Supplementary material

Table of Contents

[1. ART eligibility criteria 2](#_Toc531701656)

[2. Estimation of HIV-related mortality 3](#_Toc531701657)

[3. Tracing study details 7](#_Toc531701658)

[4. Sensitivity analyses 10](#_Toc531701659)

[References 22](#_Toc531701660)

# 1. ART eligibility criteria

Table S1: Countries and territories represented and ART eligibility criteria

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region | Country | # patients | Year of switching to ART eligibility at CD4 | Source |
|  |  |  | <350 | <500 | None |  |
| Asia-Pacific | Cambodia | 1856 | 2010 | 2015 | 2016 | Tymejczyk [1], IAPAC [2] |
| China | 44 | 2010 | - | 2016 | Gupta [3], IAPAC [2]  |
| Hong Kong  SAR | 867 | 2011 | 2013 | - | Tymejczyk [1] |
| India | 7294 | 2011 | - | 2017 | Tymejczyk [1], IAPAC [2] |
| Indonesia | 1037 | 2011 | - | - | Gupta [3], Tymejczyk [1] |
| Japan | 67 | - | 2011 | 2016 | Tor Petersen (personal communication), IAPAC [2] |
| Malaysia | 162 | 2011 | 2014 | 2016 | Gupta [3], Tor Petersen (personal communication), IAPAC [2] |
| Philippines | 199 | 2014 | - | - | IAPAC [2] |
| Singapore | 2562 | - | - | - |  |
| South Korea | 411 | - | - | 2013 | IAPAC [2] |
| Taiwan | 161 | - | 2013 | 2016 | Ellen Brazier (personal communication) |
| Thailand | 875 | 2010 | - | 2014 | Gupta [3], IAPAC [2] |
| Vietnam | 562 | 2011 | 2015 | - | Gupta [3], Tymejczyk [1], IAPAC [2] |
| Latin America | Brazil | 2243 | 2008 | 2012 | 2013 | Peter Rebeiro (personal communication), Gupta [3] |
|  | Chile | 1111 | 2010 | 2013 | - | Gupta [3], IAPAC [2] |
|  | Haiti | 7739 | 2011 | 2014 | 2016 | Gupta [3], Peter Rebeiro (personal communication), IAPAC [2] |
|  | Honduras | 599 | 2009 | 2013 | - | Peter Rebeiro (personal communication), Gupta [3] |
|  | Mexico | 861 | 2009 | 2012 | 2014 | Gupta [3], Peter Rebeiro (personal communication), IAPAC [2] |
|  | Peru | 3207 | 2012 | 2015 | - | Gupta [3], IAPAC [2] |
| North America | Canada | 1772 | 2013 | - | - | IAPAC [2] |
| USA | 22288 | 2006 | 2009 | 2012 | Peter Rebeiro (personal communication), Gupta [3] |
| Central  Africa | Burundi | 429 | 2010 | 2014 | 2016 | Gupta [4], IAPAC [2] |
| DRC | 253 | 2010 | 2013 | - | Gupta [4] |
| East  Africa | Kenya | 68283 | 2011 | 2014 | 2016 | Gupta [4], IAPAC [2] |
| Tanzania | 7673 | 2012 | 2014 | - | Gupta [4] |
| Uganda | 32980 | 2011 | 2013 | 2016 | Gupta [4], IAPAC [2] |
| Southern | Lesotho | 7820 | 2007 | 2014 | 2016 | Gupta [4] |
|  Africa | Malawi | 20172 | 2011 | 2014 | 2016 | Gupta [4] |
|  | Mozambique | 3671 | 2012 | - | 2016 | Gupta [4], IAPAC [2] |
|  | South Africa | 72997 | 2011 | 2015 | 2016 |  |
|  | Zambia | 136436 | 2010 | 2013 | 2016 | Gupta [4], IAPAC [2] |
|  | Zimbabwe | 15576 | 2010 | 2013 | 2016 | Gupta [4], IAPAC [2] |
| West  Africa | Benin | 2756 | 2012 | - | - | Gupta [4] |
| Burkina Faso | 5760 | 2008 | - | - | Gupta [4] |
|  | Côte d’Ivoire | 11489 | 2013 | - | - | Gupta [4] |
|  | Guinea | 651 | 2011 | - | - | Gupta [4] |
|  | Guinea-Bissau | 2979 | - | - | - |  |
|  | Mali | 2134 | 2008 | 2013 | - | Gupta [4] |
|  | Nigeria | 9866 | 2010 | 2014 | - | Gupta [4], IAPAC [2] |
|  | Senegal | 317 | - | - | - | Eligibility still at 200 (Gupta [4]) |
|  | Togo | 3810 | 2009 | 2015 | - | Didier Ekouevi (personal communication) |

# 2. Estimation of HIV-related mortality

In the Spectrum model, IeDEA estimates of all-cause mortality in ART patients were converted into estimates of HIV-related mortality using United Nations Population Division estimates of non-HIV mortality in each region, from the 2017 World Population Prospects update [5]. The latter non-HIV mortality rates were subtracted from the IeDEA all-cause mortality rates in order to obtain the Spectrum assumptions about HIV-related mortality (John Stover, personal communication). Table S2 summarizes the United Nations Population Division estimates of non-HIV mortality, as used in Spectrum.

Table S2: Annual non-HIV mortality rates over the 2010-2015 period

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IeDEAregion | Asia-Pacific | Latin Americaand Caribbean | NorthAmerica | EastAfrica | Central Africa | SouthernAfrica | WestAfrica |
| WPPregion | South-Central Asia | Latin Americaand Caribbean | NorthAmerica | EastAfrica | CentralAfrica | SouthernAfrica | WestAfrica |
| Males |  |  |  |  |  |  |  |
|  15-24 | 0.00124 | 0.00169 | 0.00082 | 0.00370 | 0.00276 | 0.00197 | 0.00447 |
|  25-34 | 0.00211 | 0.00257 | 0.00133 | 0.00521 | 0.00427 | 0.00480 | 0.00575 |
|  35-44 | 0.00382 | 0.00333 | 0.00192 | 0.00727 | 0.00698 | 0.01073 | 0.00752 |
|  45+ | 0.00780 | 0.00596 | 0.00448 | 0.01109 | 0.01063 | 0.01768 | 0.01218 |
| Females |  |  |  |  |  |  |  |
|  15-24 | 0.00114 | 0.00054 | 0.00032 | 0.00274 | 0.00194 | 0.00186 | 0.00429 |
|  25-34 | 0.00139 | 0.00087 | 0.00061 | 0.00436 | 0.00339 | 0.00473 | 0.00569 |
|  35-44 | 0.00214 | 0.00156 | 0.00119 | 0.00646 | 0.00552 | 0.00771 | 0.00672 |
|  45+ | 0.00455 | 0.00338 | 0.00285 | 0.00887 | 0.00770 | 0.00961 | 0.00955 |

WPP = World Population Prospects

Table S3 shows the assumed HIV-specific mortality rates in Spectrum for the Asia-Pacific region, after subtracting the non-HIV mortality rates in Table S3 from the all-cause IeDEA mortality estimates, in the 2011-2014 period. As an example of how the mortality rates are calculated, the mortality rate in women aged 25-34 who started ART at a CD4 count of 100-199, in the period 6-11 months after starting ART, is calculated as 0.045 × 0.86 × 1.22 × 0.36 × 0.43 – 0.00139 = 0.0058, where the 0.045 is the base mortality rate for Asia and the Americas, 0.86 is the female adjustment factor, 1.22 is the age 25-34 adjustment factor, 0.36 is the CD4 100-199 adjustment, 0.43 is the 6-11 month adjustment (all from Table 3 of the main text), and 0.00139 is the non-HIV mortality rate (from Table S2). The 0.0058 rate is the same as the rate of 0.58 per 100 person years shown in Table S3 for women with this covariate pattern. In some categories (for example men aged 35-44 who started ART at CD4 ≥500 cells/µl, more than 12 months previously) the assumed HIV-specific mortality rates are set to zero because the all-cause mortality rate in IeDEA ART patients is less than the non-HIV mortality rate. Similar tables of Spectrum mortality assumptions are shown for Latin America (Table S4), North America (Table S5), Central Africa (Table S6), East Africa (Table S7), Southern Africa (Table S8) and West Africa (Table S9).

Table S3: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the Asia-Pacific region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 0.338 | 0.577 | 0.569 | 0.878 | 1.461 | 3.020 | 4.330 |
|  |  | 25-34 | 0.354 | 0.647 | 0.638 | 1.015 | 1.728 | 3.636 | 5.240 |
|  |  | 35-44 | 0.259 | 0.591 | 0.581 | 1.009 | 1.817 | 3.980 | 5.798 |
|  |  | 45+ | 0.222 | 0.741 | 0.724 | 1.393 | 2.655 | 6.033 | 8.871 |
|  | 6-11 | 15-24 | 0.076 | 0.179 | 0.176 | 0.309 | 0.561 | 1.236 | 1.802 |
|  |  | 25-34 | 0.033 | 0.160 | 0.156 | 0.319 | 0.628 | 1.453 | 2.147 |
|  |  | 35-44 | 0.000 | 0.039 | 0.035 | 0.220 | 0.569 | 1.505 | 2.291 |
|  |  | 45+ | 0.000 | 0.000 | 0.000 | 0.161 | 0.706 | 2.168 | 3.395 |
|  | 12+ | 15-24 | 0.046 | 0.078 | 0.077 | 0.181 | 0.244 | 0.406 | 0.390 |
|  |  | 25-34 | 0.000 | 0.000 | 0.000 | 0.106 | 0.171 | 0.340 | 0.324 |
|  |  | 35-44 | 0.000 | 0.000 | 0.000 | 0.000 | 0.018 | 0.195 | 0.177 |
|  |  | 45+ | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.252 | 0.221 |
| Female | 0-5 | 15-24 | 0.282 | 0.487 | 0.481 | 0.745 | 1.245 | 2.582 | 3.705 |
|  |  | 25-34 | 0.345 | 0.596 | 0.588 | 0.912 | 1.523 | 3.160 | 4.534 |
|  |  | 35-44 | 0.335 | 0.620 | 0.611 | 0.978 | 1.671 | 3.526 | 5.084 |
|  |  | 45+ | 0.402 | 0.847 | 0.833 | 1.406 | 2.488 | 5.384 | 7.818 |
|  | 6-11 | 15-24 | 0.058 | 0.146 | 0.144 | 0.258 | 0.474 | 1.052 | 1.538 |
|  |  | 25-34 | 0.070 | 0.179 | 0.176 | 0.316 | 0.580 | 1.288 | 1.882 |
|  |  | 35-44 | 0.023 | 0.147 | 0.143 | 0.302 | 0.601 | 1.403 | 2.077 |
|  |  | 45+ | 0.000 | 0.108 | 0.102 | 0.350 | 0.818 | 2.070 | 3.123 |
|  | 12+ | 15-24 | 0.049 | 0.080 | 0.079 | 0.177 | 0.238 | 0.393 | 0.378 |
|  |  | 25-34 | 0.030 | 0.062 | 0.061 | 0.164 | 0.226 | 0.388 | 0.372 |
|  |  | 35-44 | 0.000 | 0.000 | 0.000 | 0.102 | 0.168 | 0.337 | 0.320 |
|  |  | 45+ | 0.000 | 0.000 | 0.000 | 0.111 | 0.228 | 0.529 | 0.500 |

Mortality estimates are for individuals with no history of injecting drug use.

Table S4: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the Latin America region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 0.744 | 1.218 | 1.203 | 1.814 | 2.966 | 6.052 | 8.644 |
|  |  | 25-34 | 0.861 | 1.441 | 1.422 | 2.170 | 3.581 | 7.357 | 10.530 |
|  |  | 35-44 | 0.935 | 1.592 | 1.571 | 2.418 | 4.018 | 8.298 | 11.895 |
|  |  | 45+ | 1.383 | 2.410 | 2.377 | 3.700 | 6.197 | 12.882 | 18.499 |
|  | 6-11 | 15-24 | 0.226 | 0.431 | 0.424 | 0.689 | 1.187 | 2.521 | 3.643 |
|  |  | 25-34 | 0.227 | 0.478 | 0.469 | 0.793 | 1.403 | 3.036 | 4.408 |
|  |  | 35-44 | 0.215 | 0.500 | 0.491 | 0.857 | 1.549 | 3.400 | 4.956 |
|  |  | 45+ | 0.260 | 0.704 | 0.690 | 1.262 | 2.342 | 5.234 | 7.663 |
|  | 12+ | 15-24 | 0.201 | 0.271 | 0.268 | 0.494 | 0.630 | 0.984 | 0.949 |
|  |  | 25-34 | 0.128 | 0.201 | 0.198 | 0.432 | 0.575 | 0.943 | 0.907 |
|  |  | 35-44 | 0.069 | 0.145 | 0.143 | 0.388 | 0.537 | 0.921 | 0.883 |
|  |  | 45+ | 0.123 | 0.259 | 0.255 | 0.692 | 0.959 | 1.646 | 1.579 |
| Female | 0-5 | 15-24 | 0.729 | 1.135 | 1.122 | 1.646 | 2.634 | 5.279 | 7.502 |
|  |  | 25-34 | 0.871 | 1.368 | 1.352 | 1.993 | 3.203 | 6.440 | 9.160 |
|  |  | 35-44 | 0.930 | 1.494 | 1.476 | 2.202 | 3.573 | 7.244 | 10.327 |
|  |  | 45+ | 1.359 | 2.239 | 2.211 | 3.345 | 5.486 | 11.217 | 16.032 |
|  | 6-11 | 15-24 | 0.285 | 0.460 | 0.455 | 0.681 | 1.108 | 2.253 | 3.214 |
|  |  | 25-34 | 0.327 | 0.542 | 0.535 | 0.812 | 1.336 | 2.736 | 3.912 |
|  |  | 35-44 | 0.314 | 0.557 | 0.550 | 0.864 | 1.457 | 3.044 | 4.378 |
|  |  | 45+ | 0.396 | 0.776 | 0.764 | 1.255 | 2.181 | 4.660 | 6.742 |
|  | 12+ | 15-24 | 0.299 | 0.366 | 0.364 | 0.579 | 0.710 | 1.048 | 1.015 |
|  |  | 25-34 | 0.280 | 0.350 | 0.347 | 0.571 | 0.708 | 1.059 | 1.025 |
|  |  | 35-44 | 0.228 | 0.301 | 0.298 | 0.532 | 0.675 | 1.042 | 1.006 |
|  |  | 45+ | 0.349 | 0.479 | 0.475 | 0.893 | 1.148 | 1.804 | 1.740 |

Mortality estimates are for individuals with no history of injecting drug use.

Table S5: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the North America region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 0.264 | 0.443 | 0.437 | 0.668 | 1.104 | 2.272 | 3.252 |
|  |  | 25-34 | 0.290 | 0.509 | 0.502 | 0.785 | 1.318 | 2.747 | 3.947 |
|  |  | 35-44 | 0.288 | 0.536 | 0.528 | 0.849 | 1.454 | 3.073 | 4.434 |
|  |  | 45+ | 0.301 | 0.689 | 0.677 | 1.177 | 2.122 | 4.651 | 6.776 |
|  | 6-11 | 15-24 | 0.068 | 0.145 | 0.143 | 0.243 | 0.431 | 0.936 | 1.360 |
|  |  | 25-34 | 0.050 | 0.144 | 0.141 | 0.264 | 0.495 | 1.112 | 1.632 |
|  |  | 35-44 | 0.016 | 0.123 | 0.120 | 0.258 | 0.520 | 1.220 | 1.809 |
|  |  | 45+ | 0.000 | 0.044 | 0.038 | 0.255 | 0.664 | 1.757 | 2.676 |
|  | 12+ | 15-24 | 0.347 | 0.428 | 0.425 | 0.686 | 0.845 | 1.254 | 1.214 |
|  |  | 25-34 | 0.313 | 0.397 | 0.394 | 0.665 | 0.831 | 1.257 | 1.215 |
|  |  | 35-44 | 0.274 | 0.362 | 0.359 | 0.643 | 0.816 | 1.261 | 1.218 |
|  |  | 45+ | 0.385 | 0.543 | 0.538 | 1.045 | 1.354 | 2.150 | 2.072 |
| Female | 0-5 | 15-24 | 0.264 | 0.418 | 0.413 | 0.611 | 0.985 | 1.986 | 2.826 |
|  |  | 25-34 | 0.301 | 0.489 | 0.483 | 0.726 | 1.183 | 2.408 | 3.437 |
|  |  | 35-44 | 0.292 | 0.506 | 0.499 | 0.774 | 1.292 | 2.681 | 3.847 |
|  |  | 45+ | 0.357 | 0.690 | 0.680 | 1.109 | 1.919 | 4.087 | 5.909 |
|  | 6-11 | 15-24 | 0.096 | 0.163 | 0.160 | 0.246 | 0.408 | 0.841 | 1.204 |
|  |  | 25-34 | 0.096 | 0.177 | 0.174 | 0.279 | 0.477 | 1.007 | 1.452 |
|  |  | 35-44 | 0.059 | 0.151 | 0.148 | 0.267 | 0.492 | 1.092 | 1.597 |
|  |  | 45+ | 0.000 | 0.137 | 0.132 | 0.318 | 0.668 | 1.606 | 2.394 |
|  | 12+ | 15-24 | 0.378 | 0.455 | 0.452 | 0.702 | 0.853 | 1.245 | 1.207 |
|  |  | 25-34 | 0.365 | 0.445 | 0.443 | 0.702 | 0.860 | 1.267 | 1.227 |
|  |  | 35-44 | 0.327 | 0.411 | 0.408 | 0.679 | 0.844 | 1.270 | 1.228 |
|  |  | 45+ | 0.512 | 0.662 | 0.657 | 1.142 | 1.437 | 2.198 | 2.124 |

Mortality estimates are for individuals with no history of injecting drug use.

Table S6: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the Central Africa region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 3.927 | 4.992 | 5.622 | 7.246 | 10.514 | 18.315 | 31.897 |
|  |  | 25-34 | 3.676 | 4.715 | 5.330 | 6.915 | 10.104 | 17.718 | 30.974 |
|  |  | 35-44 | 3.461 | 4.514 | 5.138 | 6.744 | 9.977 | 17.693 | 31.130 |
|  |  | 45+ | 4.026 | 5.316 | 6.079 | 8.045 | 12.002 | 21.447 | 37.893 |
|  | 6-11 | 15-24 | 1.539 | 1.999 | 2.271 | 2.972 | 4.383 | 7.752 | 13.617 |
|  |  | 25-34 | 1.345 | 1.794 | 2.059 | 2.744 | 4.121 | 7.409 | 13.133 |
|  |  | 35-44 | 1.098 | 1.553 | 1.822 | 2.516 | 3.912 | 7.244 | 13.047 |
|  |  | 45+ | 1.135 | 1.691 | 2.021 | 2.870 | 4.579 | 8.658 | 15.759 |
|  | 12+ | 15-24 | 1.228 | 2.345 | 2.286 | 2.692 | 3.136 | 4.577 | 5.960 |
|  |  | 25-34 | 0.744 | 1.613 | 1.568 | 1.883 | 2.229 | 3.350 | 4.427 |
|  |  | 35-44 | 0.342 | 1.114 | 1.073 | 1.354 | 1.661 | 2.656 | 3.612 |
|  |  | 45+ | 0.169 | 1.084 | 1.036 | 1.368 | 1.732 | 2.912 | 4.045 |
| Female | 0-5 | 15-24 | 3.208 | 4.070 | 4.580 | 5.894 | 8.539 | 14.853 | 25.845 |
|  |  | 25-34 | 2.982 | 3.823 | 4.321 | 5.603 | 8.185 | 14.346 | 25.075 |
|  |  | 35-44 | 2.813 | 3.666 | 4.170 | 5.470 | 8.087 | 14.332 | 25.207 |
|  |  | 45+ | 3.349 | 4.392 | 5.010 | 6.601 | 9.804 | 17.448 | 30.759 |
|  | 6-11 | 15-24 | 1.275 | 1.647 | 1.868 | 2.435 | 3.577 | 6.304 | 11.051 |
|  |  | 25-34 | 1.095 | 1.458 | 1.673 | 2.227 | 3.342 | 6.003 | 10.636 |
|  |  | 35-44 | 0.901 | 1.269 | 1.487 | 2.048 | 3.178 | 5.875 | 10.572 |
|  |  | 45+ | 1.009 | 1.459 | 1.726 | 2.413 | 3.796 | 7.097 | 12.845 |
|  | 12+ | 15-24 | 0.907 | 1.725 | 1.682 | 1.979 | 2.304 | 3.359 | 4.372 |
|  |  | 25-34 | 0.518 | 1.155 | 1.121 | 1.352 | 1.605 | 2.426 | 3.214 |
|  |  | 35-44 | 0.209 | 0.774 | 0.744 | 0.949 | 1.174 | 1.903 | 2.603 |
|  |  | 45+ | 0.132 | 0.802 | 0.766 | 1.010 | 1.276 | 2.140 | 2.970 |

Table S7: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the East Africa region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 3.954 | 5.049 | 5.698 | 7.368 | 10.730 | 18.754 | 32.725 |
|  |  | 25-34 | 3.699 | 4.768 | 5.401 | 7.031 | 10.312 | 18.143 | 31.779 |
|  |  | 35-44 | 3.550 | 4.634 | 5.275 | 6.927 | 10.253 | 18.191 | 32.012 |
|  |  | 45+ | 4.126 | 5.452 | 6.238 | 8.260 | 12.330 | 22.046 | 38.962 |
|  | 6-11 | 15-24 | 1.498 | 1.971 | 2.251 | 2.972 | 4.424 | 7.889 | 13.922 |
|  |  | 25-34 | 1.302 | 1.763 | 2.037 | 2.740 | 4.157 | 7.539 | 13.428 |
|  |  | 35-44 | 1.120 | 1.588 | 1.865 | 2.579 | 4.015 | 7.442 | 13.411 |
|  |  | 45+ | 1.152 | 1.724 | 2.064 | 2.937 | 4.695 | 8.890 | 16.195 |
|  | 12+ | 15-24 | 0.805 | 1.677 | 1.631 | 1.948 | 2.295 | 3.420 | 4.500 |
|  |  | 25-34 | 0.393 | 1.072 | 1.036 | 1.283 | 1.553 | 2.428 | 3.269 |
|  |  | 35-44 | 0.085 | 0.688 | 0.656 | 0.875 | 1.115 | 1.892 | 2.638 |
|  |  | 45+ | 0.000 | 0.567 | 0.530 | 0.789 | 1.074 | 1.995 | 2.880 |
| Female | 0-5 | 15-24 | 3.226 | 4.112 | 4.637 | 5.988 | 8.709 | 15.203 | 26.511 |
|  |  | 25-34 | 2.979 | 3.844 | 4.356 | 5.676 | 8.331 | 14.669 | 25.706 |
|  |  | 35-44 | 2.816 | 3.693 | 4.212 | 5.549 | 8.240 | 14.665 | 25.851 |
|  |  | 45+ | 3.350 | 4.424 | 5.059 | 6.696 | 9.990 | 17.853 | 31.545 |
|  | 6-11 | 15-24 | 1.237 | 1.620 | 1.847 | 2.430 | 3.605 | 6.410 | 11.293 |
|  |  | 25-34 | 1.039 | 1.412 | 1.633 | 2.203 | 3.350 | 6.087 | 10.853 |
|  |  | 35-44 | 0.849 | 1.228 | 1.452 | 2.029 | 3.191 | 5.966 | 10.796 |
|  |  | 45+ | 0.943 | 1.406 | 1.681 | 2.388 | 3.810 | 7.206 | 13.118 |
|  | 12+ | 15-24 | 0.586 | 1.224 | 1.191 | 1.423 | 1.677 | 2.500 | 3.291 |
|  |  | 25-34 | 0.233 | 0.730 | 0.704 | 0.884 | 1.082 | 1.723 | 2.338 |
|  |  | 35-44 | 0.000 | 0.389 | 0.366 | 0.526 | 0.702 | 1.271 | 1.818 |
|  |  | 45+ | 0.000 | 0.340 | 0.313 | 0.503 | 0.711 | 1.385 | 2.033 |

Table S8: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the Southern Africa region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 4.504 | 5.694 | 6.399 | 8.215 | 11.869 | 20.592 | 35.781 |
|  |  | 25-34 | 4.108 | 5.270 | 5.958 | 7.730 | 11.297 | 19.810 | 34.635 |
|  |  | 35-44 | 3.577 | 4.755 | 5.452 | 7.248 | 10.864 | 19.493 | 34.519 |
|  |  | 45+ | 3.924 | 5.366 | 6.219 | 8.418 | 12.843 | 23.405 | 41.796 |
|  | 6-11 | 15-24 | 1.833 | 2.347 | 2.651 | 3.435 | 5.014 | 8.781 | 15.340 |
|  |  | 25-34 | 1.501 | 2.003 | 2.300 | 3.065 | 4.606 | 8.282 | 14.684 |
|  |  | 35-44 | 0.935 | 1.444 | 1.745 | 2.520 | 4.082 | 7.808 | 14.297 |
|  |  | 45+ | 0.690 | 1.313 | 1.681 | 2.631 | 4.542 | 9.103 | 17.045 |
|  | 12+ | 15-24 | 1.382 | 2.555 | 2.493 | 2.919 | 3.385 | 4.898 | 6.350 |
|  |  | 25-34 | 0.749 | 1.661 | 1.613 | 1.945 | 2.308 | 3.485 | 4.615 |
|  |  | 35-44 | 0.018 | 0.829 | 0.786 | 1.080 | 1.403 | 2.448 | 3.452 |
|  |  | 45+ | 0.000 | 0.486 | 0.436 | 0.785 | 1.167 | 2.406 | 3.595 |
| Female | 0-5 | 15-24 | 3.619 | 4.582 | 5.153 | 6.622 | 9.580 | 16.640 | 28.933 |
|  |  | 25-34 | 3.240 | 4.180 | 4.737 | 6.171 | 9.058 | 15.949 | 27.947 |
|  |  | 35-44 | 2.993 | 3.946 | 4.511 | 5.964 | 8.890 | 15.874 | 28.035 |
|  |  | 45+ | 3.646 | 4.813 | 5.504 | 7.283 | 10.864 | 19.413 | 34.297 |
|  | 6-11 | 15-24 | 1.457 | 1.873 | 2.120 | 2.754 | 4.032 | 7.080 | 12.389 |
|  |  | 25-34 | 1.130 | 1.536 | 1.777 | 2.396 | 3.643 | 6.619 | 11.800 |
|  |  | 35-44 | 0.855 | 1.266 | 1.510 | 2.138 | 3.401 | 6.417 | 11.669 |
|  |  | 45+ | 1.029 | 1.532 | 1.831 | 2.599 | 4.146 | 7.837 | 14.265 |
|  | 12+ | 15-24 | 0.970 | 1.829 | 1.784 | 2.095 | 2.437 | 3.544 | 4.607 |
|  |  | 25-34 | 0.426 | 1.095 | 1.059 | 1.302 | 1.568 | 2.430 | 3.257 |
|  |  | 35-44 | 0.028 | 0.621 | 0.590 | 0.806 | 1.042 | 1.807 | 2.542 |
|  |  | 45+ | 0.000 | 0.690 | 0.653 | 0.908 | 1.188 | 2.095 | 2.965 |

Table S9: Spectrum inputs: HIV mortality rates (per 100 person years) among ART patients in the West Africa region, in the 2011-2014 period

|  |  |  |  |
| --- | --- | --- | --- |
| Sex | Duration | Age | Baseline CD4 cell count |
|  | (months) |  | ≥500 | 350-499 | 250-349 | 200-249 | 100-199 | 50-99 | <50 |
| Male | 0-5 | 15-24 | 3.756 | 4.821 | 5.451 | 7.075 | 10.343 | 18.143 | 31.726 |
|  |  | 25-34 | 3.528 | 4.567 | 5.182 | 6.767 | 9.957 | 17.570 | 30.826 |
|  |  | 35-44 | 3.406 | 4.459 | 5.083 | 6.689 | 9.922 | 17.639 | 31.075 |
|  |  | 45+ | 3.872 | 5.161 | 5.924 | 7.890 | 11.847 | 21.292 | 37.738 |
|  | 6-11 | 15-24 | 1.368 | 1.828 | 2.100 | 2.801 | 4.212 | 7.581 | 13.446 |
|  |  | 25-34 | 1.197 | 1.646 | 1.911 | 2.596 | 3.973 | 7.261 | 12.985 |
|  |  | 35-44 | 1.043 | 1.498 | 1.768 | 2.461 | 3.857 | 7.190 | 12.992 |
|  |  | 45+ | 0.980 | 1.537 | 1.867 | 2.715 | 4.424 | 8.503 | 15.605 |
|  | 12+ | 15-24 | 1.057 | 2.174 | 2.115 | 2.521 | 2.965 | 4.406 | 5.789 |
|  |  | 25-34 | 0.596 | 1.465 | 1.420 | 1.735 | 2.081 | 3.202 | 4.279 |
|  |  | 35-44 | 0.287 | 1.059 | 1.019 | 1.299 | 1.606 | 2.602 | 3.558 |
|  |  | 45+ | 0.014 | 0.930 | 0.881 | 1.214 | 1.578 | 2.758 | 3.891 |
| Female | 0-5 | 15-24 | 2.973 | 3.834 | 4.345 | 5.659 | 8.304 | 14.617 | 25.610 |
|  |  | 25-34 | 2.752 | 3.593 | 4.091 | 5.373 | 7.955 | 14.117 | 24.846 |
|  |  | 35-44 | 2.694 | 3.546 | 4.051 | 5.351 | 7.967 | 14.213 | 25.087 |
|  |  | 45+ | 3.164 | 4.208 | 4.826 | 6.417 | 9.619 | 17.264 | 30.574 |
|  | 6-11 | 15-24 | 1.040 | 1.412 | 1.632 | 2.200 | 3.342 | 6.068 | 10.815 |
|  |  | 25-34 | 0.865 | 1.229 | 1.444 | 1.997 | 3.112 | 5.773 | 10.406 |
|  |  | 35-44 | 0.781 | 1.149 | 1.367 | 1.929 | 3.059 | 5.756 | 10.452 |
|  |  | 45+ | 0.824 | 1.275 | 1.541 | 2.228 | 3.611 | 6.913 | 12.661 |
|  | 12+ | 15-24 | 0.672 | 1.490 | 1.447 | 1.744 | 2.069 | 3.124 | 4.136 |
|  |  | 25-34 | 0.288 | 0.925 | 0.892 | 1.123 | 1.376 | 2.197 | 2.985 |
|  |  | 35-44 | 0.089 | 0.654 | 0.625 | 0.830 | 1.055 | 1.783 | 2.483 |
|  |  | 45+ | 0.000 | 0.617 | 0.582 | 0.825 | 1.092 | 1.955 | 2.785 |

# 3. Tracing study details

Table S10 summarizes the characteristics of the studies used in developing the imputation model. With the exception of the study of Holmes *et al* [6], these studies are the same studies as included in the individual patient data meta-analysis of Chammartin *et al* [7]. However, in some cases the sample sizes are substantially smaller than those in the published studies because our analysis is limited to (a) individuals for whom a vital status could be determined and (b) individuals who had baseline CD4 cell count information. The sample size was particularly small for the study of Ardura-Garcia *et al* [8] because this study was conducted mainly in children, and our analysis was limited to individuals who were aged 15 and older.

Table S10: Characteristics of tracing studies

|  |  |  |  |
| --- | --- | --- | --- |
| Study | Location | Period of lastpatient contact | n |
| Ardura-Garcia *et al* [8] | Malawi | 2007-2010 | 5 |
| Rachlis *et al* [9] | Kenya | 2002-2011 | 396 |
| Caluwaerts *et al* [10] | Mozambique | 2003-2007 | 114 |
| Geng *et al* [11] | Kenya, Uganda, Tanzania | 2008-2011 | 414 |
| Gunguwo *et al* [12] | Zimbabwe | 2010 | 48 |
| Kato *et al* [13] | Zambia | 2010 | 48 |
| Kiragga *et al* [14] | Uganda | 2004-2007 | 45 |
| Mben *et al* [15] | Cameroon | 2002-2007 | 237 |
| Tweya *et al* [16] | Malawi | 2001-2010 | 1738 |
| Holmes *et al* [6] | Zambia | 2004-2015 | 1706 |

Table S11 summarizes information regarding the traced individuals. Southern African tracing studies accounted for 77% of all traced patients. 55% of traced patients had their last follow-up visit within the first 12 months after starting ART. Two thirds of the traced patients started ART in the 2006-2010 period, and 63% had baseline CD4 cell counts <200 cells/µl.

Table S11: Characteristics of traced individuals

|  |  |  |
| --- | --- | --- |
| Characteristic | n | % |
| Sex |  |  |
|  Male | 2068 | 43.5% |
|  Female | 2683 | 56.5% |
| Age at ART initiation (years) |  |  |
|  15-24 | 506 | 10.7% |
|  25-34 | 1910 | 40.2% |
|  35-44 | 1535 | 32.3% |
|  45+ | 800 | 16.8% |
| Region |  |  |
|  Central Africa | 237 | 5.0% |
|  East Africa | 855 | 18.0% |
|  Southern Africa | 3659 | 77.0% |
| Time since ART initiation at LTFU (months) |  |  |
|  0-5  | 1773 | 37.3% |
|  6-11 | 857 | 18.0% |
|  12-23 | 878 | 18.5% |
|  24-35 | 422 | 8.9% |
|  36+ | 821 | 17.3% |
| CD4 cell count at ART initiation (cells/µl) |  |  |
|  0-49 | 912 | 19.2% |
|  50-99 | 752 | 15.8% |
|  100-199 | 1339 | 28.2% |
|  200-249 | 530 | 11.2% |
|  250-349 | 644 | 13.6% |
|  350-499 | 327 | 6.9% |
|  500+ | 247 | 5.2% |
| Year of ART initiation |  |  |
|  2001-2005 | 372 | 7.8% |
|  2006-2010 | 3188 | 67.1% |
|  2011-2015 | 1191 | 25.1% |

# 4. Sensitivity analyses

Figure S1 summarizes the sensitivity analyses.



Figure S1: Summary of sensitivity analyses

Analyses highlighted in yellow correspond only to sub-Saharan African cohorts, analyses highlighted in blue correspond only to the Asian and American regions, and analyses highlighted in green correspond to all regions.

Table S12 compares the results with and without separate terms for West and Central Africa. The results of the regression model are virtually unchanged when separate terms are included for West and Central Africa, except that in the first 12 months after ART initiation, mortality in Central Africa appears to be significantly lower than in East Africa, while mortality in West Africa is fractionally higher than that in East Africa (though not significantly so). As a result, there is a slight reduction in the inter-cohort variation in mortality, with the standard deviation of random effects reducing from 0.42 to 0.37.

Table S12: Multivariable analysis of mortality after ART initiation in sub-Saharan Africa

|  |  |  |
| --- | --- | --- |
|  | 1st 12 months | >12 months |
|  | Main analysis | Central Africaeffect included | Main analysis | Central Africaeffect included |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.81 (0.79-0.83) | 0.81 (0.79-0.83) | 0.73 (0.71-0.76) | 0.73 (0.71-0.75) |
| Age group\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 0.98 (0.92-1.03) | 0.97 (0.92-1.03) | 0.78 (0.72-0.84) | 0.79 (0.73-0.86) |
|  35-44 | 0.99 (0.94-1.04) | 0.99 (0.94-1.04) | 0.69 (0.64-0.74) | 0.70 (0.65-0.76) |
|  45+ | 1.21 (1.13-1.29) | 1.21 (1.14-1.29) | 0.82 (0.76-0.88) | 0.83 (0.77-0.90) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.07 (1.04-1.11) | 1.07 (1.03-1.11) | 2.05 (1.84-2.28) | 2.08 (1.90-2.28) |
|  2007-2010 | 1.03 (1.00-1.06) | 1.03 (1.00-1.06) | 1.22 (1.18-1.27) | 1.23 (1.18-1.27) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.00 (0.94-1.05) | 0.99 (0.94-1.04) | 0.91 (0.88-0.94) | 0.91 (0.87-0.95) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.58 (0.56-0.60) | 0.58 (0.56-0.60) | 0.78 (0.74-0.82) | 0.78 (0.75-0.81) |
|  100-199 | 0.34 (0.33-0.34) | 0.33 (0.32-0.34) | 0.55 (0.53-0.57) | 0.55 (0.53-0.57) |
|  200-249 | 0.23 (0.22-0.25) | 0.24 (0.22-0.25) | 0.48 (0.44-0.52) | 0.47 (0.44-0.51) |
|  250-349 | 0.18 (0.17-0.19) | 0.18 (0.17-0.19) | 0.41 (0.39-0.44) | 0.42 (0.39-0.44) |
|  350-499 | 0.16 (0.14-0.19) | 0.16 (0.14-0.18) | 0.42 (0.36-0.49) | 0.43 (0.36-0.05) |
|  500+ | 0.13 (0.10-0.17) | 0.13 (0.10-0.17) | 0.24 (0.08-0.77) | 0.29 (0.11-0.75) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | - | - |
|  6-11 months | 0.43 (0.42-0.44) | 0.43 (0.42-0.45) | - | - |
| Region\* |  |  |  |  |
|  East Africa | 1.00 | 1.00 | 1.00 | 1.00 |
|  South Africa | 0.85 (0.55-1.32) | 0.85 (0.58-1.25) | 0.97 (0.61-1.54) | 0.97 (0.62-1.52) |
|  Southern Africa (excl. RSA) | 1.09 (0.70-1.68) | 1.09 (0.74-1.60) | 1.34 (0.84-2.15) | 1.33 (0.84-2.12) |
|  West (/& Central) Africa | 0.97 (0.67-1.40) | 1.15 (0.83-1.60) | 1.28 (0.87-1.89) | 1.33 (0.89-1.99) |
|  Central Africa | - | 0.51 (0.31-0.83) | - | 1.15 (0.66-2.00) |
| Baseline mortality† | 33.1 (24.0-45.6) | 33.2 (25.0-44.0) | 4.9 (3.5-6.9) | 4.8 (3.4-6.7) |
| Standard deviation of random effects | 0.42 (0.31-0.51) | 0.37 (0.28-0.45) | 0.45 (0.33-0.54) | 0.44 (0.34-0.53) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). ART = antiretroviral treatment; RSA = Republic of South Africa.

We conducted a sensitivity analysis to assess the effect of including additional duration categories for durations more than 12 months after ART initiation (Table S13). As noted in the main text (Figure 2), period effects were less significant in this analysis, and mortality rates decreased significantly with increasing time since ART initiation. The effects of baseline CD4 count on mortality were slightly stronger than in the main analysis, but other covariates had similar effects when compared to the main analysis.

Table S13: Multivariable analysis of mortality more than 12 months after ART initiation, and effects of additional duration categories

|  |  |  |
| --- | --- | --- |
|  | Asia and Americas | Sub-Saharan Africa |
|  | Main analysis | Additionaldurationcategories | Main analysis | Additionaldurationcategories |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.96 (0.85-1.08) | 0.96 (0.85-1.08) | 0.73 (0.71-0.76) | 0.75 (0.73-0.77) |
| Age group (years)\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 1.04 (0.69-1.57) | 1.10 (0.73-1.66) | 0.78 (0.72-0.84) | 0.84 (0.79-0.91) |
|  35-44 | 1.09 (0.72-1.63) | 1.17 (0.78-1.76) | 0.69 (0.64-0.74) | 0.79 (0.73-0.86) |
|  45+ | 1.94 (1.30-2.90) | 2.12 (1.42-3.17) | 0.82 (0.76-0.88) | 0.95 (0.88-1.04) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.68 (1.23-2.28) | 1.42 (1.03-1.94) | 2.05 (1.84-2.28) | 1.53 (1.36-1.71) |
|  2007-2010 | 1.26 (1.13-1.40) | 1.16 (1.04-1.30) | 1.22 (1.18-1.27) | 1.07 (1.04-1.11) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 0.84 (0.71-0.98) | 0.86 (0.73-1.01) | 0.91 (0.88-0.94) | 0.97 (0.94-1.01) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 1.03 (0.90-1.18) | 1.03 (0.90-1.18) | 0.78 (0.74-0.82) | 0.77 (0.74-0.80) |
|  100-199 | 0.71 (0.63-0.81) | 0.71 (0.63-0.81) | 0.55 (0.53-0.57) | 0.54 (0.52-0.56) |
|  200-249 | 0.59 (0.49-0.72) | 0.58 (0.48-0.70) | 0.48 (0.44-0.52) | 0.43 (0.39-0.46) |
|  250-349 | 0.39 (0.33-0.47) | 0.38 (0.32-0.45) | 0.41 (0.39-0.44) | 0.36 (0.34-0.38) |
|  350-499 | 0.39 (0.31-0.49) | 0.37 (0.30-0.47) | 0.42 (0.36-0.49) | 0.30 (0.26-0.35) |
|  500+ | 0.33 (0.25-0.43) | 0.31 (0.24-0.41) | 0.24 (0.08-0.77) | 0.22 (0.09-0.57) |
| Time since ART start\* |  |  |  |  |
|  12-23 months | - | 1.00 | - | 1.00 |
|  24-35 months | - | 0.85 (0.74-0.97) | - | 0.78 (0.75-0.81) |
|  ≥36 months |  | 0.75 (0.67-0.84) |  | 0.62 (0.60-0.64) |
| Injecting drug use history\* | 1.67 (1.43-1.95) | 1.67 (1.43-1.95) | - | - |
| Region\* |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | - | - |
|  Latin America | 2.18 (1.23-3.83) | 2.16 (1.23-3.78) | - | - |
|  North America | 2.52 (1.58-4.01) | 2.49 (1.57-3.95) | - | - |
|  East Africa | - | - | 1.00 | 1.00 |
|  South Africa | - | - | 0.97 (0.61-1.54) | 0.99 (0.64-1.54) |
|  Southern Africa (excl. RSA) | - | - | 1.34 (0.84-2.15) | 1.29 (0.82-2.02) |
|  West and Central Africa | - | - | 1.28 (0.87-1.89) | 1.27 (0.88-1.85) |
| Baseline mortality† | 0.5 (0.3-0.9) | 0.6 (0.4-1.0) | 4.9 (3.5-6.9) | 6.0 (4.3-8.4) |
| Standard deviation of random effects | 0.60 (0.44-0.84) | 0.60 (0.43-0.83) | 0.45 (0.33-0.54) | 0.43 (0.31-0.52) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). ART = antiretroviral treatment; RSA = Republic of South Africa.

Further analyses were conducted to compare the characteristics of patients with and without baseline CD4 counts (Table S14). The fraction of patients with missing baseline CD4 counts was substantially higher in the African regions (33.9%) than in the other regions (13.0%). Within the African regions, missing baseline CD4 count was much more common in patients starting ART in the 2014-2017 period, possibly because of reduced reliance on CD4 testing since the adoption of universal ART eligibility guidelines. Within the other regions, baseline CD4 count was more likely to be missing in patients who started ART in the 2011-2013 period.

Table S14: Comparison of baseline characteristics of patients with and without baseline CD4 values

|  |  |  |
| --- | --- | --- |
|  | Asia and Americas | Sub-Saharan Africa |
|  | With baselineCD4 (n, %) | Missing baselineCD4 (n, %) | With baselineCD4 (n, %) | Missing baselineCD4 (n, %) |
| No. of patients | 63272 | 9468 | 511187 | 262491 |
| Sex |  |  |  |  |
|  Male | 46019 (72.7%) | 6454 (68.2%) | 186547 (36.5%) | 92536 (35.3%) |
|  Female | 17253 (27.3%) | 3014 (31.8%) | 324640 (63.5%) | 169955 (64.7%) |
| Age group (years) |  |  |  |  |
|  15-24 | 5916 (9.4%) | 857 (9.1%) | 53369 (10.4%) | 35632 (13.6%) |
|  25-34 | 19781 (31.3%) | 3350 (35.4%) | 199448 (39.0%) | 101847 (38.8%) |
|  35-44 | 18844 (29.8%) | 2665 (28.1%) | 163757 (32.0%) | 78782 (30.0%) |
|  45+ | 18731 (29.6%) | 2596 (27.4%) | 94613 (18.5%) | 46230 (17.6%) |
| Period of ART  initiation |  |  |  |  |
|  2001-2007 | 13701 (21.7%) | 2151 (22.7%) | 106485 (20.8%) | 42311 (16.1%) |
|  2008-2010 | 19599 (31.0%) | 2247 (23.7%) | 143143 (28.0%) | 44144 (16.8%) |
|  2011-2013 | 19513 (30.8%) | 3666 (38.7%) | 143936 (28.2%) | 67341 (25.7%) |
|  2014-2017 | 10459 (16.5%) | 1404 (14.8%) | 117623 (23.0%) | 108695 (41.4%) |

Numbers presented are totals prior to other exclusions (i.e. including patients with missing or invalid outcomes and patients who qualified for ART based only on clinical criteria).

To assess the impact of including patients with missing baseline CD4 counts, multiple imputation by chained equations [17] was used to assign baseline CD4 values to patients with missing CD4 values. Imputation was conducted using the ICE command in Stata 15.0 (StataCorp, College Station, TX, USA), 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 (0 if alive, 1 if dead in the original patient record), and time to outcome. Table S15 compares the results from the main analysis with those from the analysis in which missing baseline CD4 values are imputed, for Asia and the Americas, while Table S16 shows the corresponding comparison for sub-Saharan Africa. In Asia and the Americas, the imputation of missing baseline CD4 values makes almost no difference to the regression model estimates (as might be expected, given the relatively small fraction of patients with missing data). However, in sub-Saharan Africa, where a more substantial fraction of patients have missing baseline CD4 values, baseline CD4 count appears to exert less influence on mortality during the first 12 months of ART in the imputation analysis than in the main analysis. This might be because imputed CD4 values don’t correlate strongly enough with the ‘true’ (unobserved) CD4 values, i.e. the imputation model may not be strongly predictive.

Table S15: Multivariable analysis of mortality after ART initiation in Asia and the Americas

|  |  |  |
| --- | --- | --- |
|  | 1st 12 months | >12 months |
|  | Main analysis | Imputation ofbaseline CD4 | Main analysis | Imputation ofbaseline CD4 |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.86 (0.76-0.97) | 0.85 (0.75-0.95) | 0.96 (0.85-1.08) | 0.95 (0.85-1.07) |
| Age group\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 1.22 (0.93-1.61) | 1.27 (0.97-1.66) | 1.04 (0.69-1.57) | 0.98 (0.67-1.44) |
|  35-44 | 1.39 (1.06-1.82) | 1.45 (1.11-1.89) | 1.09 (0.72-1.63) | 1.00 (0.69-1.45) |
|  45+ | 2.17 (1.66-2.84) | 2.29 (1.76-2.98) | 1.94 (1.30-2.90) | 1.78 (1.23-2.58) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.43 (1.22-1.66) | 1.45 (1.25-1.69) | 1.68 (1.23-2.28) | 1.65 (1.23-2.20) |
|  2007-2010 | 1.20 (1.07-1.36) | 1.27 (1.13-1.42) | 1.26 (1.13-1.40) | 1.21 (1.09-1.35) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.01 (0.81-1.25) | 1.00 (0.81-1.24) | 0.84 (0.71-0.98) | 0.87 (0.75-1.02) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.71 (0.62-0.80) | 0.71 (0.63-0.81) | 1.03 (0.90-1.18) | 1.01 (0.87-1.16) |
|  100-199 | 0.36 (0.31-0.41) | 0.37 (0.33-0.43) | 0.71 (0.63-0.81) | 0.71 (0.62-0.81) |
|  200-249 | 0.22 (0.18-0.29) | 0.24 (0.19-0.32) | 0.59 (0.49-0.72) | 0.59 (0.49-0.72) |
|  250-349 | 0.16 (0.13-0.19) | 0.17 (0.14-0.21) | 0.39 (0.33-0.47) | 0.39 (0.33-0.47) |
|  350-499 | 0.16 (0.12-0.20) | 0.16 (0.12-0.20) | 0.39 (0.31-0.49) | 0.38 (0.30-0.47) |
|  500+ | 0.10 (0.07-0.15) | 0.01 (0.07-0.15) | 0.33 (0.25-0.43) | 0.31 (0.23-0.40) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | - | - |
|  6-11 months | 0.43 (0.39-0.48) | 0.44 (0.39-0.48) | - | - |
| Injecting drug use history\* | 1.56 (1.28-1.90) | 1.50 (1.23-1.83) | 1.67 (1.43-1.95) | 1.64 (1.42-1.91) |
| Region\* |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | 1.00 | - |
|  Latin America | 1.98 (1.10-3.57) | 2.03 (1.09-3.78) | 2.18 (1.23-3.83) | 2.02 (1.13-3.59) |
|  North America\*\* | 0.75 (0.46-1.23) | 0.81 (0.48-1.36) | 2.52 (1.58-4.01) | 2.37 (1.48-3.80) |
| Baseline mortality† | 4.5 (2.9-6.8) | 3.8 (2.5-5.9) | 0.5 (0.3-0.9) | 0.6 (0.4-1.0) |
| Standard deviation of random effects | 0.64 (0.48-0.86) | 0.68 (0.44-0.85) | 0.60 (0.44-0.84) | 0.62 (0.38-0.79) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). \*\* Estimates for North America in the first year of ART could be under-estimated, as patients must have two HIV visits within 12 months to be enrolled in the cohort. ART = antiretroviral treatment.

Table S16: Multivariable analysis of mortality after ART initiation in sub-Saharan Africa

|  |  |  |
| --- | --- | --- |
|  | 1st 12 months | >12 months |
|  | Main analysis | Imputation ofbaseline CD4 | Main analysis | Imputation ofbaseline CD4 |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.81 (0.79-0.83) | 0.80 (0.79-0.82) | 0.73 (0.71-0.76) | 0.74 (0.73-0.76) |
| Age group\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 0.98 (0.92-1.03) | 0.97 (0.92-1.02) | 0.78 (0.72-0.84) | 0.80 (0.73-0.87) |
|  35-44 | 0.99 (0.94-1.04) | 0.97 (0.93-1.02) | 0.69 (0.64-0.74) | 0.71 (0.66-0.77) |
|  45+ | 1.21 (1.13-1.29) | 1.15 (1.09-1.21) | 0.82 (0.76-0.88) | 0.84 (0.78-0.90) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.07 (1.04-1.11) | 1.12 (1.08-1.15) | 2.05 (1.84-2.28) | 2.26 (2.1-2.44) |
|  2007-2010 | 1.03 (1.00-1.06) | 1.03 (1.01-1.05) | 1.22 (1.18-1.27) | 1.28 (1.24-1.31) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.00 (0.94-1.05) | 1.03 (0.99-1.07) | 0.91 (0.88-0.94) | 0.94 (0.92-0.97) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.58 (0.56-0.60) | 0.63 (0.61-0.65) | 0.78 (0.74-0.82) | 0.77 (0.74-0.80) |
|  100-199 | 0.34 (0.33-0.34) | 0.40 (0.39-0.41) | 0.55 (0.53-0.57) | 0.55 (0.53-0.58) |
|  200-249 | 0.23 (0.22-0.25) | 0.30 (0.28-0.32) | 0.48 (0.44-0.52) | 0.50 (0.47-0.53) |
|  250-349 | 0.18 (0.17-0.19) | 0.24 (0.22-0.25) | 0.41 (0.39-0.44) | 0.42 (0.40-0.44) |
|  350-499 | 0.16 (0.14-0.19) | 0.21 (0.19-0.23) | 0.42 (0.36-0.49) | 0.41 (0.37-0.47) |
|  500+ | 0.13 (0.10-0.17) | 0.17 (0.13-0.21) | 0.24 (0.08-0.77) | 0.35 (0.17-0.71) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | - | - |
|  6-11 months | 0.43 (0.42-0.44) | 0.45 (0.44-0.46) | - | - |
| Region\* |  |  |  |  |
|  East Africa | 1.00 | 1.00 | 1.00 | 1.00 |
|  South Africa | 0.85 (0.55-1.32) | 0.84 (0.58-1.22) | 0.97 (0.61-1.54) | 0.94 (0.61-1.45) |
|  Southern Africa (excl. RSA) | 1.09 (0.70-1.68) | 1.18 (0.81-1.71) | 1.34 (0.84-2.15) | 1.45 (0.95-2.23) |
|  West and Central Africa | 0.97 (0.67-1.40) | 1.03 (0.75-1.41) | 1.28 (0.87-1.89) | 1.34 (0.93-1.94) |
| Baseline mortality† | 33.1 (24.0-45.6) | 30.8 (23.3-40.6) | 4.9 (3.5-6.9) | 4.8 (3.5-6.6) |
| Standard deviation of random effects | 0.42 (0.31-0.51) | 0.37 (0.27-0.44) | 0.45 (0.33-0.54) | 0.42 (0.31-0.5) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). ART = antiretroviral treatment; RSA = Republic of South Africa.

In a further sensitivity analysis, we aimed to assess whether the unusual results in North America might be due to unusual age distribution of ART patients in this region. Although the results in the main analysis are age-adjusted, we hypothesized that treating age as a categorical variable (with a particularly broad upper age interval, viz. 45 years and older) might lead to some bias in the estimation of the effects of the other predictors of mortality. We therefore considered three alternative models: (1) a model in which a cubic polynomial was used to model the effect of age; (2) a model in which restricted cubic splines were used to model the effect of age [18]; and (3) a model in which a number of 5-year age groups were included in the regression model (15-19, 20-24, … 75-79, 80+). The rc\_spline command in STATA was used to fit the second model; in this model, 4 knots were included at ages 24, 36, 45 and 61. Table S17 compares the different models of mortality in the first 12 months after ART initiation in Asia and the Americas, while Table S18 compares the same models for the period more than 12 months after ART initiation. None of the alternative models suggest materially different conclusions from those in the main analysis, and the difference in mortality between North America and the Asia-Pacific is virtually unchanged.

Table S17: Multivariable analysis of mortality in the first 12 months after ART initiation in Asia and the Americas, comparing different models of the age effect

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Main analysis | Model 1:Cubic polynomial | Model 2:Cubicsplines | Model 3:5-year agegroupings |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.86 (0.76-0.97) | 0.86 (0.76-0.97) | 0.86 (0.76-0.97) | 0.86 (0.76-0.97) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.43 (1.22-1.66) | 1.45 (1.24-1.69) | 1.45 (1.24-1.69) | 1.45 (1.24-1.69) |
|  2007-2010 | 1.20 (1.07-1.36) | 1.21 (1.08-1.37) | 1.21 (1.07-1.37) | 1.21 (1.07-1.36) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.01 (0.81-1.25) | 1.01 (0.81-1.26) | 1.01 (0.81-1.26) | 1.01 (0.81-1.26) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.71 (0.62-0.80) | 0.70 (0.61-0.79) | 0.70 (0.61-0.79) | 0.70 (0.61-0.80) |
|  100-199 | 0.36 (0.31-0.41) | 0.35 (0.31-0.40) | 0.35 (0.31-0.40) | 0.35 (0.31-0.40) |
|  200-249 | 0.22 (0.18-0.29) | 0.22 (0.17-0.28) | 0.22 (0.17-0.28) | 0.22 (0.17-0.29) |
|  250-349 | 0.16 (0.13-0.19) | 0.15 (0.12-0.19) | 0.15 (0.12-0.19) | 0.15 (0.12-0.19) |
|  350-499 | 0.16 (0.12-0.20) | 0.16 (0.12-0.20) | 0.16 (0.12-0.20) | 0.16 (0.12-0.20) |
|  500+ | 0.10 (0.07-0.15) | 0.10 (0.07-0.15) | 0.10 (0.07-0.15) | 0.10 (0.07-0.14) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | 1.00 | 1.00 |
|  6-11 months | 0.43 (0.39-0.48) | 0.44 (0.39-0.48) | 0.43 (0.39-0.48) | 0.43 (0.39-0.48) |
| Injecting drug use history\* | 1.56 (1.28-1.90) | 1.66 (1.36-2.03) | 1.67 (1.36-2.04) | 1.66 (1.35-2.02) |
| Region\* |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | 1.00 | - |
|  Latin America | 1.98 (1.10-3.57) | 1.99 (1.11-3.58) | 2.00 (1.11-3.58) | 1.99 (1.11-3.58) |
|  North America\*\* | 0.75 (0.46-1.23) | 0.74 (0.45-1.22) | 0.75 (0.46-1.22) | 0.75 (0.46-1.22) |
| Standard deviation of random effects | 0.64 (0.48-0.86) | 0.63 (0.47-0.85) | 0.63 (0.47-0.85) | 0.63 (0.47-0.85) |

\* Incidence rate ratio (adjusted). \*\* Estimates for North America in the first year of ART could be under-estimated, as patients must have two HIV visits within 12 months to be enrolled in the cohort. ART = antiretroviral treatment.

Table S18: Multivariable analysis of mortality more than 12 months after ART initiation in Asia and the Americas, comparing different models of the age effect

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Main analysis | Model 1:Cubic polynomial | Model 2:Cubicsplines | Model 3:5-year agegroupings |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.96 (0.85-1.08) | 0.96 (0.85-1.09) | 0.96 (0.85-1.08) | 0.96 (0.85-1.08) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.68 (1.23-2.28) | 1.74 (1.28-2.37) | 1.74 (1.28-2.37) | 1.73 (1.27-2.36) |
|  2007-2010 | 1.26 (1.13-1.40) | 1.29 (1.15-1.43) | 1.29 (1.16-1.43) | 1.28 (1.15-1.43) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 0.84 (0.71-0.98) | 0.83 (0.7-0.97) | 0.83 (0.7-0.97) | 0.83 (0.7-0.97) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 1.03 (0.90-1.18) | 1.02 (0.88-1.17) | 1.02 (0.88-1.17) | 1.02 (0.89-1.17) |
|  100-199 | 0.71 (0.63-0.81) | 0.70 (0.61-0.79) | 0.70 (0.61-0.79) | 0.70 (0.61-0.79) |
|  200-249 | 0.59 (0.49-0.72) | 0.58 (0.48-0.71) | 0.58 (0.48-0.70) | 0.58 (0.48-0.71) |
|  250-349 | 0.39 (0.33-0.47) | 0.38 (0.32-0.46) | 0.38 (0.32-0.46) | 0.38 (0.32-0.46) |
|  350-499 | 0.39 (0.31-0.49) | 0.39 (0.31-0.49) | 0.39 (0.31-0.49) | 0.39 (0.31-0.49) |
|  500+ | 0.33 (0.25-0.43) | 0.31 (0.24-0.41) | 0.31 (0.24-0.41) | 0.31 (0.24-0.41) |
| Injecting drug use history\* | 1.67 (1.43-1.95) | 1.83 (1.57-2.14) | 1.82 (1.56-2.13) | 1.83 (1.57-2.14) |
| Region\* |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | 1.00 | 1.00 |
|  Latin America | 2.18 (1.23-3.83) | 2.21 (1.27-3.86) | 2.20 (1.26-3.84) | 2.20 (1.26-3.84) |
|  North America | 2.52 (1.58-4.01) | 2.53 (1.60-3.99) | 2.51 (1.59-3.97) | 2.52 (1.59-3.98) |
| Standard deviation of random effects | 0.60 (0.44-0.84) | 0.59 (0.43-0.83) | 0.59 (0.43-0.83) | 0.59 (0.43-0.82) |

\* Incidence rate ratio (adjusted).

CD4 cell counts are highly variable within individual patients, and the measured CD4 count at a point in time might not be an accurate reflection of the patient’s ‘true’ CD4 count (averaged across many measurements within the space of a few days). The observed distribution of baseline CD4 counts and the ‘true’ distribution of baseline CD4 counts may differ, and the use of CD4-based ART eligibility criteria has a particular effect on this relationship, as patients whose observed CD4 cell counts are below their ‘true’ CD4 counts are more likely to be initiated on ART when CD4-based eligibility criteria apply. The effect of the patient’s observed CD4 count on their mortality risk may therefore be dependent on the CD4 eligibility criteria that are in place. To test this hypothesis, we ran the model with the inclusion of a ‘guideline effect’ (a categorical variable indicating the CD4 threshold that applied at the date the patient initiated ART). In the analysis of the Asian and American data, the inclusion of the guideline effect made almost no difference to the regression results, although there appeared to be slightly less of a decline in mortality over time, when considering the first 12 months after ART initiation (Table S19). None of the guideline effects were statistically significant.

Table S19: Multivariable analysis of mortality after ART initiation in Asia and the Americas

|  |  |  |
| --- | --- | --- |
|  | 1st 12 months | >12 months |
|  | Main analysis | Guideline effectincluded | Main analysis | Guideline effectincluded |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.86 (0.76-0.97) | 0.85 (0.76-0.96) | 0.96 (0.85-1.08) | 0.95 (0.85-1.08) |
| Age group\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 1.22 (0.93-1.61) | 1.22 (0.93-1.60) | 1.04 (0.69-1.57) | 1.03 (0.68-1.56) |
|  35-44 | 1.39 (1.06-1.82) | 1.38 (1.05-1.81) | 1.09 (0.72-1.63) | 1.08 (0.72-1.62) |
|  45+ | 2.17 (1.66-2.84) | 2.16 (1.65-2.82) | 1.94 (1.30-2.90) | 1.93 (1.29-2.88) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.43 (1.22-1.66) | 1.32 (1.06-1.64) | 1.68 (1.23-2.28) | 1.72 (1.26-2.35) |
|  2007-2010 | 1.20 (1.07-1.36) | 1.14 (0.97-1.34) | 1.26 (1.13-1.40) | 1.24 (1.11-1.39) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.01 (0.81-1.25) | 1.09 (0.87-1.37) | 0.84 (0.71-0.98) | 0.83 (0.7-0.97) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.71 (0.62-0.80) | 0.71 (0.62-0.81) | 1.03 (0.90-1.18) | 1.03 (0.90-1.19) |
|  100-199 | 0.36 (0.31-0.41) | 0.36 (0.31-0.41) | 0.71 (0.63-0.81) | 0.72 (0.63-0.81) |
|  200-249 | 0.22 (0.18-0.29) | 0.22 (0.18-0.29) | 0.59 (0.49-0.72) | 0.58 (0.48-0.71) |
|  250-349 | 0.16 (0.13-0.19) | 0.16 (0.13-0.19) | 0.39 (0.33-0.47) | 0.38 (0.32-0.46) |
|  350-499 | 0.16 (0.12-0.20) | 0.16 (0.13-0.21) | 0.39 (0.31-0.49) | 0.40 (0.32-0.50) |
|  500+ | 0.10 (0.07-0.15) | 0.01 (0.07-0.15) | 0.33 (0.25-0.43) | 0.34 (0.26-0.44) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | - | - |
|  6-11 months | 0.43 (0.39-0.48) | 0.44 (0.39-0.48) | - | - |
| Injecting drug use history\* | 1.56 (1.28-1.90) | 1.55 (1.27-1.89) | 1.67 (1.43-1.95) | 1.66 (1.43-1.94) |
| Region\* |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | 1.00 | - |
|  Latin America | 1.98 (1.10-3.57) | 2.02 (1.12-3.67) | 2.18 (1.23-3.83) | 2.17 (1.24-3.80) |
|  North America\*\* | 0.75 (0.46-1.23) | 0.81 (0.49-1.36) | 2.52 (1.58-4.01) | 2.49 (1.56-3.97) |
| CD4 eligibility criterion |  |  |  |  |
|  <200 cells/µl | - | 1.00 | - | 1.00 |
|  <350 cells/µl | - | 0.99 (0.83-1.18) | - | 1.13 (0.99-1.30) |
|  <500 cells/µl | - | 0.79 (0.62-1.02) | - | 0.99 (0.81-1.22) |
|  All | - | 0.79 (0.54-1.16) | - | 0.75 (0.47-1.20) |
| Baseline mortality† | 4.5 (2.9-6.8) | 4.7 (3-7.4) | 0.5 (0.3-0.9) | 0.5 (0.3-0.9) |
| Standard deviation of random effects | 0.64 (0.48-0.86) | 0.64 (0.48-0.86) | 0.60 (0.44-0.84) | 0.60 (0.43-0.83) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). \*\* Estimates for North America in the first year of ART could be under-estimated, as patients must have two HIV visits within 12 months to be enrolled in the cohort. ART = antiretroviral treatment.

Similarly, the inclusion of guideline effects has no effect in the regression model of mortality during the first 12 months after ART initiation in sub-Saharan Africa (Table S20). However, the inclusion of guideline effects does change the estimated effect of baseline CD4 count slightly when considering mortality rates more than 12 months after ART initiation, and in this analysis the effect of the ART eligibility criteria is statistically significant. Consistent with what might be expected if the inclusion of CD4-based ART eligibility criteria introduces a bias towards individuals whose ‘true’ CD4 is above the eligibility threshold, mortality rates are lowest when the CD4-based eligibility criteria are most restrictive.

Table S20: Multivariable analysis of mortality after ART initiation in sub-Saharan Africa

|  |  |  |
| --- | --- | --- |
|  | 1st 12 months | >12 months |
|  | Main analysis | Guideline effectincluded | Main analysis | Guideline effectincluded |
| Sex\* |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.81 (0.79-0.83) | 0.81 (0.79-0.83) | 0.73 (0.71-0.76) | 0.74 (0.73-0.76) |
| Age group\* |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 0.98 (0.92-1.03) | 0.98 (0.94-1.03) | 0.78 (0.72-0.84) | 0.81 (0.75-0.88) |
|  35-44 | 0.99 (0.94-1.04) | 0.99 (0.95-1.04) | 0.69 (0.64-0.74) | 0.74 (0.68-0.80) |
|  45+ | 1.21 (1.13-1.29) | 1.22 (1.16-1.28) | 0.82 (0.76-0.88) | 0.89 (0.82-0.96) |
| Follow-up period\* |  |  |  |  |
|  2001-2006 | 1.07 (1.04-1.11) | 1.10 (1.04-1.16) | 2.05 (1.84-2.28) | 2.25 (2.05-2.46) |
|  2007-2010 | 1.03 (1.00-1.06) | 1.05 (1.01-1.10) | 1.22 (1.18-1.27) | 1.33 (1.28-1.38) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.00 (0.94-1.05) | 1.05 (0.99-1.11) | 0.91 (0.88-0.94) | 0.84 (0.80-0.87) |
| Baseline CD4 cell count  (cells/µl)\* |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.58 (0.56-0.60) | 0.58 (0.56-0.60) | 0.78 (0.74-0.82) | 0.78 (0.75-0.81) |
|  100-199 | 0.34 (0.33-0.34) | 0.33 (0.32-0.34) | 0.55 (0.53-0.57) | 0.54 (0.53-0.56) |
|  200-249 | 0.23 (0.22-0.25) | 0.23 (0.22-0.25) | 0.48 (0.44-0.52) | 0.39 (0.36-0.43) |
|  250-349 | 0.18 (0.17-0.19) | 0.18 (0.17-0.19) | 0.41 (0.39-0.44) | 0.34 (0.32-0.37) |
|  350-499 | 0.16 (0.14-0.19) | 0.17 (0.14-0.19) | 0.42 (0.36-0.49) | 0.33 (0.28-0.38) |
|  500+ | 0.13 (0.10-0.17) | 0.13 (0.10-0.17) | 0.24 (0.08-0.77) | 0.22 (0.07-0.69) |
| Time since ART start\* |  |  |  |  |
|  0-5 months | 1.00 | 1.00 | - | - |
|  6-11 months | 0.43 (0.42-0.44) | 0.43 (0.42-0.45) | - | - |
| Region\* |  |  |  |  |
|  East Africa | 1.00 | 1.00 | 1.00 | 1.00 |
|  South Africa | 0.85 (0.55-1.32) | 0.85 (0.55-1.30) | 0.97 (0.61-1.54) | 0.98 (0.62-1.56) |
|  Southern Africa (excl. RSA) | 1.09 (0.70-1.68) | 1.07 (0.70-1.65) | 1.34 (0.84-2.15) | 1.27 (0.79-2.04) |
|  West and Central Africa | 0.97 (0.67-1.40) | 0.97 (0.68-1.40) | 1.28 (0.87-1.89) | 1.28 (0.86-1.90) |
| CD4 eligibility |  |  |  |  |
|  <200 | - | 1.00 | - | 1.00 |
|  <350 | - | 1.05 (1.00-1.10) | - | 1.37 (1.32-1.43) |
|  <500 | - | 0.97 (0.91-1.03) | - | 1.60 (1.48-1.74) |
|  All | - | 0.97 (0.87-1.08) | - | 2.10 (1.45-3.04) |
| Baseline mortality† | 33.1 (24.0-45.6) | 32.2 (23.4-44.3) | 4.9 (3.5-6.9) | 4.2 (3.0-6.0) |
| Standard deviation of random effects | 0.42 (0.31-0.51) | 0.42 (0.31-0.51) | 0.45 (0.33-0.54) | 0.45 (0.33-0.55) |

\* Incidence rate ratio (adjusted). † Per 100 person years, in individuals with baseline covariate pattern (males aged 15-24 followed up in the 2011-2014 period, with baseline CD4 cell count <50 cells/µl). ART = antiretroviral treatment; RSA = Republic of South Africa.

To test the sensitivity of the model results to the piecewise-constant hazard assumption, we also compared the Poisson regression model to a Cox proportional hazard models with frailty effects (which function in the same way as random effects), as shown in the Tables S21 and S22. Most of the variables have similar effects on mortality in the two analyses, especially in the first 12 months after ART initiation. However, when considering mortality more than 12 months after ART initiation, the effects of calendar year in the African cohorts are less significant in the Cox proportional hazards model than in the Poisson model. Similarly in the analysis of Asian and American mortality data more than 12 months after ART initiation, the difference between mortality in 2001-2006 and mortality in 2011-2014 is less substantial in the Cox proportional hazards model (aHR 1.41, 95% CI: 1.03-1.94) than in the Poisson model (aIRR 1.68, 95% CI: 1.23-2.28). These results are consistent with the sensitivity analysis in Figure 2 and Table S13 (which similarly consider the effect of relaxing the ‘piecewise constant hazard’ assumption to some degree). In addition, the difference in mortality between Latin America and Asia-Pacific appears less substantial in the Cox proportional hazards model than in the Poisson model. In the analysis of African mortality more than 12 months after ART initiation, the protective effect of older age also appears less significant in the Cox proportional hazards model than in the Poisson regression model (again consistent with the sensitivity analysis in Table S13).

Table S21: Multivariable analysis of mortality after ART initiation in Asia and the Americas

|  |  |  |
| --- | --- | --- |
|  | Poisson regression, random effects | Cox model, frailty effects |
|  | 1st 12 months | >12 months | 1st 12 months | >12 months |
| Sex |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.86 (0.76-0.97) | 0.96 (0.85-1.08) | 0.86 (0.76-0.97) | 0.96 (0.85-1.08) |
| Age group (years) |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 1.22 (0.93-1.61) | 1.04 (0.69-1.57) | 1.24 (0.95-1.63) | 1.11 (0.73-1.67) |
|  35-44 | 1.39 (1.06-1.82) | 1.09 (0.72-1.63) | 1.41 (1.08-1.85) | 1.18 (0.79-1.77) |
|  45+ | 2.17 (1.66-2.84) | 1.94 (1.30-2.90) | 2.20 (1.68-2.88) | 2.13 (1.42-3.18) |
| Follow-up period |  |  |  |  |
|  2001-2006 | 1.43 (1.22-1.66) | 1.68 (1.23-2.28) | 1.37 (1.18-1.60) | 1.41 (1.03-1.94) |
|  2007-2010 | 1.20 (1.07-1.36) | 1.26 (1.13-1.40) | 1.19 (1.06-1.34) | 1.17 (1.04-1.31) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.01 (0.81-1.25) | 0.84 (0.71-0.98) | 1.03 (0.82-1.28) | 0.84 (0.71-1.00) |
| Baseline CD4 cell count  (cells/µl) |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.71 (0.62-0.80) | 1.03 (0.90-1.18) | 0.71 (0.62-0.80) | 1.03 (0.90-1.18) |
|  100-199 | 0.36 (0.31-0.41) | 0.71 (0.63-0.81) | 0.36 (0.31-0.41) | 0.71 (0.63-0.81) |
|  200-249 | 0.22 (0.18-0.29) | 0.59 (0.49-0.72) | 0.22 (0.18-0.29) | 0.58 (0.48-0.71) |
|  250-349 | 0.16 (0.13-0.19) | 0.39 (0.33-0.47) | 0.16 (0.13-0.19) | 0.38 (0.32-0.45) |
|  350-499 | 0.16 (0.12-0.20) | 0.39 (0.31-0.49) | 0.16 (0.12-0.20) | 0.37 (0.30-0.47) |
|  500+ | 0.10 (0.07-0.15) | 0.33 (0.25-0.43) | 0.10 (0.07-0.15) | 0.32 (0.24-0.41) |
| Time since ART start |  |  |  |  |
|  0-5 months | 1.00 | - | - | - |
|  6-11 months | 0.43 (0.39-0.48) | - | - | - |
| Injecting drug use history | 1.56 (1.28-1.90) | 1.67 (1.43-1.95) | 1.58 (1.3-1.93) | 1.68 (1.44-1.96) |
| Region |  |  |  |  |
|  Asia-Pacific | 1.00 | 1.00 | 1.00 | 1.00 |
|  Latin America | 1.98 (1.10-3.57) | 2.18 (1.23-3.83) | 1.77 (1.01-3.08) | 1.90 (1.11-3.28) |
|  North America\* | 0.75 (0.46-1.23) | 2.52 (1.58-4.01) | 0.71 (0.45-1.14) | 2.58 (1.64-4.04) |

Results presented are adjusted incidence rate ratios (for the Poisson model) and adjusted hazard ratios (for the Cox proportional hazards model). \* Estimates for North America in the first year of ART could be under-estimated, as patients must have two HIV visits within 12 months to be enrolled in the cohort. ART = antiretroviral treatment.

Table S22: Multivariable analysis of mortality after ART initiation in sub-Saharan Africa

|  |  |  |
| --- | --- | --- |
|  | Poisson regression, random effects | Cox model, frailty effects |
|  | 1st 12 months | >12 months | 1st 12 months | >12 months |
| Sex |  |  |  |  |
|  Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  Female | 0.81 (0.79-0.83) | 0.73 (0.71-0.76) | 0.82 (0.8-0.83) | 0.76 (0.74-0.77) |
| Age group (years) |  |  |  |  |
|  15-24 | 1.00 | 1.00 | 1.00 | 1.00 |
|  25-34 | 0.98 (0.92-1.03) | 0.78 (0.72-0.84) | 0.99 (0.95-1.03) | 0.87 (0.81-0.93) |
|  35-44 | 0.99 (0.94-1.04) | 0.69 (0.64-0.74) | 1.00 (0.96-1.05) | 0.82 (0.76-0.87) |
|  45+ | 1.21 (1.13-1.29) | 0.82 (0.76-0.88) | 1.23 (1.17-1.29) | 1.00 (0.93-1.06) |
| Follow-up period |  |  |  |  |
|  2001-2006 | 1.07 (1.04-1.11) | 2.05 (1.84-2.28) | 1.03 (0.99-1.07) | 1.35 (1.24-1.48) |
|  2007-2010 | 1.03 (1.00-1.06) | 1.22 (1.18-1.27) | 1.02 (0.99-1.05) | 1.06 (1.03-1.09) |
|  2011-2014 | 1.00 | 1.00 | 1.00 | 1.00 |
|  2015-2017 | 1.00 (0.94-1.05) | 0.91 (0.88-0.94) | 1.00 (0.96-1.04) | 1.02 (0.99-1.05) |
| Baseline CD4 cell count  (cells/µl) |  |  |  |  |
|  0-49 | 1.00 | 1.00 | 1.00 | 1.00 |
|  50-99 | 0.58 (0.56-0.60) | 0.78 (0.74-0.82) | 0.58 (0.57-0.60) | 0.77 (0.75-0.80) |
|  100-199 | 0.34 (0.33-0.34) | 0.55 (0.53-0.57) | 0.33 (0.32-0.34) | 0.54 (0.53-0.56) |
|  200-249 | 0.23 (0.22-0.25) | 0.48 (0.44-0.52) | 0.23 (0.22-0.25) | 0.39 (0.37-0.42) |
|  250-349 | 0.18 (0.17-0.19) | 0.41 (0.39-0.44) | 0.18 (0.17-0.19) | 0.35 (0.33-0.37) |
|  350-499 | 0.16 (0.14-0.19) | 0.42 (0.36-0.49) | 0.17 (0.16-0.18) | 0.32 (0.29-0.36) |
|  500+ | 0.13 (0.10-0.17) | 0.24 (0.08-0.77) | 0.13 (0.10-0.16) | 0.27 (0.14-0.52) |
| Time since ART start |  |  |  |  |
|  0-5 months | 1.00 | - | - | - |
|  6-11 months | 0.43 (0.42-0.44) | - | - | - |
| Region |  |  |  |  |
|  East Africa | 1.00 | 1.00 | 1.00 | 1.00 |
|  South Africa | 0.85 (0.55-1.32) | 0.97 (0.61-1.54) | 0.91 (0.60-1.38) | 1.02 (0.66-1.59) |
|  Southern Africa (excl. RSA) | 1.09 (0.70-1.68) | 1.34 (0.84-2.15) | 1.13 (0.74-1.73) | 1.40 (0.90-2.18) |
|  West and Central Africa | 0.97 (0.67-1.40) | 1.28 (0.87-1.89) | 1.08 (0.76-1.54) | 1.31 (0.90-1.90) |

Results presented are adjusted incidence rate ratios (for the Poisson model) and adjusted hazard ratios (for the Cox proportional hazards model).

# References

1. Tymejczyk O, Brazier E, Yiannoutsos C, Wools-Kaloustian K, Althoff K, Crabtree-Ramirez B*, et al.* HIV treatment eligibility expansion and timely antiretroviral treatment initiation following enrollment in HIV care: A metaregression analysis of programmatic data from 22 countries. *PLoS Medicine* 2018; **15**:e1002534.

2. International Association of Providers of AIDS Care. Global HIV Policy Watch. 2018. Available: <http://www.hivpolicywatch.org/>. Accessed 2 Sept 2018

3. Gupta S, Williams B, Montaner J. Realizing the potential of treatment as prevention: global ART policy and treatment coverage. *Current HIV/AIDS Reports* 2014; **11**:479-486.

4. Gupta S, Granich R. When will sub-Saharan Africa adopt HIV treatment for all? *Southern African Journal of HIV Medicine* 2016; **17**:a459.

5. United Nations Department of Economic and Social Affairs Population Division. World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. 2017. Available: <https://population.un.org/wpp/Publications/Files/WPP2017_KeyFindings.pdf>. Accessed 29 Nov 2018

6. Holmes CB, Sikazwe I, Sikombe K, Eshun-Wilson I, Czaicki N, Beres LK*, et al.* Estimated mortality on HIV treatment among active patients and patients lost to follow-up in 4 provinces of Zambia: Findings from a multistage sampling-based survey. *PLoS Medicine* 2018; **15**:e1002489.

7. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN*, et al.* Outcomes of patients lost to follow-up in African antiretroviral therapy programs: individual patient data meta-analysis. *Clinical Infectious Diseases* 2018; **67**:1643-1652.

8. Ardura-Garcia C, Feldacker C, Tweya H, Chaweza T, Kalulu M, Phiri S*, et al.* Implementation and Operational Research: Early Tracing of Children Lost to Follow-Up From Antiretroviral Treatment: True Outcomes and Future Risks. *J Acquir Immune Defic Syndr* 2015; **70**:e160-167.

9. Rachlis B, Ochieng D, Geng E, Rotich E, Ochieng V, Maritim B*, et al.* Implementation and operational research: evaluating outcomes of patients lost to follow-up in a large comprehensive care treatment program in western Kenya. *Journal of Acquired Immune Deficiency Syndrome* 2015; **68**:e46-55.

10. Caluwaerts C, Maendaenda R, Maldonado F, Biot M, Ford N, Chu K. Risk factors and true outcomes for lost to follow-up individuals in an antiretroviral treatment programme in Tete, Mozambique. *International Health* 2009; **1**:97-101.

11. Geng EH, Odeny TA, Lyamuya RE, Nakiwogga-Muwanga A, Diero L, Bwana M*, et al.* Estimation of mortality among HIV-infected people on antiretroviral treatment in East Africa: a sampling based approach in an observational, multisite, cohort study. *Lancet HIV* 2015; **2**:e107-116.

12. Gunguwo H, Chaibva CN, Maseko U, Mabhena TS, Mantula F, Luzane TL*, et al.* True outcomes of patients lost to follow-up on antiretroviral therapy at a large central hospital OI/ART clinicin Bulawayo, Zimbabwe [abstract TUPE064]. *XIX International AIDS Conference*. Washington DC, USA; 2012.

13. Kato T, Yasutaka Y, Komada K, Miyano S, Watara J, Christphoer D*, et al.* Further investigation to address the details of the poor outcome based on prospective cohort study of HIV- infected patients in rural area of Zambia [abstract TULBPE38]. *7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*. Kuala Lumpur, Malaysia; 2013.

14. Kiragga AN, Castelnuovo B, Musomba R, Levin J, Kambugu A, Manabe YC*, et al.* Comparison of methods for correction of mortality estimates for loss to follow-up after ART initiation: a case of the Infectious Diseases Institute, Uganda. *PLoS One* 2013; **8**:e83524.

15. Mben JM, Kouanfack C, Essomba CN, Mbougua JB, Kenfack A, Tonfack CA*, et al.* Operational research and HIV policy and guidelines: lessons from a study of patients lost to follow-up from a public antiretroviral treatment program in Cameroon. *Journal of Public Health Policy* 2012; **33**:462-477.

16. Tweya H, Feldacker C, Estill J, Jahn A, Ng'ambi W, Ben-Smith A*, et al.* Are they really lost? "True" status and reasons for treatment discontinuation among HIV infected patients on antiretroviral therapy considered lost to follow up in urban Malawi. *PLoS One* 2013; **8**:e75761.

17. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine* 1999; **18**:681-694.

18. Shepherd BE, Rebeiro PF. Assessing and interpreting the association between continuous covariates and outcomes in observational studies of HIV using splines. *Journal of Acquired Immune Deficiency Syndrome* 2017; **74**:e60-e63.