All-cause mortality in HIV-positive adults starting combination antiretroviral therapy: correcting for loss to follow-up

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Objective: To estimate mortality in HIV-positive patients starting combination antiretroviral therapy (ART) and to discuss different approaches to calculating correction factors to account for loss to follow-up.

Methods: A total of 222 096 adult HIV-positive patients who started ART 2009–2014 in clinics participating in the International epidemiology Databases to Evaluate AIDS collaboration in 43 countries in sub-Saharan Africa, Asia Pacific, Latin America, and North America were included. To allow for underascertainment of deaths due to loss to follow-up, two correction factors (one for the period 0–6 months on ART and one for later periods) or 168 correction factors (combinations of two sexes, three time periods after ART initiation, four age groups, and seven $CD4^+$ groups) based on tracing patients lost in Kenya and data linkages in South Africa were applied. Corrected mortality rates were compared with a worst case scenario assuming all patients lost to follow-up had died.

Results: Loss to follow-up differed between regions; rates were lowest in central Africa and highest in east Africa. Compared with using two correction factors (1.64 for the initial ART period and 2.19 for later), applying 168 correction factors (range 1.03–4.75) more often resulted in implausible mortality rates that exceeded the worst case scenario. Corrected mortality rates varied widely, ranging from 0.2 per 100 person-years to 54 per 100 person-years depending on region and covariates.

Conclusion: Implausible rates were less common with the simpler approach based on two correction factors. The corrected mortality rates will be useful to international agencies, national programmes, and modellers.

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Introduction

The survival of HIV-positive patients on antiretroviral therapy (ART) is an important indicator of ART programmes' effectiveness and is key to informing public health policy [1,2]. Estimations of mortality in HIV-positive patients on ART rely on the complete ascertainment of deaths. However, many patients starting ART are lost to follow-up, especially in sub-Saharan Africa, and their mortality is typically higher compared with patients retained in care [3–5]. Deaths among patients lost to follow-up are not generally recorded, leading to underestimation of overall, programme-level mortality. Several correction methods to reduce this bias have been proposed [6–8], which rely on vital status information of a sample of patients lost to follow-up obtained through tracing or data linkages with civil registries [4,5,9].

The International epidemiology Databases to Evaluate AIDS (IeDEA) collaboration is a consortium of HIV cohort studies and clinical databases with regional networks in sub-Saharan Africa, North and Latin America, and Asia Pacific [10–12]. IeDEA is an important source of regional HIV/AIDS data, which has been used, for example, in the Spectrum projection package (Avenir Health, Glastonbury, CT, USA) developed for the Joint United Nations Program on HIV/AIDS (UNAIDS) [13]. Spectrum is a modelling package that supports national programmes to make annual estimates of the number of people living with HIV by age and sex, the number of new infections and AIDS deaths, and the need for ART and its impact [13,14].

In 2012, the IeDEA consortium provided UNAIDS with mortality estimates for patients on ART for use in the Spectrum projection package [8]. In that study, a two-stage approach was used to adjust for biases in mortality estimation resulting from loss to follow-up. Initially, correction factors were determined on the basis of data from programmes tracing patients lost to follow-up in Kenya [15] and from linkages with population registries in South Africa [9]. Then the correction factors were applied to adjust mortality rates from other regions [8]. The aim of this analysis is to update the previous estimates and to refine and study the mortality correction methods.

Methods

Data sources

We included longitudinal patient-level data from HIV cohorts in the seven regions of the IeDEA collaboration: central Africa, east Africa, southern Africa, west Africa, Asia Pacific, Latin America (Caribbean, central, and South America), and North America [10–12]. Forty-three countries contributed data: Rwanda, Burundi, and Democratic Republic of the Congo (central Africa); Uganda, Kenya, and Tanzania (east Africa); South Africa, Zambia, Zimbabwe, Malawi, Lesotho, and Mozambique (southern Africa); Côte d'Ivoire, Nigeria, Togo, Burkina Faso, Mali, Benin, Guinea-Bissau, Senegal, and Guinea (west Africa); India, Singapore, Cambodia, Vietnam, Thailand, Hong Kong, Philippines, Malaysia, Taiwan, Japan, Republic of Korea, China, and Indonesia (Asia Pacific); Haïti, Peru, Brazil, Chile, Argentina, Mexico, and Honduras (Latin America); and USA and Canada (North America). In all of the cohorts, data were collected at enrolment, ART initiation, and at each follow-up visit. Pooling of data and their use in collaborative analyses was approved by local ethics committees and institutional review boards.

For two of the regions, data included information about outcomes in patients lost to follow-up: the cohorts from the Republic of South Africa had linked their patients to the national death registry, and cohorts in Kenya carried out tracing of patients lost to follow-up to ascertain their vital status. For the other countries of the east and southern African regions and the five other regions, no information on mortality in patients lost to follow-up was available. In North America and Latin America, some cohorts linked patients to vital registries and updated the outcomes of these patients in their databases. However, they did not record whether or not a death was ascertained through linkage to a vital registry.

Inclusion criteria, collection of variables, and definitions

We included patients aged at least 15 years who were ART-naïve at enrolment, started ART between 2009 and 2014, and had at least 1 day of follow-up. ART was defined as a combination of at least three antiretroviral drugs. Data included patient sex, age, $CD4^+$ cell count at start of ART, date of starting ART, and outcome. The $CD4^+$ cell count at ART start was defined as the measurement closest to the date of starting therapy within a window of 182 days before and 14 days after ART initiation. To match the structure of the Spectrum model, age was grouped into four categories (15–24, 25–34, 35–44, and $\geq$45 years) and $CD4^+$ cell count at ART start into seven categories (<50, 50–99, 100–199, 200–249, 250–349, 350–499, and $\geq$500 cells/μl). Outcomes included death and loss to follow-up. Patients were considered lost to follow-up if their last visit was more than 182 days prior to database closure and there was no record of their death or transfer [16]. The Kenyan cohorts recorded whether a patient had been traced or not, and the South African linkage cohorts recorded whether a patient had a valid South African civil identification (ID) number.

Estimation of crude mortality rates

We used exponential survival models to estimate mortality rates not adjusted for loss to follow-up. We assumed a piecewise constant hazard for three time periods (0–6, 6–12, and $\geq$12 months after starting ART)

and included the covariates sex, age, and $CD4^+$ cell count at ART start. In addition, we modelled the period 0–6 months separately from the other two periods to allow for potentially different effects of covariates on mortality shortly after starting treatment. The follow-up of all patients without a death record was administratively censored at the last visit in the unadjusted analysis. Models were fit using the penalized maximum likelihood estimation procedure proposed by Gertheiss and Tutz [17], which accounts for the ordinal nature of the $CD4^+$ covariate. This procedure smoothes coefficients across categories of the $CD4^+$ cell count at ART start so that they become more similar to those of adjacent $CD4^+$ cell count categories, which reduces overfitting and improves prediction. We determined the penalization parameter for each region separately, minimizing deviances in a 10-fold cross-validation.

Correction for loss to follow-up

We multiplied the crude mortality rates by correction factors to adjust them for loss to follow-up. We calculated three different sets of correction factors, one from the Kenyan tracing data and two from the South African linkage data. For Kenya, we determined the correction factors in the same way as in 2012 [8]: first we calculated crude mortality rate estimates for all subgroups by fitting the survival model and treating patients lost to follow-up as administratively censored. Then, we included the ascertained outcomes of traced patients, weighted observations as proposed by Frangakis and Rubin [18], and fitted the model to the updated data to obtain adjusted mortality rate estimates. The correction factors were derived by dividing the adjusted rate estimates by the crude estimates. This led to a Kenyan set of 168 correction factors, one for each covariate subgroup (two sexes × three time periods × four age groups × seven $CD4^+$ groups).

For the South African data, we fitted the survival model including an additional covariate, which indicated whether or not a patient had an ID and was therefore linkable to the vital registry. The first of the two sets of correction factors was defined as the estimated effect of this linkage indicator. This entailed two correction factors, one for the initial ART period (0–6 months) and one for later ART, which were modelled separately. In a further analysis, we allowed for two-way interactions between the linkage indicator and the other covariates. We then defined the correction factors as the estimated effect of the linkage indicator and its interactions. As with Kenya, this resulted in a set with 168 correction factors. In contrast to Kenya, this approach allowed statistical testing of whether the inclusion of any of the two-way interactions improved the model.

Measuring variability

We used the bootstrap case resampling method for regression analyses to generate sampling errors both for crude mortality rate estimates and correction factors. Assuming independence of the two, we derived the total variance around the adjusted mortality estimates by adding the two variances.

Sensitivity analyses

We used sensitivity analyses to gauge the plausibility of corrected mortality rate estimates. We compared the three sets of corrected mortality rates with crude estimates and estimates from worst and best case scenarios. The worst case scenario assumed that all patients lost to follow-up had died at their last visit. The best case scenario assumed that all patients lost to follow-up were alive at database closure.

Results

Selection of eligible patients

After excluding patients with missing $CD4^+$ cell count at the start of ART or no follow-up visit after ART was initiated, 222 096 patients were included in the analyses (Table 1): 8043 from central Africa, 61 315 from east Africa, 109 434 from southern Africa, 21 713 from west Africa, 7425 from Asia Pacific, 7017 from Latin America, and 7149 from North America. A total of 30 292 patients were enrolled in Kenyan cohorts with tracing programmes and 35 674 South African patients in cohorts in which vital registry linkage was available. Of these 35 674 patients, 13 749 (39%) had no ID and could not be linked.

Baseline characteristics and loss to follow-up

For all African regions, the proportion of women among all patients initiating ART was about twice the proportion of men, whereas for non-African regions the opposite was the case (Table 1). The median age at the start of ART ranged from 33 years in the east African cohorts without tracing to 39 years in North America. The median $CD4^+$ cell count at ART initiation ranged from 157 cells/μl in southern African cohorts with vital registry linkage to 336 cells/μl in North America.

Rates of loss to follow-up differed widely between regions. Rates were lowest in central Africa and highest in east Africa (Table 2). For all African regions, rates of loss to follow-up declined with longer ART duration. In non-African regions, the decline was less consistent: in Asia Pacific, the rate of loss to follow-up was highest in the first 6 months of ART but stayed constant afterwards, in North America rates declined slightly, and in Latin America the rate of loss to follow-up stayed fairly constant.

Crude mortality rate estimates

Crude mortality rates were generally highest in southern Africa; slightly lower in east and west Africa; lower in central Africa, Latin America, and Asia Pacific; and clearly lowest in North America (Supplementary Tables S1–S7,

Table 1. Patient characteristics at the start of antiretroviral therapy by region.

	Regions without linkage or tracing							Regions with linkage or tracing	
	Central Africa	East Africa (no tracing)	Southern Africa (no linkage)	West Africa	Asia Pacific	Latin America	North America	East Africa (tracing)	Southern Africa (linkage)
No. of patients	8043	31 023	73 760	21 713	7425	7017	7149	30 292	35 674
Sex									
Male	2695 (34%)	11 365 (37%)	27 172 (37%)	7193 (33%)	5097 (69%)	4348 (62%)	5473 (77%)	10 849 (36%)	12 603 (35%)
Female	5348 (66%)	19 658 (63%)	46 588 (63%)	14 520 (67%)	2328 (31%)	2669 (38%)	1676 (23%)	19 443 (64%)	23 071 (65%)
Age (years)									
Median (IQR)	34 (28–42)	33 (27–40)	35 (29–42)	37 (31–45)	37 (31–44)	36 (29–44)	39 (30–48)	37 (30–45)	35 (29–42)
15–24	1053 (13%)	3604 (12%)	7491 (10%)	1324 (6%)	516 (7%)	816 (12%)	840 (12%)	2001 (7%)	3321 (9%)
25–34	3185 (40%)	12 537 (40%)	28 820 (39%)	7651 (35%)	2617 (35%)	2505 (36%)	2056 (29%)	9170 (30%)	14 725 (41%)
35–44	2409 (30%)	9400 (30%)	23 690 (32%)	7517 (35%)	2644 (36%)	2102 (30%)	1906 (27%)	10 302 (34%)	11 254 (32%)
45+	1396 (17%)	5482 (18%)	13 759 (19%)	5221 (24%)	1648 (22%)	1594 (23%)	2347 (33%)	8819 (29%)	6374 (18%)
$CD4^+$ cell count (cells/μl)									
Median (IQR)	275 (174–342)	207 (96–324)	198 (108–295)	181 (82–291)	170 (58–283)	210 (85–205)	336 (190–488)	173 (74–279)	157 (80–231)
<50	450 (6%)	4565 (15%)	7586 (10%)	3676 (17%)	1631 (22%)	1149 (16%)	677 (9%)	5489 (18%)	5662 (16%)
50–99	556 (7%)	3456 (11%)	9176 (12%)	2707 (12%)	973 (13%)	772 (11%)	406 (6%)	4127 (14%)	5447 (15%)
100–199	1425 (18%)	6997 (23%)	20 523 (28%)	5432 (25%)	1594 (21%)	1422 (20%)	787 (11%)	7663 (25%)	12 213 (34%)
200–249	938 (12%)	3448 (11%)	9938 (13%)	2610 (12%)	857 (12%)	827 (12%)	551 (8%)	3522 (12%)	5132 (14%)
250–349	2923 (36%)	6473 (21%)	17 141 (23%)	4076 (19%)	1471 (20%)	1952 (28%)	1336 (19%)	5986 (20%)	5367 (15%)
350–499	961 (12%)	3513 (11%)	5802 (8%)	1825 (8%)	591 (8%)	620 (9%)	1702 (24%)	1970 (7%)	1172 (3%)
≥500	790 (10%)	2571 (8%)	3594 (5%)	1387 (6%)	308 (4%)	275 (4%)	1690 (24%)	1535 (5%)	681 (2%)

IQR, interquartile range.

Table 2. Rates of loss to follow-up and duration of antiretroviral therapy by region.

	Regions without linkage or tracing							Regions with linkage or tracing	
	Central Africa	East Africa (no tracing)	Southern Africa (no linkage)	West Africa	Asia Pacific	Latin America	North America	East Africa (tracing)	Southern Africa (linkage)[a]
Loss to follow-up rate (95% CI) (per 100 person-years)									
<6 months ART	7.3 (6.5–8.3)	27.0 (26.1–27.9)	14.9 (14.5–15.3)	21.9 (21.0–22.8)	18.0 (16.7–19.5)	13.2 (12.0–14.5)	16.7 (15.4–18.2)	53.0 (51.8–54.3)	29.5 (28.1–31.0)
6–12 months ART	6.4 (5.6–7.3)	15.0 (14.2–15.7)	7.9 (7.5–8.2)	12.7 (11.9–13.5)	10.6 (9.5–11.9)	11.9 (10.7–13.2)	16.4 (14.9–18.0)	34.0 (32.9–35.2)	20.0 (18.7–21.5)
≥12 months ART	5.4 (5.0–5.8)	9.3 (8.9–9.6)	6.3 (6.1–6.5)	10.8 (10.4–11.1)	10.6 (10.0–11.3)	13.7 (12.9–14.4)	15.8 (14.8–16.7)	23.3 (22.7–23.9)	17.0 (16.1–17.9)
Median years on ART before lost to follow-up (IQR)									
	1.34 (0.55–2.39)	0.60 (0.19–1.44)	0.76 (0.21–1.86)	1.11 (0.39–2.54)	1.17 (0.37–2.32)	1.46 (0.64–2.34)	1.07 (0.46–1.95)	0.68 (0.24–1.52)	0.63 (0.24–1.44)

ART, antiretroviral therapy, CI, confidence interval, IQR, interquartile range.
[a]Based on patients who could not be linked to the vital registry.

http://links.lww.com/QAD/B7). Crude mortality was highest in patients with $CD4^+$ cell counts less than 50 cells/μl at ART initiation and declined with increasing $CD4^+$ cell count, although the decline was only modest for the highest four $CD4^+$ categories. Crude mortality was highest in the first 6 months after starting therapy for all regions except North America, where mortality did not vary much by duration of therapy.

Correction factors and sensitivity analysis

The three sets of correction factors are illustrated in Fig. 1 and given in Supplementary Table S8, http://links.lww.com/QAD/B7. The South African set with two correction factors implied that underascertainment of death was less pronounced in the first 6 months of ART duration. The South African set with 168 correction factors contained some high values and implausible patterns, for example, for $CD4^+$ categories 350–499 and at least 500 cells/μl (where sample sizes were small). None of the two-way interactions included in the model was statistically significant ($P > 0.05$). The Kenyan set of 168 correction factors also showed some unexpected patterns, most likely due to small sample sizes in some of the combinations of ART duration, sexes, age groups, and $CD4^+$ groups.

Implausible corrected mortality rates that exceeded the worst case scenario were observed for southern Africa,

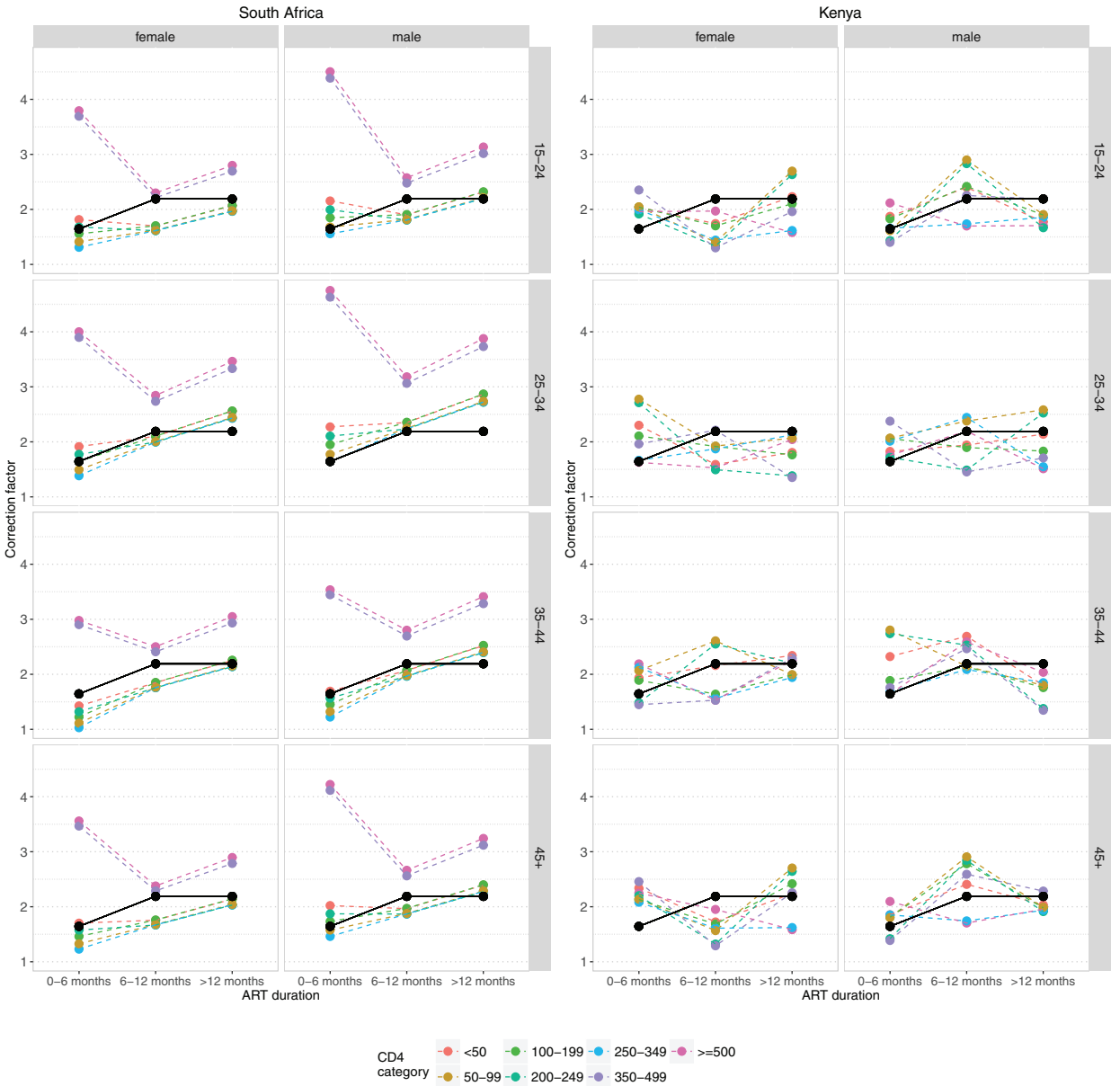

Fig. 1. Correction factors. The South African set of two correction factors is shown in black, the two sets of 168 correction factors derived from the South African and Kenyan data are shown in colour.

Table 3. Implausible corrected mortality rates exceeding the worst case scenario estimates, by set of correction factors used.

	South African correction factors		Kenyan correction factors
	Set of 2	Set of 168	Set of 168
Southern Africa[a]	6/168 (3.6%)	7/168 (4.2%)	10/168 (6.0%)
Central Africa	4/168 (2.4%)	5/168 (3.0%)	10/168 (6.0%)
Latin America	5/168 (3.0%)	5/168 (3.0%)	7/168 (4.2%)
Asia Pacific	1/168 (0.6%)	1/168 (0.6%)	2/168 (1.2%)
East Africa	0/168 (0%)	0/168 (0%)	0/168 (0%)
West Africa	0/168 (0%)	0/168 (0%)	0/168 (0%)
North America	0/168 (0%)	0/168 (0%)	0/168 (0%)

[a]Nonlinkage cohorts only.

central Africa, Latin America, and Asia Pacific. There were 16 such instances for mortality corrections with the South African set of two correction factors, 18 instances with the South African set of 168 factors, and 29 with the Kenyan set of 168 factors (Table 3). Some of these implausible rates are shown in Fig. 2, panels a–d. In west Africa, North America, and east Africa, worst case mortality estimates were high, and none of the corrected rates exceeded them (Fig. 2, panels e–g). There were no correction factors below 1; therefore, no corrected mortality rate estimates fell below the best case scenario.

Final corrected mortality rates

In the final analysis, we used the South African set of two correction factors to adjust mortality rates in all regions except in east Africa, where we used the Kenyan set of 168 correction factors. The corrected mortality rate estimates with bootstrapped 95% confidence intervals, which are used in the newest update of the Spectrum projection package, are reported in Supplementary Tables S9–S15, http://links.lww.com/QAD/B7. Similar patterns as described above for the crude mortality estimates were evident in the corrected estimates.

Discussion

Estimates of mortality and life expectancy in HIV-positive populations rely on the complete ascertainment of deaths. However, the proportion of patients lost to follow-up in HIV care programmes is high, especially in sub-Saharan Africa [3]. Patients who are lost to follow-up typically experience higher rates of mortality than those remaining in care [4,5], so failing to account for deaths among all patients who started ART leads to an underestimation of overall, programme-level mortality. Use of information from tracing patients lost to follow-up and linkages with vital registries has repeatedly resulted in upward revision of mortality estimates [7,19,20].

In this study, we multiplied crude mortality rates by correction factors to adjust for biases resulting from loss to follow-up. We used three different sets of correction factors that were calculated based on the outcomes of tracing patients lost to follow-up in Kenya and linkage of HIV programme data with the national death registry in South Africa. Corrected mortality estimates differed depending on the set of correction factors, and implausible corrected rates were observed with all three sets. Implausible rates were more common with the two sets of 168 correction factors than with the simpler approach based on two factors only. None of the two-way interactions included in the model for the South African set of 168 correction factors reached conventional levels of statistical significance. The poorer performance of the two large sets of correction factors might therefore be due to overfitting, which occurred despite using a penalized maximum likelihood estimation procedure [17] that will have reduced overfitting to some extent. In the final analysis, we decided to use the more conservative approach based on two correction factors only for all regions except for east Africa. For east Africa, we used the Kenyan correction factors, as they might better represent the regional pattern of mortality among patients lost to follow-up in east Africa.

Compared with the earlier analysis published in 2012 [8], the mortality estimates calculated in this study were somewhat higher. This is probably explained by the different composition of the study population, with a shift to countries with higher mortality. For example, in the previous analysis, the Republic of South Africa was the only country in the southern African region. In the present study, we also included data from Zambia, Zimbabwe, Malawi, Mozambique, and Lesotho. Determinants of mortality were however similar for the 2012 and the current analysis, with high mortality rates in the first 6 months of ART and with low $CD4^+$ cell counts, which decreased with longer ART duration and higher $CD4^+$ cell counts. It would be worthwhile to examine trends over calendar years as recent studies have shown that in African programmes mortality among patients lost to follow-up appears to have declined in recent years [5,21]. This may be due to higher $CD4^+$ cell counts at the start of ART and to an increase in undocumented transfers to other clinics [5,21]. For example, a study in Lilongwe, Malawi found that among patients lost to follow-up and found to be alive on tracing, a majority (56%) were still on

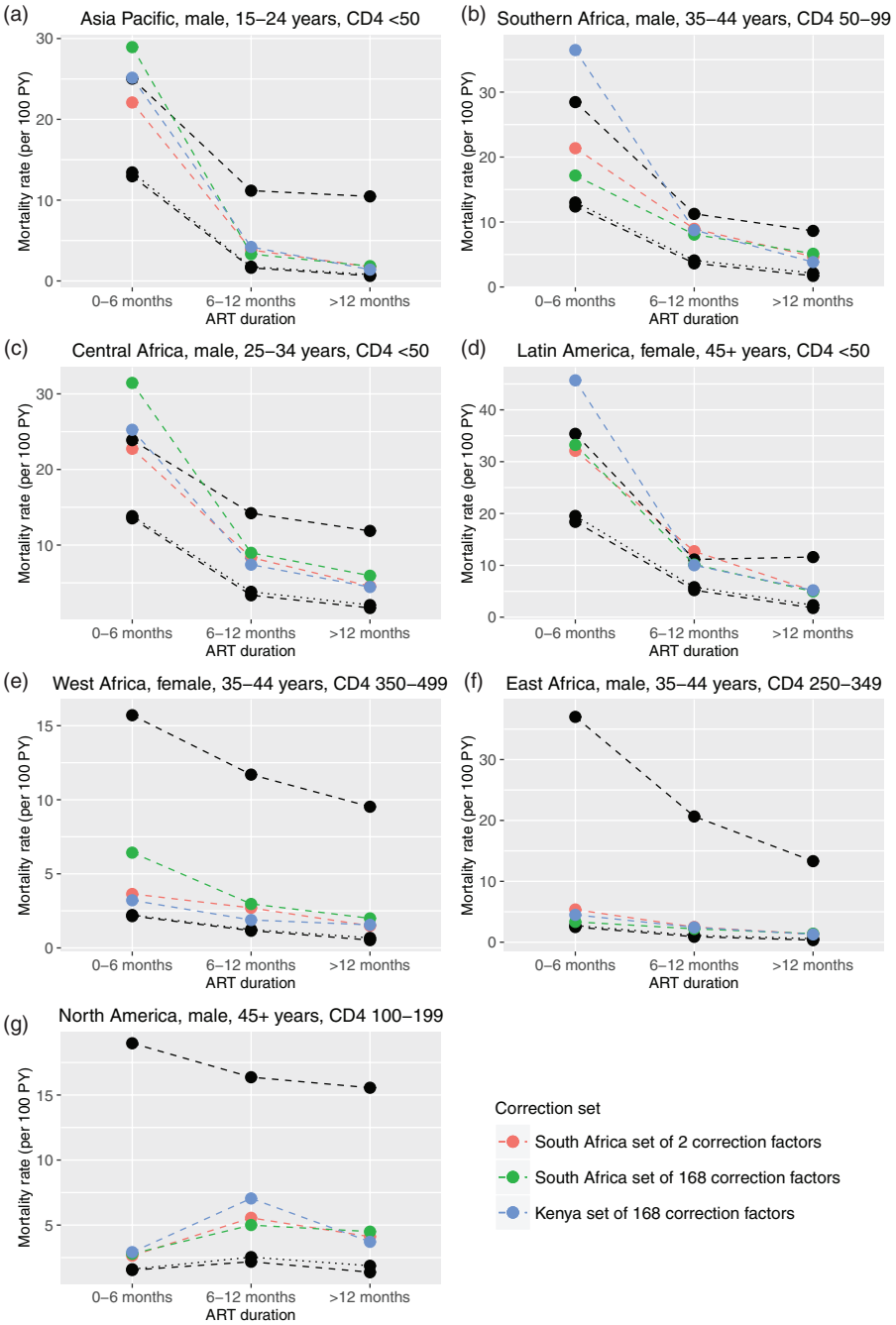

Fig. 2. Examples of sensitivity analyses for Asia Pacific (a), southern Africa (b), central Africa (c), Latin America (d), west Africa (e), east Africa (f) and North America (g). The different corrected mortality estimates are compared with worst case scenario estimates (upper black dashed line) and best case scenario estimates (lower black dashed line) and crude mortality (black dotted line). Crude mortality and mortality from best case scenario are closely similar.

ART sourced from another clinic [22]. Similarly, a study of adults starting ART in Uganda, Tanzania, and Kenya found that 59% of patients interviewed had reconnected to care at a different clinic [23].

Our study has several limitations. The comparisons with worst and best case scenarios were useful to detect implausible mortality rates, but the range between estimates from the two scenarios was wide. It is impossible to know with any precision how appropriate mortality corrections were. In general, by applying correction factors originating from one region to correct mortality estimates in another region, we assumed that both mortality in patients lost to follow-up and rates of loss to follow-up were similar in the two regions. As determinants and rates of loss to follow-up and mortality differ

between treatment programmes within and across countries and regions, it seems unlikely that the situation in South Africa and Kenya and the correction factors from these countries accurately capture the underestimation of mortality rates in other African countries, the Asia Pacific region, and countries in North or Latin America [8]. This in turn might be the reason why none of the three sets achieved corrected mortality estimates that stayed within best and worst case boundaries in all regions. Also, as in Latin America and North America, linkage to vital registries was performed occasionally in some cohorts, the crude mortality estimates might already capture some of the mortality of patients lost to follow-up. Applying the South African correction factors to these regions might thus result in an overestimation of mortality.

The correction factors themselves might also be subject to bias: in Kenya and elsewhere, tracing programmes do not trace a random sample of the patients who were lost to follow-up but are imbedded into routine patient outreach efforts [20,24,25]. Moreover, not all patients lost are successfully located. In a recent systematic review of tracing studies, we found that about 80% of patients could be located but this percentage varied widely across studies [21]. With the linkage data from South Africa, this problem is less important: bias will only arise if patients with an ID differ systematically from those without ID, and the effect of this bias cannot be minimized by the covariates included in the model. One study found that patients with ID are similar to the patients without ID in terms of their demographic and baseline clinical characteristics [9].

These limitations notwithstanding, the large number of patients included from many different countries and settings is an important strength of this analysis. In the absence of empirical data from tracing patients lost to follow-up [4,5] or from linkages with vital registries [9], the application of the correction factors calculated in this study are likely to result in more appropriate estimates of mortality at the treatment programme and population level than naïve and uncorrected estimates. The mortality estimates can be used by treatment programme managers and policy-makers and to inform mathematical modelling and projections such as those produced by the Spectrum modelling package [13,14].

To overcome the limitations of using correction factors derived from empirical data from only two African countries, we are in the process of compiling a large database of outcomes from efforts by ART treatment programmes to trace and ascertain the vital status of patients lost to follow-up. We identified 32 eligible studies from 12 countries in sub-Saharan Africa [21] and are in the process of obtaining the individual patient data from these studies. In a future update of this analysis, we will be able to include setting-specific data for many more countries than in the present analysis, thus improving the accuracy of corrected mortality estimates for HIV-positive patients who started ART in sub-Saharan Africa, the region where loss to follow-up is common [3]. Similar studies in other regions are warranted.

In conclusion, the tracing of patients lost to follow-up should be an integral part of ART programmes and ideally be done on a continuous basis, with dedicated data collection and analysis, so that patients who interrupted ART can be reconnected to care, records can be updated for patients who self-transferred to another clinic, and programme and country-level estimates of mortality in people on ART can be corrected appropriately for loss to follow-up.

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Conflicts of interest

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