LIFE EXPECTANCIES OF HIV-POSITIVE ADULTS RECEIVING ANTIRETROVIRAL TREATMENT IN SOUTH AFRICA

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ABSTRACT

The question of whether and to what extent HIV-positive adults are insurable remains contentious due to the absence of long-term estimates of mortality in patients receiving antiretroviral treatment (ART). Most published estimates of life expectancies of HIV-positive adults have been based on data from high-income countries, and these estimates may not be applicable to South Africa. This study aims to estimate life expectancies of patients receiving ART in South Africa, using data from a collaboration of eight South African ART programmes operating mainly in the public health sector. Patient records are linked to the South African national population register and inverse probability weighting is used to ensure that mortality estimates are representative of all patients starting ART, regardless of their level of adherence or retention in the ART programmes. Relative survival models are fitted to the data, allowing for differences in HIV-related mortality over three different treatment durations. The resulting life expectancies vary substantially by patients' age, sex and CD4 count at time of ART initiation, with those in patients starting ART at higher CD4 counts coming close to the corresponding life expectancies in HIV-negative adults.

KEYWORDS

Antiretroviral treatment; HIV/AIDS; life expectancy; South Africa

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1. INTRODUCTION

The question of whether and to what extent HIV-positive adults are insurable remains contentious due to the absence of long-term estimates of mortality in patients receiving antiretroviral treatment (ART). Several estimates of the life expectancy of HIV-positive adults in high-income countries have been published (May et al., 2011; McDavid Harrison et al., 2010; Hogg et al., 2008; Van Sighem et al., 2010; Lima et al., 2007; Lloyd-Smith et al., 2006; Fang et al., 2007; Keiser et al., 2004; Lohse et al., 2007), and many of these studies have shown dramatic improvements in life expectancy following the introduction of highly active ART. However, only one previous study has directly estimated the life expectancy of patients receiving ART in a developing country (Mills et al., 2011). The dearth of estimates from developing countries is a reflection of both the later introduction of ART (with less time to accumulate long-term survival data) and the problems associated with obtaining accurate mortality estimates in these countries. High rates of loss to follow-up (Fox & Rosen, 2010), together with high mortality in those lost to follow-up (Brinkhof et al., 2009b), mean that mortality is often substantially under-estimated. In the absence of reliable empirical estimates, modellers have made conservative assumptions about the life expectancy of adults starting ART in developing countries, typically around 10 years (Mahy et al., 2010; Walensky et al., 2010; Johnson & Dorrington 2006). Uncertainty regarding long-term HIV mortality is frequently manifested in insurers' refusal of life insurance applications by HIV-positive individuals, or acceptance on very restrictive terms.

In South Africa there exists a unique opportunity to obtain accurate estimates of ART mortality in a developing country experiencing a generalised HIV epidemic. With around 90% of adult deaths recorded through the country's vital registration system (Dorrington et al., 2001; Boulle et al., 2010; Fox et al., 2010; Dorrington & Bradshaw, 2011), South Africa is perhaps the only African country with levels of vital registration high enough to permit independent estimation of mortality rates in patients (Setel et al., 2007). HIV/AIDS has had a profound demographic impact in South Africa (Dorrington et al., 2001; Birnbaum et al., 2011; Herbst et al.,2011), but access to ART has expanded rapidly since 2004, with ART reaching almost 1.8 million South Africans by the middle of 2011 (Johnson, 2012). The combination of high mortality ascertainment and large patient numbers allows for greater precision in the estimation of ART mortality than is possible in most developing countries. The objective of the present study is to estimate the life expectancy of patients starting ART in South Africa, using data from a large collaboration of ART programmes.

2. METHODS

2.1 Cohort Description

The International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) is a collaboration of ART programmes in southern Africa (Egger et al., 2011). This analysis is limited to eight programmes providing ART to adults in South Africa (Cornell et al., 2009; 2010): the Aurum treatment programme, Gugulethu clinic, the Hlabisa HIV treatment and care programme, the Khayelitsha HIV treatment programme, Masiphumelele clinic, McCord Hospital, Themba Lethu Clinic and Tygerberg Academic Hospital. Treatment centres are situated across three of South Africa's nine provinces (Western Cape, Gauteng and KwaZulu-Natal), mostly in urban areas, and most programmes operate in the public health sector. Over the period to which this analysis relates (2001–2009), South African treatment guidelines in the public health sector recommended that adult ART initiation be deferred until the patient's CD4 count was below 200/µl or the patient had progressed to WHO clinical stage IV (Department of Health, 2003).

2.2 Selection of Patients and Variable Definitions

Patients were included in the analysis if they were aged 15 or older at the time of starting ART, and started ART in 2001 or later. Patients were excluded from the analysis if they had missing baseline CD4 values (baseline CD4 was defined as the CD4 measurement closest to the time of ART initiation, occurring within 182 days before and 14 days after the date of ART initiation). Patients were also excluded if their baseline viral load was below 400 copies/ml, as such patients were unlikely to be ART-naïve (baseline viral load was defined as the viral load measurement closest to the time of ART initiation, occurring within 182 days before and 3 days after the date of ART initiation).

Patients were considered to be 'lost to follow-up' (LTFU) if there was no record of their attendance at the clinic for at least 182 days prior to database closure and there was no information on their patient records regarding the reason for their non-attendance. The date of database closure differed for each of the participating programmes, and was calculated as the last recorded visit date in each programme. The date of analysis closure was defined for each programme to be the date 182 days prior to the date of database closure, in order to allow sufficient time to determine the LTFU status of each patient. These dates of analysis closure were between 24 May 2007 and 14 September 2009.

2.3 Estimation of Mortality

In calculating exposure, we define observation time to begin when the patient first starts ART, and censor patient follow-up time at the date of death, the date at which the patient was transferred out of the programme, or the date of analysis closure, whichever occurs first. In the case of patients who are LTFU, the approach to calculating exposure differs depending on whether the programme has recorded the patient's identity number

and used this information to check the vital status of the patient against the national population register. In the case of patients LTFU with ID information, observation time is censored at the date of analysis closure or the date of death recorded on the population register, whichever date occurs first. Inverse probability weighting is used to ensure that LTFU patients with IDs are weighted up to represent the LTFU patients without IDs. This means assigning zero weight to the LTFU patients who have no ID (so that the censoring date for these patients is irrelevant) and assigning weights equal to the inverse of the probability of having ID information, in those patients who have ID information. This approach has been used previously in estimating mortality rates in South African patients receiving ART (Boulle et al., 2010; Van Cutsem et al., 2011), and is analogous to the weighting methods that are commonly used to correct for non-informative censoring through double sampling (Frangakis and Rubin, 2001). Similar inverse probability weighting methods have been used to obtain 'corrected' estimates of mortality in ART patients in other African settings, where the 'double sampling' is based on actively tracing a subset of LTFU patients (An et al., 2009; Yiannoutsos et al., 2008; Geng et al., 2008) rather than checking against the national population register for the subset of LTFU patients with ID information. These 'corrected' estimates of mortality in African ART programmes have been shown to be substantially higher than those estimated if all LTFU patients are censored at the date of LTFU (An et al., 2009; Yiannoutsos et al., 2008; Geng et al., 2008; Fox et al., 2010).

Inverse probability weights are calculated by applying a logistic regression model to the LTFU patients, to predict the probability of having recorded ID information. Explanatory variables included in the logistic regression are age, sex, CD4 count, year of ART initiation, and time to LTFU after starting ART. The probabilities estimated by the logistic regression model were scaled up by a constant factor to ensure that after assigning zero weight to all LTFU patients without ID information, the average weight in all LTFU patients was equal to 1. Patients who were not LTFU were all assigned a weight of 1.

The inverse probability weights are fixed for each individual, so that the survivor function can be considered as a weighted average of two survivor functions: one for patients who are LTFU and one for patients who are not LTFU. Frangakis and Rubin (2001) show that this approach can lead to biased estimates of the true survivor function, and that a more correct approach would be to use time-varying weights. However, the loss of accuracy due to using fixed weights is likely to be relatively small in most applications. For example, Yiannoutsos et al. (2008) found that the cumulative probability of death one year after starting ART was 10.5% when using fixed weights and 10.7% when using time-varying weights.

This method is based on the assumption that patients with IDs have similar mortality to patients without IDs, after controlling for observed covariates. This assumption may be problematic in some situations. For example, foreign immigrants would often not have IDs, but might experience mortality different from that in individuals born in South Africa (McCarthy et al., 2009). Since nationality is not

recorded in our dataset, there is no adjustment for potential differences in mortality between immigrants and locals, and hence some bias may arise. However, the fraction of patients who are immigrants is likely to be too small to materially influence the overall results.

2.4 Relative Survival Model

Relative survival models evaluate the excess mortality attributable to a particular disease, in a cohort of patients with the disease, when compared to the mortality in a comparable group of individuals in the general population who do not have the disease (Dickman et al., 2004; Ederer et al., 1961). The mortality rate in a patient with certain characteristics (represented by covariate vector **z**) can be expressed as follows:

$$\mu(\mathbf{z}) = \mu^0(\mathbf{z}) + \exp(\mathbf{z}\boldsymbol{\beta}),$$

where $\mu^0(\mathbf{z})$ is the mortality rate that would be expected in an individual with the same characteristics who does not have the disease, and $\boldsymbol{\beta}$ is a vector of coefficients reflecting the effect of each of the covariates on the disease-specific mortality. As noted by Dickman et al. (2004), these mortality rates are usually modelled as piecewise constant hazards over different intervals of follow-up time, typically of 12-month length. The advantage of this approach is that it is simple to relax the assumption of proportional hazards if the hazards in different covariate strata do not remain proportional over follow-up. The relative survival approach has previously been used by Van Sighem et al. (2005; 2010) in estimating life expectancies of HIV-diagnosed adults in the Netherlands, by Bhaskaran et al. (2008) in assessing mortality trends in the CASCADE Collaboration, and by Brinkhof et al. (2009a) in estimating mortality after ART initiation in African cohorts.

In the current analysis, we apply the relative survival model separately to male and female mortality data, allowing for three covariates: age at ART initiation (x), number of complete years since ART initiation (d) and CD4 category at ART initiation (i). Individuals are grouped into one of four baseline CD4 categories: CD4 < 50/µl (i = 0), CD4 50–99/µl (i = 1), CD4 100–199/µl (i = 2) and CD4 of 200/µl or higher (i = 3).

Mathematically, the model can be expressed as follows:

$$\mu_{x,d}(i) = \mu^0_{x+d} + G_d H_d^{x+d-35} \exp(g_d(i)), \qquad (1)$$

where μ^0_{x+d} is the mortality rate that would be expected in HIV-negative individuals, G_d is the excess HIV mortality at age 35, H_d is the factor by which the excess HIV mortality increases per year of age, and $g_d(i)$ is the difference in HIV-specific mortality (on a log scale) between individuals in baseline CD4 category i and individuals with baseline CD4 counts < 50/µl. Mortality is assumed to be constant over different integer ages and integer durations. Both the CD4 effect and the age effect are

assumed to depend on duration, so that the model is fitted separately for each duration category. The rationale for fitting different baseline CD4 effects in different duration categories is that one would expect baseline CD4 to be more predictive of mortality during the first few months after starting ART than at longer durations (Cornell et al., 2010), when factors affecting the extent of the CD4 response become relatively more significant. The effect of age might also be expected to vary in relation to treatment duration: older adults tend to have greater short-term virological suppression than younger adults (Boulle et al., 2010; Nglazi et al., 2011; Fatti et al., 2010; Mutevedzi et al., 2011; Micheloud et al., 2008; Sabin et al., 2008), but their long-term CD4 recovery is less substantial than that in younger adults (Mutevedzi et al., 2011; Micheloud et al., 2008; Sabin et al., 2008; Nash et al., 2008).

The model parameters are estimated separately for each of three intervals: the first 12 months after starting ART ($d = 0$), the second 12 months after starting ART ($d = 1$) and durations of more than 24 months ($d = 2$). This means that for $d > 2$,

$$\mu_{x,d+1}(i) = \mu_{x+1,d}(i). \tag{2}$$

Over each of these three intervals, the mortality rate is assumed to be constant with respect to duration, though the mortality rate can change in relation to age. The assumption of a constant mortality rate is not realistic at short durations, but for the purpose of calculating life expectancies it is the cumulative survival probability over longer durations that is most important, and changing the interval definitions at short durations (for example, to 0–6 months in the first interval) does not change the life expectancy substantially. Increasing the lower limit on the upper duration interval (for example, to more than 36 months) could have a more material impact, but this would also lead to a loss of precision in the estimation of life expectancy, due to the relative lack of follow-up time at longer treatment durations and the sensitivity of the life expectancy to the mortality rate in the upper duration interval.

2.5 Estimation of non-HIV Mortality

Estimates on non-HIV mortality rates in South Africa were obtained from the ASSA2008 AIDS and Demographic model (Actuarial Society of South Africa, 2011). Estimates from the 2005 projection year are used in this analysis, as this was close to the median date of ART enrolment in the IeDEA-SA collaboration (Cornell et al., 2009). The ASSA2008 estimates of non-HIV mortality do not change substantially by year, and estimates of non-HIV mortality would therefore not change substantially if alternative years were selected.

2.6 Calculation of Life Expectancies

We define $l_{x,d}(i)$ to be the proportion of individuals starting ART at exact age x, in CD4 category i, who survive for d years ($l_{x,0}(i) = 1$). The proportion of individuals who survive for 1 year is

$$l_{x,1}(i) = l_{x,0}(i) \times \exp\left(-\mu_{x,0}(i)\right).$$

Similarly, the proportion who survive for 2 years is

$$l_{x,2}(i) = l_{x,1}(i) \times \exp\left(-\mu_{x,1}(i)\right),$$

and the proportion who survive for d years (where d is an integer > 2) is

$$\begin{aligned} l_{x,d}(i) &= l_{x,d-1}(i) \times \exp\left(-\mu_{x,d-1}(i)\right) \\ &= l_{x,d-1}(i) \times \exp\left(-\mu_{x+d-3,2}(i)\right), \end{aligned}$$

the latter result following from equation (2). Although we have defined $l_{x,d}(i)$ only for integer values of d, it can be considered a continuous function of d. The life expectancy of an individual starting ART at age x, in CD4 category i, is then defined as

$$\begin{aligned} e_x(i) &= \int_0^\infty l_{x,t}(i)dt \\ &\approx \left\{ \sum_{d=0}^{100-x} 0.5\left(l_{x,d}(i) + l_{x,d+1}(i)\right) \right\} + l_{x,101-x}(i)\, e_{99,2}(i), \end{aligned}$$

where $e_{99,2}(i) \approx 1/\mu_{99,2}(i)$. As there are very few individuals who would be expected to survive to age 101, the use of the approximation to the life expectancy at age 101 (which effectively assumes constant mortality after age 101) has negligible effect on the accuracy of $e_x(i)$, provided $x << 100$. The life expectancy of an individual who started ART at age x and has survived for 2 years is similarly calculated as

$$e_{x,2}(i) \approx \frac{\sum_{d=2}^{100-x} 0.5\left(l_{x,d}(i) + l_{x,d+1}(i)\right)}{l_{x,2}(i)} + \frac{l_{x,101-x}(i)}{l_{x,2}(i)} e_{99,2}(i),$$

for $x < 99$.

2.7 Comparison with Mortality in Uninfected Individuals

The life expectancies that are calculated using the relative survival model are compared with the life expectancies that would be expected in HIV-negative South Africans of the same age and sex. Because these HIV-negative life expectancies are calculated using mortality rates in HIV-negative individuals, they represent the life expectancies of individuals who *remain* HIV-negative in future, and are therefore higher than the life expectancies of currently HIV-negative individuals who may become infected with HIV in future (this difference may be substantial due to the high lifetime risk of HIV in many African countries (Gregson & Garnett, 2000; Blacker & Zaba, 1997; Wambura et al., 2007; Johnson et al., 2012)).

The non-HIV mortality rates are also used in calculating the proportion of patients who are expected to die from non-HIV causes. The probability that death is unrelated to HIV, for an individual starting ART at exact age *x*, in CD4 category *i*, is

$$\left\{\sum_{d=0}^{100-x}\left(l_{x,d}(i)-l_{x,d+1}(i)\right)\times\frac{\mu^{0}_{x+d}}{\mu_{x,d}(i)}\right\}+l_{x,101-x}(i)\times\frac{\mu^{0}_{101}}{\mu_{99,2}(i)}. \quad (3)$$

2.8 Calculation of Likelihood Function

For individuals in CD4 category *i* at the time of ART initiation, aged *x* in the first 12 months after starting ART, we define $Y_{x,0}(i)$ to be the exposure and $R_{x,0}(i)$ to be the number of deaths during the first 12 months after starting ART. Observation time is censored upon turning age *x* + 1 and deaths exclude those that occur after turning age *x* + 1. Observation time includes individuals who turned age *x* during their first year on ART, with observation time starting from when they turned *x*. It is assumed that deaths are Poisson-distributed, with the expected number of deaths being

$$Y_{x,0}(i)\times\mu_{x,0}(i),$$

where $\mu_{x,0}(i)$ is the mortality rate predicted by the relative survival model in equation (1). The likelihood of observing $R_{x,0}(i)$ deaths is thus

$$L_{x,0}(i)=\frac{\exp\left(-Y_{x,0}(i)\mu_{x,0}(i)\right)\left(Y_{x,0}(i)\mu_{x,0}(i)\right)^{R_{x,0}(i)}}{R_{x,0}(i)!}.$$

The log of the likelihood, for all ages and CD4 categories, is

$$\log(L_0)=\log\left(\prod_{i=0}^{3}\prod_{x}L_{x,0}(i)\right)$$

$$=\sum_{i=0}^{3}\sum_{x}-Y_{x,0}(i)\mu_{x,0}(i)+R_{x,0}(i)\log\left(Y_{x,0}(i)\mu_{x,0}(i)\right)-\log\left(R_{x,0}(i)!\right). \quad (4)$$

The likelihood L_0 can be considered a function of five parameters from equation (1): G_0, H_0, $g_0(1)$, $g_0(2)$ and $g_0(3)$.

Similarly, for individuals aged *x* in the second 12 months after starting ART, in CD4 category *i* at the time of ART initiation, we define $Y_{x-1,1}(i)$ to be the exposure and $R_{x-1,1}(i)$ to be the number of deaths, during the second 12 months after starting ART. The log likelihood for the second 12 months after starting ART, $\log(L_1)$, is calculated using a formula similar to that in equation (4), and is a function of the parameters G_1, H_1, $g_1(1)$, $g_1(2)$ and $g_1(3)$.

Finally, we define $Y_{x-2,2}(i)$ to be the exposure for individuals aged *x* more than

24 months after starting ART, who were in CD4 category *i* at the time of starting ART. This includes individuals who were aged *x* at 24 months and individuals who turned *x* after 24 months, but excludes observation time after individuals turn age (*x* + 1). We define $R_{x-2,2}(i)$ to be the number of deaths in individuals who were aged *x* at the time of death, more than 24 months after ART initiation, of those who were in CD4 category *i* at the time of ART initiation. The log likelihood for the post-24 month follow-up period, $\log(L_2)$, is calculated using the same approach as before.

Although we have not included subscripts to indicate sex, all analyses are conducted separately for males and females. There are thus six separate models fitted to the IeDEA Southern Africa data (for three different duration categories and for males and females separately). The $Y_{x-d,d}(i)$ and $R_{x-d,d}(i)$ values are generated for each of the six models using STATA version 11.0 (StataCorp, College Station, TX, USA).

2.9 Model fitting and Life Table Calculation

We fitted the relative survival model to the data using a maximum likelihood approach in STATA 11.0, using the likelihood definitions in section 2.8. Parametric bootstrapping was used to generate 1000 alternative parameter estimates (Efron & Tibshirani, 1986). We developed a C++ programme to calculate the life table and life expectancy for the various combinations of age, sex and baseline CD4 categories, using the formulas detailed in section 2.6. The programme was also used to estimate the fraction of patients starting ART who were expected to die from causes unrelated to HIV. We ran this programme for each of the 1000 bootstrap-sampled parameter estimates to generate distributions of life expectancy estimates, and calculated means and 95% confidence intervals from these.

2.10 Sensitivity analyses

We estimated life expectancy for patients who had survived 24 months since ART initiation, to assess the sensitivity of the results to the high early mortality after ART initiation. Similarly, to assess the effect of continuity of care, we ran the model for individuals whose successive clinic visits were never more than 6 months apart, and whose last clinic visit was not more than 6 months before the date of death or date of analysis closure. To assess sensitivity to non-HIV mortality rates, the relative survival model was refitted after increasing the assumed non-HIV mortality rates by 50%. Because the relative survival approach differs substantially from the more widely-used abridged life table method, we also estimated life expectancy using the abridged life table approach, with an upper age interval of 55 and older (Chiang, 1972; Chiang, 1968). Finally, to assess the effect of including patients with missing baseline CD4 values, we repeated the analysis after assigning CD4 values to these patients using multiple imputation (Molenberghs & Kenward, 2007).

3. RESULTS

3.1 Patient Characteristics and Mortality

Analysis was based on 45 250 adults who started ART between 2001 and 2009. Table 1 shows the patient characteristics at the time of ART initiation. Relatively few patients were aged 55 or older (3.9%), and relatively few patients had CD4 counts ≥200/µl (14.3%). Following ART initiation, 2 659 deaths were recorded in patient record systems and 8 603 patients were lost to follow-up. Of the latter, 4 229 had ID records, and in these LTFU patients with ID records, 1 230 deaths were identified in the population register. After including deaths recorded in the population register and applying the inverse probability weighting, there were 5 239 deaths during 77 446 person-years, for a mean follow-up of 1.71 years. The mortality rate was 67.7 per 1000 person-years of observation (PYO), and was substantially higher in males (79.5 per 1000 PYO) than in females (59.0 per 1000 PYO). The estimated model parameters are included in Table 2, and model fits to the corrected mortality data are shown in Figure 1. Almost all model estimates lie within the 95% confidence intervals around the observed rates, indicating good model fit, although confidence intervals tend to be wide at older ages, because of the low numbers of older patients.

Table 1 Patient characteristics at start of ART

Characteristic	n	%	Characteristic	n	%
Sex			Age		
Male	18 653	41.2%	15–24	3 211	7.1%
Female	26 597	58.8%	25–34	18 385	40.6%
Year of ART initiation			35–44	15 029	33.2%
≤ 2003	1 644	3.6%	45–54	6 881	15.2%
2004	4 567	10.1%	55+	1 744	3.9%
2005	8 195	18.1%	CD4 count		
2006	11 685	25.8%	<50/µl	12 153	26.9%
2007	9 658	21.3%	50–99/µl	9 123	20.2%
2008	6 261	13.8%	100–199/µl	17 508	38.7%
2009	3 240	7.2%	≥200/µl	6 466	14.3%

3.2 Life expectancies

Table 3 summarises the model estimates of life expectancies at ART initiation. The most significant factor determining life expectancy of treated patients was age at ART initiation; the average life expectancy of men starting ART varied between 25.6 years (95% CI: 24.1–27.2) at age 20 and 8.9 years (95% CI: 7.7–10.1) at age 60, while corresponding estimates in women were 32.2 (95% CI: 30.2–34.3) and 14.4 (95% CI:

12.7–15.6) respectively. Life expectancies were also significantly influenced by baseline CD4 counts; life expectancies of individuals with baseline CD4 counts of ≥200/µl were roughly 40–60% greater than life expectancies of individuals with baseline CD4 counts of <50/µl. Life expectancies in patients with baseline CD4 counts ≥200/µl were between 75% and 87% of those in HIV-negative adults of the same age and sex (Figure 2).

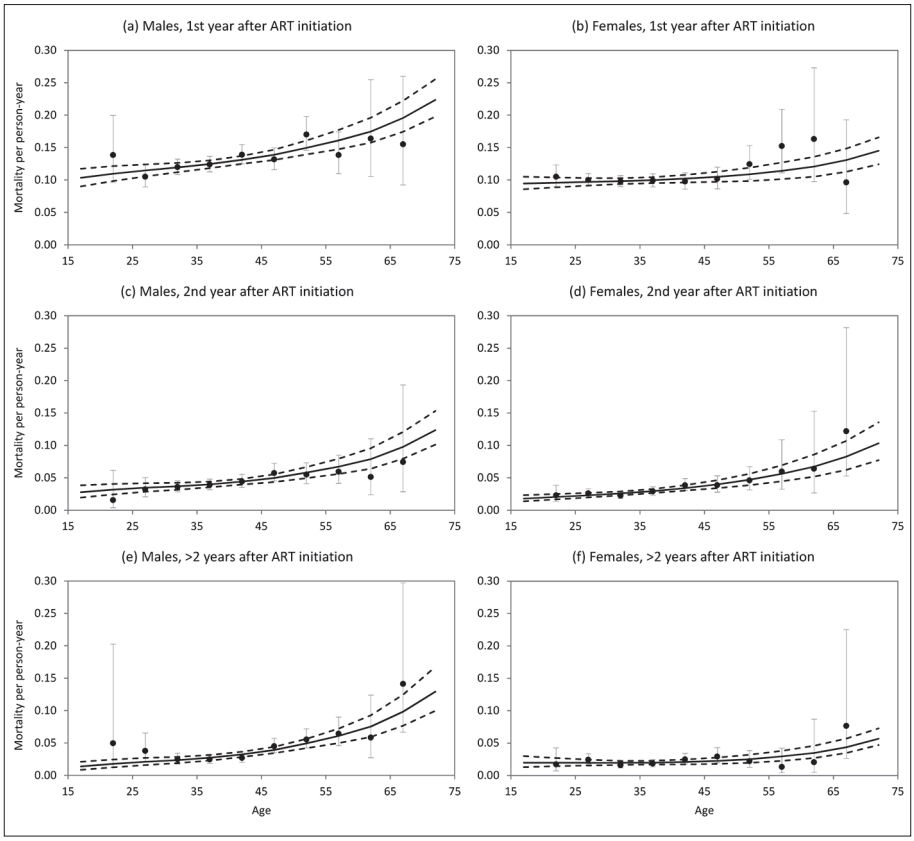

FIGURE 1 Calibration of the relative survival model to IeDEA-SA mortality data
Dots represent observed mortality rates (calculated over 5-year age groups, and plotted at the midpoint of each 5-year age range). Vertical lines represent 95% confidence intervals around the observed rates of mortality. Model means are represented by solid lines, and dashed lines represent 95% confidence intervals for the model estimates. In all comparisons, mortality rates are standardised to the baseline CD4 distribution in Table 1.

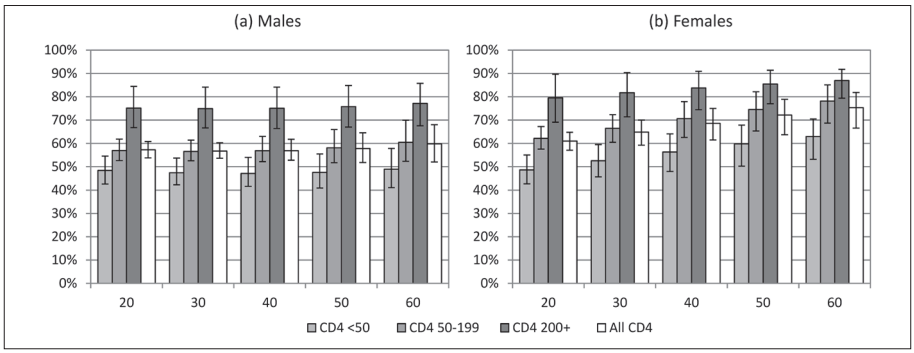

FIGURE 2 Life expectancies of patients starting ART, as proportions of life expectancies of HIV-negative adults of the same age and sex

Proportions are plotted by sex, age at ART initiation and baseline CD4 count. Bars represent means, and error bars represent 95% confidence intervals.

TABLE 2 Mortality rates and model estimates

		Males, by time since start of ART			Females, by time since start of ART		
	Symbol	<12 months	12–24 months	>24 months	<12 months	12–24 months	>24 months
Number of deaths		1871	420	310	2035	390	213
Person years		14456	9433	8857	21066	13424	10209
Crude mortality rate per 1000 PYO		129.5	44.6	35.0	96.6	29.1	20.8
HIV mortality in 35-year olds with baseline CD4 <50	G_d	0.226 (0.210–0.241)	0.055 (0.045–0.066)	0.022 (0.015–0.029)	0.198 (0.185–0.211)	0.043 (0.036–0.051)	0.022 (0.016–0.028)
Increase in HIV mortality for each 10-year increase in age	$(H_d)^{10}$	1.080 (1.023–1.142)	1.149 (0.986–1.318)	1.357 (1.101–1.625)	1.020 (0.963–1.071)	1.270 (1.106–1.423)	0.968 (0.756–1.180)
Hazard ratio relative to CD4 <50							
Baseline CD4 50–99	$\exp(g_d(1))$	0.53 (0.46–0.60)	0.59 (0.42–0.80)	0.85 (0.49–1.36)	0.45 (0.40–0.51)	0.53 (0.39–0.72)	1.02 (0.64–1.52)
Baseline CD4 100–199	$\exp(g_d(2))$	0.29 (0.26–0.33)	0.39 (0.27–0.52)	1.05 (0.70–1.54)	0.24 (0.21–0.27)	0.40 (0.30–0.51)	0.70 (0.45–1.04)
Baseline CD4 200+	$\exp(g_d(3))$	0.19 (0.15–0.23)	0.37 (0.22–0.55)	0.42 (0.18–0.75)	0.23 (0.19–0.28)	0.38 (0.23–0.54)	0.33 (0.10–0.63)

95% confidence intervals are shown in brackets. PYO = person-year of observation.

TABLE 3 Life expectancies at ART initiation by age, sex and baseline CD4 count

Age	Males with baseline CD4				Uninfected men
	<50	50-199*	200+	All*	
20	21.7 (19.1–24.4)	25.5 (23.6–27.7)	33.7 (29.9–37.8)	25.6 (24.1–27.2)	44.8
25	19.5 (17.3–22.0)	23.1 (21.4–25.0)	30.5 (27.2–34.3)	23.2 (21.9–24.5)	40.7
30	17.4 (15.5–19.7)	20.8 (19.3–22.6)	27.5 (24.5–30.9)	20.8 (19.7–22.1)	36.7
35	15.5 (13.7–17.6)	18.5 (17.2–20.3)	24.5 (21.8–27.6)	18.6 (17.5–19.9)	32.8
40	13.6 (12.0–15.5)	16.4 (15.0–18.1)	21.6 (19.1–24.2)	16.3 (15.2–17.8)	28.8
45	11.8 (10.2–13.6)	14.3 (12.9–16.0)	18.8 (16.6–21.0)	14.2 (13.0–15.7)	24.9
50	10.1 (8.7–11.8)	12.3 (11.0–14.0)	16.1 (14.2–18.0)	12.3 (11.0–13.7)	21.2
55	8.6 (7.3–10.1)	10.6 (9.3–12.1)	13.7 (12.0–15.3)	10.5 (9.3–11.9)	17.9
60	7.3 (6.1–8.6)	9.0 (7.8–10.4)	11.4 (10.0–12.7)	8.9 (7.7–10.1)	14.8
Age	**Females with baseline CD4**				**Uninfected women**
	<50	50-199*	200+	All*	
20	25.7 (22.5–29.1)	32.9 (30.4–35.5)	42.0 (36.5–47.4)	32.2 (30.2–34.3)	52.9
25	24.5 (21.4–27.6)	31.1 (28.6–33.6)	39.0 (34.0–43.5)	30.4 (28.2–32.6)	48.3
30	23.0 (20.0–26.1)	29.1 (26.5–31.7)	35.8 (31.3–39.6)	28.4 (26.0–30.7)	43.8
35	21.4 (18.4–24.3)	27.0 (24.2–29.6)	32.6 (28.7–35.7)	26.3 (23.7–28.6)	39.4
40	19.7 (16.8–22.4)	24.7 (21.9–27.2)	29.3 (26.0–31.8)	24.0 (21.5–26.2)	34.9
45	17.8 (15.1–20.3)	22.3 (19.6–24.6)	26.0 (23.2–28.0)	21.6 (19.2–23.6)	30.7
50	15.9 (13.4–18)	19.8 (17.4–21.8)	22.7 (20.5–24.3)	19.2 (16.9–21.0)	26.6
55	13.9 (11.7–15.7)	17.3 (15.2–19.0)	19.6 (17.8–20.8)	16.7 (14.8–18.3)	22.7
60	12.0 (10.2–13.5)	14.9 (13.1–16.3)	16.6 (15.2–17.5)	14.4 (12.7–15.6)	19.1

95% confidence intervals are shown in brackets

* Standardised to the baseline CD4 distribution in Table 1.

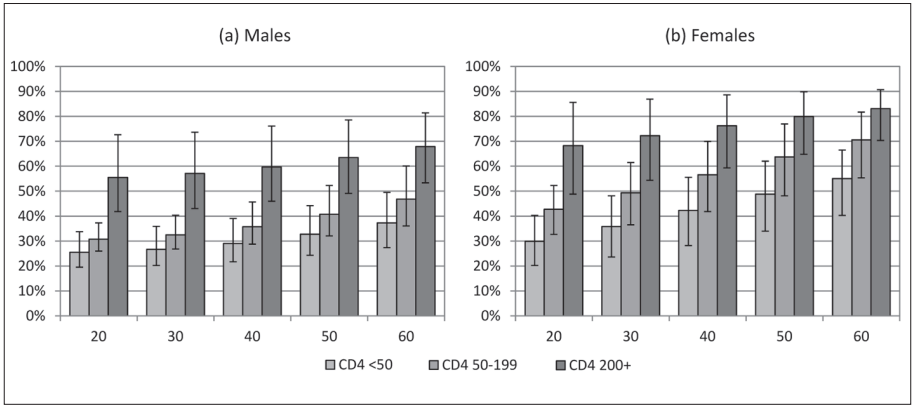

FIGURE 3 Proportion of individuals starting ART who are expected to die from causes unrelated to HIV

Proportions are plotted by sex, age at ART initiation and baseline CD4 count. Bars represent means, and error bars represent 95% confidence intervals.

Figure 3 shows the estimated fraction of patients starting ART who are expected to die from causes unrelated to HIV, if non-HIV mortality rates are the same as in the HIV-negative population. This fraction was higher at older ages (up to 68% in men and 83% in women), as the estimated mortality rates in the HIV-negative population increased more steeply with respect to age than the excess HIV mortality rates in ART patients. The fraction was also higher in women than in men, because HIV-related mortality increased more steeply with respect to age in men than in women, at longer treatment durations (Table 2).

3.3 Comparison with Abridged Life Table Method

Table 4 compares estimates of life expectancy by age, sex and baseline CD4 count, calculated using three different methods. (For the purpose of this comparison, patients with baseline CD4 counts ≥200 are excluded, due to the small sample sizes, which lead to highly unstable estimates when using the abridged life table method.) The relative survival model (RS) is the model described previously. Two approaches to applying the abridged life table method are considered: an approach in which means and standard errors are calculated using parametric bootstrapping (with 1000 replications), and the more widely-used approach, developed by Chiang, in which Taylor series are used to approximate the standard errors (Chiang 1968; 1972).

The relative survival approach yields higher estimates of life expectancy than the abridged life table approaches at young ages, and the extent of this difference is greatest in patients starting ART at low CD4 counts. At older ages, in patients with higher baseline CD4 counts, the abridged life table methods yield slightly higher estimates of life expectancy than the relative survival approach. The abridged life table approach

does not take into consideration differences in mortality rates by ART duration, and recently-enrolled individuals who are at a high mortality risk are therefore over-represented if there is a short average follow-up time. The differences in mortality by duration are greatest in individuals who start ART at very low CD4 counts (Table 2), and the extent of the bias in estimating life expectancy using abridged life tables is therefore greatest in low CD4 categories. Exposure at younger ages is also likely to include greater proportions of recently-enrolled individuals than exposure at older ages. This partially explains why the abridged life table method under-estimates life expectancy by relatively more in young individuals.

Table 4 Comparison of life expectancy estimates from the relative survival model (RS), abridged life table method with bootstrapping (ALB) and abridged life table method developed by Chiang (ALC)

	Baseline CD4 <50			Baseline CD4 50–99			Baseline CD4 100–199		
	RS	ALB	ALC	RS	ALB	ALC	RS	ALB	ALC
Men									
Age 25	19.5 (1.19)	7.1 (0.37)	7.1 (0.35)	23.4 (1.51)	12.8 (0.86)	12.8 (0.84)	22.9 (1.08)	18.6 (0.81)	18.5 (0.74)
Age 35	15.5 (1.01)	7.5 (0.27)	7.5 (0.26)	18.8 (1.23)	12.0 (0.54)	12.0 (0.47)	18.4 (0.93)	16.2 (0.66)	16.1 (0.46)
Age 45	11.8 (0.89)	7.1 (0.46)	7.0 (0.35)	14.4 (1.02)	10.1 (0.78)	10.0 (0.51)	14.2 (0.89)	14.2 (0.88)	14.1 (0.42)
Age 55	8.6 (0.74)	7.9 (1.19)	7.6 (–)	10.6 (0.81)	11.6 (1.75)	11.3 (–)	10.6 (0.80)	12.0 (1.38)	11.8 (–)
Women									
Age 25	24.5 (1.60)	8.6 (0.30)	8.6 (0.29)	27.6 (1.88)	18.1 (1.94)	17.1 (0.67)	32.9 (1.55)	25.1 (1.39)	24.8 (0.64)
Age 35	21.4 (1.52)	9.1 (0.36)	9.0 (0.32)	24.3 (1.75)	19.2 (3.39)	17.4 (0.77)	28.4 (1.47)	22.9 (1.85)	22.6 (0.67)
Age 45	17.8 (1.33)	8.4 (0.57)	8.3 (0.43)	20.4 (1.53)	19.9 (5.90)	16.9 (0.95)	23.3 (1.27)	20.1 (2.45)	19.7 (0.71)
Age 55	13.9 (1.02)	6.0 (1.01)	5.8 (–)	16.0 (1.16)	23.4 (11.2)	17.8 (–)	18.0 (0.95)	20.0 (3.84)	19.4 (–)

Standard errors are shown in brackets.

The reversal of the difference between the relative survival and abridged life table estimates at the older ages is likely to be because of the assumption, made in the abridged life table method, that mortality rates are constant in the upper age interval.

If mortality rates are actually increasing in relation to age over the upper age interval (55+ in this analysis), then estimating a constant mortality rate based on individuals who tend to be at the lower end of the interval can lead to significant over-estimation of the life expectancy in the upper age interval. This bias offsets the bias described in the previous paragraph, so that the abridged life table method under-estimates life expectancy by less at older ages than at younger ages, and might even over-estimate life expectancy.

Although average estimates of life expectancy are similar when comparing the abridged life table method with bootstrapping (ALB) and the abridged life table method developed by Chiang (ALC), the Chiang method yields substantially lower standard error estimates, particularly for patients starting ART at older ages. This is likely to be because the Chiang method ignores uncertainty regarding the mortality rate in the upper age interval. This would not be a major source of discrepancy if relatively few patients survived to the upper age interval, but because the lower limit on the upper age interval is relatively low in this analysis (age 55), ignoring the uncertainty in the upper age interval leads to substantial exaggeration of precision. This exaggeration of precision is greatest for those patients starting ART who have the greatest probability of surviving to age 55, i.e. older patients and patients starting ART with high CD4 counts.

In summary, the abridged life table method has three potential limitations when it is used to estimate life expectancies of HIV-positive patients starting ART. Firstly, the method does not take into account differences in mortality by duration, and this is likely to lead to under-estimation of life expectancy if average follow-up time is short, especially in patients starting ART at low CD4 counts. Secondly, the method assumes a constant rate of mortality in the upper age interval, which is likely to lead to the life expectancy in the upper age interval (and at older ages) being over-estimated. Thirdly, the method recommended by Chiang for calculating standard errors tends to exaggerate the precision associated with the life expectancy, particularly at older ages.

3.4 Comparison with Estimates obtained using Imputation

For 7 312 (13.9%) of the eligible adults starting ART, no CD4 measurement was available in the period between 182 days before and 14 days after starting ART. Multiple imputation by chained equations (Van Buuren et al., 1999) was used to assign baseline CD4 values to these patients with missing CD4 values. Imputation was conducted using the ICE command in Stata 11.0, with five imputations. The observed CD4 values were transformed using a square root transformation before the imputation was conducted, in order to achieve a more 'normal' distribution of baseline CD4 values. The imputation model included age, sex, CD4 count (on square root scale), year, cohort, outcome, time to outcome and inverse probability weight. Life expectancies calculated using multiple imputation (MI) are compared with those calculated after excluding patients with missing baseline CD4 counts (EX), in Table 5.

TABLE 5 Comparison of life expectancy estimates obtained when excluding patients with missing baseline CD4 counts (EX) and when using multiple imputation (MI) to assign baseline CD4 values to patients with missing information

	CD4 <50		CD4 50-199*		CD4 200+		All*	
	EX	MI	EX	MI	EX	MI	EX	MI
Men								
Age 25	19.5 (1.19)	20.3 (1.19)	23.1 (0.90)	23.2 (0.92)	30.5 (1.88)	29.5 (2.18)	23.2 (0.66)	23.3 (0.66)
Age 35	15.5 (1.01)	16.6 (1.00)	18.5 (0.79)	19.3 (0.80)	24.5 (1.52)	24.2 (1.65)	18.6 (0.63)	19.2 (0.62)
Age 45	11.8 (0.89)	13.0 (0.86)	14.3 (0.79)	15.2 (0.77)	18.8 (1.18)	18.8 (1.19)	14.2 (0.68)	15.1 (0.66)
Age 55	8.6 (0.74)	9.7 (0.69)	10.6 (0.73)	11.5 (0.67)	13.7 (0.86)	13.9 (0.81)	10.5 (0.65)	11.4 (0.60)
Women								
Age 25	24.5 (1.60)	25.7 (1.49)	31.1 (1.30)	31.9 (1.26)	39.0 (2.44)	38.3 (2.49)	30.4 (1.09)	31.1 (1.04)
Age 35	21.4 (1.52)	22.3 (1.42)	27.0 (1.38)	27.5 (1.29)	32.6 (1.80)	32.0 (1.86)	26.3 (1.24)	26.7 (1.16)
Age 45	17.8 (1.33)	18.4 (1.25)	22.3 (1.27)	22.5 (1.17)	26.0 (1.26)	25.6 (1.32)	21.6 (1.16)	21.8 (1.09)
Age 55	13.9 (1.02)	14.2 (0.96)	17.3 (0.98)	17.5 (0.90)	19.6 (0.81)	19.3 (0.87)	16.7 (0.90)	16.9 (0.85)

Standard errors are shown in brackets. * Standardised to the baseline CD4 distribution in Table 1.

When considering all patients together, the MI estimates are slightly higher than the EX estimates, suggesting that patients with missing CD4 values tend to be healthier on average than those with recorded baseline CD4 values. MI estimates are substantially higher than EX estimates at low CD4 counts, but tend to be slightly lower than EX estimates at high CD4 counts. This probably reflects the lack of precision in the assignment of missing baseline CD4 values; if a high proportion of patients with imputed baseline CD4 count of <50/μl were in fact in higher baseline CD4 categories, then we would expect the MI estimates of life expectancy to be higher than the EX estimates at CD4 <50/μl. Conversely, if a high proportion of patients with imputed baseline CD4 count of ≥200/μl were in fact in lower baseline CD4 categories, then we would expect the MI estimates of life expectancy to be lower than the EX estimates at CD4 ≥200/μl.

3.5 Further Sensitivity Analyses

Further sensitivity analyses are presented in Table 6. Estimates of life expectancy were marginally higher in patients who had survived their first two years after starting ART when compared with life expectancies at the time of ART initiation. Life expectancies were substantially higher in patients who had survived their first two years after starting ART and did not interrupt therapy for more than six months, although this difference was less in women than in men. After refitting the model with 50% higher non-HIV mortality rates, life expectancy estimates were reduced by 1–2 years in women, but little change was observed in male life expectancy estimates.

Table 6 Sensitivity analysis: life expectancies in patients starting ART with CD4 counts of 100–199/μl

	Main analysis	Patients who started ART >2 years previously	Patients who started ART >2 years previously, with no treatment interruption >6m	Non-HIV mortality rates increased by 50%
Men				
Age 25	22.9 (20.9–25.1)	23.9 (21.7–26.6)	31.6 (26.4–37.2)	22.7 (20.6–24.8)
Age 35	18.4 (16.8–20.5)	19.2 (17.3–21.5)	26.0 (21.3–30.3)	18.5 (16.9–20.3)
Age 45	14.2 (12.7–16.2)	14.7 (13.0–16.9)	20.2 (15.5–23.5)	14.3 (12.8–15.8)
Age 55	10.6 (9.2–12.3)	10.8 (9.2–12.8)	14.8 (10.6–17.2)	10.4 (9.1–11.6)
Women				
Age 25	32.9 (29.9–35.8)	33.9 (30.6–37.1)	36.8 (30.1–42.0)	31.7 (29.0–34.3)
Age 35	28.4 (25.4–31.0)	29.4 (26.2–32.2)	30.6 (24.1–34.9)	27.0 (24.6–29.1)
Age 45	23.3 (20.5–25.5)	24.3 (21.2–26.8)	24.3 (18.4–27.8)	21.5 (19.6–23.1)
Age 55	18.0 (15.9–19.6)	18.9 (16.4–20.8)	18.4 (13.3–21.0)	16.1 (14.7–17.1)

95% confidence intervals are shown in brackets. Main analysis includes all patients with CD4 measurements at time of ART initiation, and includes follow-up of individuals who interrupt therapy. Life expectancies in the main analysis are calculated from the time of ART initiation, using the relative survival method.

4. DISCUSSION

This analysis suggests that South African patients starting ART have life expectancies around 80% of normal life expectancy, provided that they start treatment before their CD4 count drops below 200/μl. Life expectancy is also higher in patients who do not interrupt treatment. Although these results are encouraging, programmes in resource-limited settings experience major challenges with late diagnosis, low uptake of CD4 testing, loss from pre-ART care and delayed ART initiation (Rosen & Fox,

2011). Individuals who start ART also frequently interrupt treatment in the South African setting (Kranzer et al., 2010), and these interruptions are often associated with poorer immunological recovery and the development of drug resistance (Kranzer & Ford, 2011). Health services need to overcome these challenges if near-normal life expectancies are to be achieved for the majority of HIV-positive South Africans.

South African treatment guidelines have recently changed and it is now recommended that all asymptomatic HIV-infected adults should start ART when their CD4 counts fall below 350/μl. Coupled with recent campaigns to increase the uptake of HIV testing (Pillay et al., 2012) and dramatic growth in rates of ART enrolment in South Africa (Johnson, 2012), this should lead to a substantially increased proportion of patients starting ART at CD4 counts above 200/μl. However, over the period to which this analysis relates, most of the patients starting ART at CD4 counts above 200/μl did so because they qualified for treatment on clinical grounds. Such patients are likely to experience higher mortality than asymptomatic patients with CD4 counts above 200/μl (Brinkhof et al., 2009a; Egger et al., 2002). These estimates of life expectancy in early initiators may therefore be under-estimates of the life expectancies in future, when a greater fraction of these early initiators are likely to be asymptomatic.

A key strength of this analysis is that it incorporates data from the South African population register to obtain more accurate estimates of mortality than are usually possible in African countries. Because patients with ID information are not censored at the date of loss to follow-up, these estimates of life expectancy are inclusive of patients who are not retained in care. However, there is likely to be a small proportion of deaths (probably around 5%) that are recorded neither in the patient record system nor in the vital registration system. This could lead to life expectancies being slightly exaggerated.

Predicting future mortality of ART patients is challenging. In addition to the historical bias towards enrolment of symptomatic patients, mentioned previously, these estimates do not take into account potential future reductions in mortality that may occur as new drugs and salvage regimens are introduced (Taiwo et al., 2010), and as innovations in patient management are introduced (Bärnighausen et al., 2011). It should also be noted that due to the small number of patients on ART at long durations, mortality data have been aggregated for all durations greater than 24 months. This may be reasonable, as average CD4 levels tend to stabilise after the first 24 months of treatment (Nash et al., 2008; Lok et al., 2010). However, if HIV-related mortality continues to decline with increasing ART duration, the lack of data at long durations could imply some under-estimation of life expectancy. On the other hand, the accumulation of drug resistance mutations at longer durations could imply long-term increases in HIV-related mortality, and mathematical modelling suggests that life expectancy may be sensitive to the number of treatment options available (King et al., 2003).

The principle advantage of the relative survival model, when compared with the abridged life table method that is more commonly used in the estimation of

life expectancy, is that it adjusts for differences in mortality by treatment duration, which are particularly marked in resource-limited settings (Braitstein et al., 2006). Not controlling for these differences can introduce significant bias if average follow-up time is short. Another advantage of the relative survival approach is that it incorporates information on non-HIV mortality in the general population, which is likely to be relatively more significant at older ages. This analysis suggests that a substantial proportion of deaths in ART patients are likely to be unrelated to their HIV infection. It is therefore important that comparisons of life expectancies of HIV patients in different regions take into account differences in non-HIV mortality between settings, and the relative survival model provides a framework within which this can be achieved.

Studies of life expectancies of ART patients in high-income countries that have excluded high-risk groups (intravenous drug users and patients starting ART in advanced disease) have generally estimated life expectancies that are 73–99% of those in the general population (May et al., 2011; Van Sighem et al., 2010; Lohse et al., 2007; Nakagawa et al., 2012). However, studies that have not excluded high risk groups have estimated life expectancies that are 51–66% of those in the general population (McDavid Harrison et al., 2010; Lohse et al., 2007; Losina et al., 2009). These results are roughly consistent with our ratios: 57–75% when all CD4 categories are combined, and 75–87% when analysis is restricted to patients with baseline CD4 counts ≥200/μl (Figure 2).

Only one other study in Africa has estimated the life expectancy of patients starting ART (Mills et al., 2011). This study, conducted in Uganda, estimated lower life expectancy in patients starting ART at young ages, when compared with our South African estimates, but generated higher estimates than those obtained in South Africa for patients starting ART at older ages. These differences may be partly attributable to differences in methodology, as Table 4 shows that the abridged life table method (used in the Ugandan study) is likely to generate lower estimates of life expectancy at younger ages, but higher estimates at older ages. Some of the difference may also be explained by differences in the approach to determining the mortality of patients lost to follow-up, which was assumed to be 30% in the Ugandan analysis. If the fraction of individuals LTFU who are found to have died is higher at older ages than at younger ages (Van Cutsem et al., 2011; Geng et al., 2010), the assumption of a constant fraction at all ages could lead to some under-estimation of the extent of age differences in life expectancy.

The generalisability of these findings – even within South Africa – is open to question. The South African cohorts participating in the IeDEA-SA Collaboration are relatively well-resourced programmes with substantial research support, mostly in urban centres. These programmes might therefore not be representative of all South African ART programmes. The assumption that the average non-HIV mortality rates in South Africa apply in all cohorts could also be problematic, although estimates of life expectancy did not change substantially when the model was refitted with non-

HIV mortality rates increased by 50%. Another limitation is that our approach to fitting the relative survival model ignores potential heterogeneity in mortality between cohorts. However, in a comparison of mortality rates in different South African cohorts, little difference in mortality was found (Boulle et al., 2011). These findings might not be typical of programmes in most other African countries, as South Africa is an upper middle-income country with rates of non-HIV mortality lower than in most other African countries (United Nations Department of Economic and Social Affairs Population Division, 2011). HIV-related mortality in South African ART patients may also be lower than in other African countries due to virological monitoring of ART patients, which is routine in South Africa but not in most other African countries (Keiser et al., 2011).

These results have important implications for the demographic and epidemiological models that are used to forecast the impact and cost of ART programmes in developing countries. These models have typically assumed that life expectancy after ART initiation is around 10 years (Mahy et al., 2010; Walensky et al., 2010; Johnson and Dorrington 2006). Assumptions of longer life expectancy would significantly reduce the forecasts of AIDS mortality, but would also significantly increase long-term projections of numbers of patients receiving ART. With the anticipated increase in the fraction of patients starting ART at high CD4 counts in future, long-term survival will increase even further. It is therefore critical that appropriate funding systems and innovative ways to reduce costs are put in place, to ensure the long-term sustainability of ART programmes in developing countries.

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