impact of adult HIV prevalence on national life expectancies. *HIV Med* 2005; **6:** 57–58.

2 The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372:** 293–99.

3 Mills EJ, Bakanda C, Birungi J, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Ann Intern Med* 2011; **155:** 209–16.

4 Binagwaho A, Farmer PE, Nsanzimana S, et al. Rwanda 20 years on: investing in life. *Lancet* 2014; **384:** 371–75.

5 WHO. Global update on HIV treatment 2013: results, impact and opportunities. 2013. http://www.who.int/hiv/pub/progressreports/update2013/en/ (accessed May 29, 2014).

6 Doherty M, Ford N, Vitoria M, Weiler G, Hirnschall G. The 2013 WHO guidelines for antiretroviral therapy: evidence-based recommendations to face new epidemic realities. *Curr Opin HIV AIDS* 2013; **8:** 528–34.

7 Nsanzimana S. Benefits of the implementation of the 2013 WHO guidelines on HIV treatment in combination with a test-and-treat strategy for key populations in Rwanda. International Treatment as Prevention Workshop; Vancouver, BC, Canada; April 4, 2014.

8 Chiang CL. On constructing current life tables. *J Am Stat Assoc* 1972; **67:** 538–41.

9 Eayres D, Williams ES. Evaluation of methodologies for small area life expectancy estimation. *J Epidemiol Community Health* 2004; **58:** 243–49.

10 Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS One* 2009; **4:** e5790.

11 Egger M, Spycher BD, Sidle J, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. *PLoS Med* 2011; **8:** e1000390.

12 Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. *JAMA* 2008; **300:** 506–07.

13 Romeder JM, McWhinnie JR. Potential years of life lost between ages 1 and 70: an indicator of premature mortality for health planning. *Int J Epidemiol* 1977; **6:** 143–51.

14 WHO. Global health observatory data repository. http://apps.who.int/gho/data/node.country.country-RWA (accessed May 29, 2014).

15 Johnson LF, Mossong J, Dorrington RE, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. *PLoS Med* 2013; **10:** e1001418.

16 Bor J, Herbst AJ, Newell ML, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science* 2013; **339:** 961–65.

17 Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013; **8:** e81355.

18 Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–09: systematic review. *Trop Med Int Health* 2010; **15** (suppl 1)**:** 1–15.

19 Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al, for the HPTN 052-ACTG Study Team. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis* 2014; **14:** 281–90.

20 Lundgren JD, Babiker AG, Gordin FM, Borges AH, Neaton JD. When to start antiretroviral therapy: the need for an evidence base during early HIV infection. *BMC Med* 2013; **11:** 148.

21 De Cock KM, El-Sadr WM. When to start ART in Africa—an urgent research priority. *N Engl J Med* 2013; **368:** 886–89.

22 Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365:** 493–505.

23 Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011; **365:** 1492–501.

24 Ford N, Meintjes G, Pozniak A, et al. The future role of CD4 cell count for monitoring antiretroviral therapy. *Lancet Infect Dis* 2015; **15:** 241–47.

25 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373:** 48–57.