An investigation of the age-sex pattern in Spectrum's estimates of HIV/AIDS mortality for generalized epidemics

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Abstract

An investigation of the age-sex pattern in Spectrum's estimates of
HIV/AIDS mortality for generalized epidemics

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Objective: Currently there are significant variations between the age-sex patterns of the Global Burden of Disease 2010 (GBD 2010) Study's estimates of all cause morality and UNAIDS' 2012 estimates of HIV/AIDS mortality for a number of sub-Saharan African (SSA) countries. While both estimates have their own unique limitations, the goal of this analysis was to explore assumptions used in UNAIDS' Spectrum model that influence their age-sex specific HIV/AIDS mortality estimates.

Methods: UNAIDS' Spectrum/Estimation and Projection Package (EPP) was used as the vehicle for exploration. Spectrum currently applies the same assumptions and IRRs for all countries in SSA with generalized epidemic. Assumptions about the progression of HIV infection in the absence of antiretroviral treatment and age-sex specific incidence rate ratio (IRR) were identified as two areas in Spectrum that could influence the model's age-sex patterns of HIV/AIDS mortality. Within these, four scenarios were explored; adjusting the proportion of new infections in CD4+ count categories, adjusting years lived in various CD4+ count categories, adjusting the non-AIDS mortality rate, and adjusting the IRRs. Assumption modifications were made based on alternative cohort studies, estimates from the GBD 2010 study, or country-specific data. Age-sex-specific HIV/AIDS mortality estimates were generated using these modified assumptions and these were compared to those generated using Spectrum defaults.

Results: There is wide variation in the Spectrum assumptions by cohorts and country-level DHS data. When these alternative assumptions for disease progression or IRRs are entered in Spectrum, this can shift the age group with the highest estimates of HIV/AIDS mortality and can also alter the level of mortality. The degree of estimate variation depends on the degree of assumption adjustment. When disease progression parameters are calibrated to the ALPHA survivorship data results are more similar to those generated using Spectrum's default values. The cohorts that drive Spectrum's assumptions have small sample sizes and are not necessarily representative of all SSA countries.

Conclusions: Spectrum's age-sex patterns of HIV/AIDS mortality are sensitive to disease progression parameters and IRR adjustments. When compared to other studies or more detailed data sources, Spectrum's current assumptions for these inputs do not capture the wide variability seen at the individual and subpopulation level. A systematic review of data from all potential cohort studies should be conducted and Spectrum should better propagate uncertainty in parameter values. More country-level data should also be incorporated into Spectrum, when available, to better reflect each country's unique epidemic.

Introduction

According to the Global Burden of Disease 2010 study (GBD 2010), in 2010 HIV/AIDS was the six leading cause of global deaths in all ages and the leading cause of death in age groups 25-44.[1,2] However, the HIV epidemic has disproportionately affected populations across the globe. In 2010 HIV/AIDS contributed to 38% of all death in Southern sub-Saharan Africa (SSA), was the leading cause of death in 18 of 46 SSA countries, and contributed to over 50% of total deaths in age groups 25-44 for ten SSA countries.[1] Since little data is available to estimate cause-specific or all-cause mortality for majority of SSA countries, mortality estimates for these countries are largely reliant on statistical models.

Over the past decade the Joint United Nations Programme on HIV and AIDS (UNAIDS) has been generating projections of HIV/AIDS mortality by age and sex on a bi-annual basis using the Spectrum/Estimation and Projection Package (EPP).[3,4] EPP derives country-year estimates of HIV incidence then Spectrum uses these, along with other inputs, to derive country-year-age-sex estimates of HIV/AIDS mortality. Inputs into this modeling package include surveillance and survey data, UNPOP's demographic data, data on treatment guidelines, and a number of other assumptions (such as duration from infection to death) derived from cohort studies and other sources. Spectrum/EPP has been modified and updated over the years. Estimates from this package are instrumental in epidemic planning and the allocation of scare global health resources.[5–8]

For GBD 2010, the GBD enterprise collaborated with UNAIDS, which resulted in the use of UNAIDS' 2012 estimates of HIV/AIDS mortality for the GBD 2010 study. While this was a fruitful exchange, there were some significant differences in the age-sex patterns of mortality between GBD 2010's all-cause estimates and UNAIDS' 2012 HIV/AIDS-specific estimates. These differences were most apparent for a number of SSA countries with large, generalized HIV epidemics. For example, in Zimbabwe in 2010, UNAIDS' estimates of HIV/AIDS mortality peaked in age group 35-39, while GBD 2010's estimates of all-cause mortality peaked in age group 25-29, Figure 1.[4,9] Because 48% of total mortality in ages 15-49 was attributable to HIV/AIDS in Zimbabwe in 2010, the ten year gap in estimates of peak all-cause mortality and HIV/AIDS mortality highlights inconsistencies between the two modeling processes.[1] UNAIDS' estimate of HIV/AIDS mortality was also 1.4 times greater than GBD 2010's estimate of all-cause mortality for age group 35-39 in Zimbabwe in 2010; further emphasizing inconsistencies in the modeling approaches.[4,9]

The discrepancies in these estimates are of particular importance because of an all-cause mortality adjustment that is applied as part of the GBD 2010 methodology.[10,11] The assumption underlying this adjustment is that summation of all 235 causes of death estimated in the GBD 2010 study cannot exceed the all-cause mortality estimate for a particular age-sex-county-year.[1] Because of the significant differences between UNAIDS' 2012 HIV/AIDS and GBD 2010's all-cause mortality estimates by age and sex, UNAIDS' 2012 HIV/AIDS estimates are significantly adjusted for a number of SSA countries with large epidemics. In 2010, for example, UNAIDS' estimates of HIV/AIDS mortality for Zimbabwe were reduced by roughly 35% after this all-cause mortality adjustment; this adjustment ranged from reductions of 35% in Zimbabwe and Botswana to inflations of 13% or 26% in Eritrea or Indonesia respectively [1,2,12]

There are limitations to both the GBD 2010 all-cause mortality estimates and UNAIDS' 2012 HIV/AIDS mortality estimates. In this analysis, however, I sought to identify key assumptions in the Spectrum portion of Spectrum/EPP that influence the package's age-sex patterns of HIV/AIDS mortality. Since Spectrum/EPP is designed to model one country's epidemic at a time, when a country's epidemic is specified as generalized or concentrated, a number of assumptions about the structure and progression of the epidemic are applied to that country. For generalized epidemics, the same set of assumptions are applied to all countries with this epidemic classification and not tailored to a particular country of interest. Some Spectrum assumptions are adjusted during UNAIDS' country consultation process, however, these are primarily assumptions on the number of HIV positive individuals on treatment or the distribution of different treatment regimes. The Spectrum assumptions I identified as most likely to influence age-sex patterns of HIV/AIDS mortality were those concerning progression rates between decreasing CD4+ count categories and age-sex specific incidence rate ratios (IRR). In this investigation I sought to challenge assumptions in Spectrum that are applied to all SSA countries with generalized epidemics by using data from alternative cohort studies as well as country-specific data, when available. I then explored the effect these modifications have on the age-sex patterns of Spectrum's estimates of HIV/AIDS mortality.

Methods

This investigation of Spectrum's age-sex patterns of HIV/AIDS mortality was limited to SSA countries with generalized epidemics. Countries in this region and with this epidemic classification were selected because they have the greatest number of HIV/AIDS deaths, the greatest discrepancies in age-sex patterns of mortality when compared to the GBD 2010 all-cause estimates, and because they are where adjustments to assumptions held in Spectrum will have the most noticeable effect. To conduct my analysis I downloaded Spectrum (version 4.69) from the Futures Institute's website (http://futuresinstitute.org/spectrum.aspx) on August 12, 2013. I had previously conducted my analysis using Spectrum (version 4.67), uploaded July 2, 2013, which yielded substantially different results in the age-sex patterns and HIV/AIDS mortality levels of my adjusted models. Spectrum version 4.69 was the most up-to-date version of the modeling package at the time I conducted my analysis; it includes updates that are currently being used for UNAIDS' 2013 HIV/AIDS estimation process.

The Spectrum assumptions I identified as most likely to influence the package's age-sex patterns of HIV/AIDS mortality were those concerning progression rates between decreasing CD4+ count categories and age-sex specific incidence rate ratios (IRRs). To explore these assumptions I tested four different scenarios; three of which influenced the progression rates between decreasing CD4+ counts and the other which investigated the age-sex specific IRRs. Scenario one looked at adjusting the proportion of new infections in CD4+ count categories, scenario two looked at adjusting the years spent in various CD4+ count categories, scenario three looked at adjusting the background non-AIDS mortality rate, and scenario four looked at adjusting the IRRs.

Background: Spectrum's HIV/AIDS natural history model

In Spectrum, progression rates between decreasing CD4+ count categories are modeled using a steady state model that assesses the natural history of the HIV infection in the absence of antiretroviral treatment (ART). The model is unique for four different age groups; 15 to 24, 25 to 34, 35 to 44, and 45 plus. By age group, new infections begin in one of two CD4+ count categories (<500 and 350-500) and then progress linearly between seven decreasing CD4+ count categories. As the CD4+ count categories decrease, the HIV/AIDS mortality rate in each category increases exponentially while the background non-AIDS mortality rate remains constant, Figure 2.[5,13] The initial distribution of new infections by CD4 count categories are derived from the Concentrated Action on Seroconversion to AIDS and Death in Europe (CASCADE) collaboration while values of non-AIDS mortality are based on a review by Johansson *et al.*[5,14,15] The outcome of this steady state model is the proportion of new infections alive over time. Parameters in the linear progression and exponential mortality rate equations (Table 1) are adjusted so the model outcomes fit Weibull distributions of age-specific survivorship from the Analysing

Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network; specifically the East African cohorts and a South African miners cohort (Appendix Figures 1a-1d).[16]

No raw data is used in this steady state model. Instead, modeled data on the distribution of new infections from the CASCADE collaboration and modeled age-specific survivorship curves from a subset of the ALPHA network data are used. The parameters in the linear and exponential equations are adjusted so as to minimize the sum of squared differences between the model outcomes and the predicted values from the Weibull distributions for the first 12 years of survival; this calibration is done using excel solver. While survivorship over time is what the steady state model is parameterized to fit, other outcomes from this model that are used as inputs into Spectrum are age-specific proportions of new infections and HIV/AIDS mortality rates pre-ARTs by CD4+ count categories as well as age-specific years spent in different CD4+ count categories (Table 2 & Table 3). The average number of years in each CD4+ count category is derived by taking the proportion that progress out of that CD4+ count category, dividing by that category's interval (e.g. the 200-250 CD4+ count category has an interval of 50), and then taking the inverse of this.[13] Spectrum is designed so these inputs can be sex-specific, however, the same assumptions are applied for both sexes.

Scenario 1: Adjusting the proportion of new infections in CD4+ count categories

In SSA countries with generalized epidemics, Spectrum assumes that roughly 40% of new HIV infections seroconvert with CD4+ counts below 500, Table 2. This percentage is the outcome of a statistical model conducted in the Lodi *et* al study,[14] which uses data from the CASCADE collaboration. In other papers from this European cohort and in other American cohorts, however, all study participants appeared to have CD4+ counts greater than 500 at the time of seroconversion (lower 95% confidence intervals for CD4+ counts at seroconversion do not even fall below 500).[17–20] Some literature supports lower CD4+ counts in HIV-negative African populations; but, study sizes are small and results are variable by African subpopulations.[21–23] To test Spectrum's sensitivity to the distribution of new infections by different CD4+ count categories, I adjusted the steady state model so all new infections in all age groups begin with CD4+ counts greater than 500. To do this, I modified the model in two unique ways. First, I changed the distribution of new infections by CD4+ count category without updating other model parameters. Second, I changed the distribution of new infections by CD4+ count category and then recalibrated the linear and exponential equation parameters to fit the survivorship curves from the ALPHA network. I used excel solver to minimize the sum of the squared differences between the model outcomes and

ALPHA network survivorship curves; Appendix Table 1 shows the adjusted parameters and Appendix Table 2 shows the adjusted Spectrum inputs. Both of these modifications were run through Spectrum and age-sex patterns of mortality were explored relative to outcomes generated using Spectrum's defaults (Table 2).

Scenario 2: Adjusting years spent in various CD4+ count categories

The Lodi *et al* study[14], which Spectrum uses for the distribution of new infections by CD4+ count categories, also includes estimates of time from seroconversion to CD4+ counts <500, <350, and <200 for specific age groups, sexes, and sub-populations. Instead of incorporating these values into the model, however, Spectrum assumes linear progression between decreasing CD4+ count categories. I wanted to test the effect of deriving all potential assumptions in Spectrum's steady state model from a consistent sources, thus I also inputted the years lived in different CD4 count categories from the Lodi study into Spectrum. The age groups in the Lodi study are <25, 25-30, 30-35, and 35 plus and the sub-populations are homosexual males, heterosexual males and females (MSW), and male and female injection drug users. I used the Lodi *et al* estimates for heterosexual females and males, averaged the estimates for age groups 25-30 and 30-35 to match the 25-35 Spectrum age group, and redistributed the years lived in CD4+ count 200-350 proportionately to Spectrum CD4+ count categories 200-250 and 250-350. The estimated time spent in CD4+ count categories from this study by age and sex is often significantly shorter than the current Spectrum assumptions (Table 3 and Appendix Figures 2a-2d). Using this data, I updated Spectrum's assumptions on years lived in different CD4+ count categories two different ways; first I updated only these inputs in Spectrum, and then I updated these inputs as well as parameters in the steady state model's exponential HIV/AIDS mortality rate equation so that the outcomes matched the ALPHA network's survivorship estimates; Appendix Tables 3a & 3b show updated parameters and Appendix Tables 4a & 4b show adjusted Spectrum inputs. Both modifications were run through Spectrum and compared with outcomes generated using Spectrum's defaults.

Scenario 3: Adjusting the non-AIDS mortality rate

As part of GBD 2010, non-AIDS all-cause mortality estimates are generated at the age-sex-country-year level.[9] I condensed these into non-AIDS mortality rates for the age groups used in Spectrum's steady state model and did this at both the country level as well as the aggregate level of all SSA countries with generalized epidemics, Appendix Figures 2a-2d. The age-specific non-AIDS morality rates used in Spectrum's steady state model were replaced with these country and region-specific values derived from the GBD 2010 study and the model parameters were recalibrated to match the survivorship curve from the ALPHA network; Appendix Tables 5a & 5b show updated parameters and Appendix Tables 6a & 6b show adjusted Spectrum inputs.[15] The adjusted inputs were run through Spectrum and age-sex patterns of HIV/AIDS mortality were compared with outcomes generated using Spectrum's defaults.

Scenario 4: Adjusting the incidence rate ratios

The next set of Spectrum assumptions I wanted to explore were those surrounding the age and sex-specific incidence rate ratios (IRR), which are currently inputted into Spectrum to help inform age-sex patterns of HIV/AIDS mortality. IRRs are inputted into Spectrum two different ways; there is a female to male IRR and age-sex-specific IRRs. For SSA countries with generalized epidemics, the females to male IRR is the average of values derived from country-specific DHS surveys (value 1.38). To convert the DHS prevalence data to incidence data UNAIDS uses an updated version of the Hallet *et al* method[24] that is not currently available for external use. In Spectrum, the age-sex-specific IRRs used for SSA countries with generalized epidemics are derived from the ALPHA network.[16] Peak incidence for both sexes is in age group 25-34; by sex, ratios are generated relative to this age group and smoothed across all age groups.

Using the dated, but available Hallet *et al* method,[24] I converted age-sex specific DHS prevalence data into age-sex specific incidence data for a number of SSA countries with two or more DHS surveys (the minimum number of survey necessary to apply the method). The Hallet paper[24] suggest two different approaches for converting prevalence to incidence, one that relies on mortality data and one that relies on the ALPHA network survivorship data, Appendix Figures 1a-1d. The approach that relies on survivorship data has smaller errors and is regarded as the superior approach in paper updates.[25] Consequently, I choose to use this approach for these reasons and also because it is more consistent with the data used to drive Spectrum's steady state model of HIV infection pre-ART. At the country-level there is wide variation in the female to male IRRs and the age-sex-specific IRRs, Appendix Figures 4a-4c. I ran country-specific female to male IRRs and age- sex-specific IRRs through Spectrum and compared the age-sex patterns of mortality using these assumptions with those generated using Spectrum's default IRRs.

Results

Scenario 1: Adjusting the proportion of new infections in CD4+ count categories

When all new HIV infections are assumed to have CD4+ counts greater than 500 at time of seroconversion and the parameters in the steady state model are not adjusted to match the ALPHA network survivorship data, this has a slight effect on Spectrum's age patterns of HIV/AIDS mortality over time. In Figure 3, Zambia in 2000 is an example of all the SSA countries I explored. Here the black line represents the estimates generated using Spectrum's default values (Table 2), the dashed red line represents the estimates generated by adjusting Spectrum so all new infections begin with CD4+ counts greater than 500 but not updating any other parameters, and the dashed blue line represents the estimates generated by starting all new infections with CD4+ counts greater than 500 and then updating the steady state model parameters so that the outcomes match the ALPHA network survivorship curves.

Adjusting the proportion of new infections so that all seroconvert with CD4+ counts greater than 500 does not appear to have a significant impact on Spectrum's age-sex patterns of HIV/AIDS mortality estimates, especially after the model parameters have been calibrated so that the survivorship curves match the ALPHA network. Without the calibration, when compared to Spectrum's default estimates, adjusted estimates of HIV/AIDS mortality appear to be slightly lower across age, peak mortality appears to be shifted to slightly older age groups, and the gap between the adjusted estimates and the default estimates is greater in earlier years and then narrows over time. These estimate make sense because 40% more new infections are being added to the CD4+ count category greater than 500, in which infected individuals spend significantly longer time than any other category and the HIV/AIDS mortality rate is much lower, Table 3. With this adjustment, the epidemic takes longer to progress in the population so, consequently, the timing of the epidemic and the age groups most affected by the epidemic are delayed.

Scenario 2: Adjusting years spent in various CD4+ count categories

When the years spent in different CD4+ count categories are adjusted by age and sex to match those from the Lodi *et al* study, there are noticeable changes in Spectrum's age patterns of HIV/AIDS mortality by sex. Figures 4a and 4b show the results of this analysis, by sex, for Zimbabwe in 2010; the black lines are Spectrum's default values for years lived in various CD4+ count categories (Table 3), the dashed red lines are the outcomes when years lived in CD4+ count categories >500 to 200-249 are adjusted to match those from the Lodi *et al* study,[14] and the dashed blue lines are the outcomes when years lived in CD4+ count categories >500 to 200-249 are adjusted to match those from the Lodi *et al* study and the mortality rate parameters in the steady state model are adjusted so the outcome matches survivorship from the ALPHA network.

With the significantly shorter years lived in early CD4+ count categories (Appendix Figures 2a-2d), the age-sex patterns of HIV/AIDS mortality from Spectrum are shifted to slightly younger age groups and the level of HIV/AIDS mortality increases in comparison to the age-sex patterns of HIV/AIDS mortality generated using Spectrum defaults. This makes sense because infected individuals are spending less time in CD4+ count categories with low HIV/AIDS mortality rates and progressing more quickly to categories where the steady state model has them dying from HIV/AIDS at significantly higher rates. To test the effect changing a single age groups or CD4+ count category had on the outcomes I ran several iterations of Spectrum where I only adjusted one age group or category at a time. This resulted in wildly different age-patterns of HIV/AIDS mortality estimates by sex, Appendix Figures 5a and 5b. For example, only adjusting years lived in CD4+ count category >500 resulted in a much younger epidemic (gray), while only adjusting years in lived in age groups 35-45 and 45 plus resulted in a slightly older epidemic (green).

Scenario 3: Adjusting the non-AIDS mortality rate

When the non-AIDS mortality rates in the HIV natural history model were adjusted to the GBD 2010 study values and other parameters were recalibrated to fit the ALPHA survivorship curve, the outcomes using these adjusted parameters varied little when compared to the age-patterns of HIV/AIDS mortality generated using Spectrum defaults.[15] Figures 5a and 5b show variations in the non-AIDS mortality rates by age group and the effect various non-AIDS mortality rates have on age pattern of HIV/AIDS mortality for Botswana in 2005. The black lines indicates Spectrum's default non-AIDS mortality rates, the dashed red lines indicates GBD 2010's non-AIDS mortality rates for all SSA countries with generalized epidemics, and the blue dashed lines indicates GBD 2010's Botswana-specific non-AIDS mortality rates.

The minimal changes in the age-sex patterns of Spectrum's HIV/AIDS mortality estimates are not surprising because the modifications made to the background non-AIDS mortality rate were trivial, Figure 5a.[26] The background non-AIDS mortality rates are also very low in comparison to the age and CD4+ count category-specific HIV/AIDS mortality rates and the age group with the greatest modification was 45 plus, an age group least affected by the HIV/AIDS epidemic. It is interesting, however, that the age groups 25-35 and 35-45 are the only age group that reflect any noticeable change from these background mortality rate modifications, Figure 5b. Due to the disproportionally large disease burden in these age groups, even slight adjustment to the non-AIDS mortality rates are reflected in the estimates of HIV/AIDS mortality, indicating the sensitivity of these age groups to model modifications.

Scenario 4: Adjusting the incidence rate ratios

Inputting country-specific IRRs derived from DHS data (Appendix Figures 4a-4c) into Spectrum results in age and sex patterns of HIV/AIDS mortality that are often very different from those generated using Spectrum's default IRR values (derived from the ALPHA network or averages of country-specific DHS data). Figures 6a-6d show, by sex, the differences between the IRRs derived from the age-specific DHS data for Lesotho and the effect inputting these values into Spectrum has on the model's age-sex estimates of HIV/AIDS mortality for Lesotho in 2005. In the IRR graphs (Figures 6a and 6b), the black lines are Spectrum's default IRRs and the dashed red lines are the IRRs from DHS prevalence data. In the mortality estimation graphs (Figures 6c and 6d), the black lines are the estimates generated using Spectrum's default values, the dashed red lines are the estimates generated using both the adjusted female to male IRR and the adjusted age-sex-specific IRRs derived from DHS, and the dashed blue lines are the estimates using just the adjusted age-sex-specific IRRs. The DHS female to male IRR for Lesotho is 1.12; which is slightly lower than Spectrum's default value of 1.38.[24,27,28]

In this example for Lesotho, there is a slight difference in the estimates when the female to male IRR is modified (dashed red lines). HIV/AIDS mortality increases slightly in males and decreases slightly in females, which is what one would expect when the IRR is adjusted to a slightly lower value.[24,29,30] Figures 6c and 6d also highlight the different age patterns that result from modifying the age and sex-specific IRRs. For Lesotho, the age pattern for estimates generated using the adjusted IRRs is shifted to younger ages for females, slightly older ages for males, and the estimates are more jagged across age groups as a result of the un-smoothed, adjusted age-sex-specific IRRs. Changes in age-sex patterns of HIV/AIDS mortality are seen across SSA countries when the country-specific IRRs derived from raw DHS data are inputted in place of the smoothed Spectrum curves. These changes, however, are dependent on the patterns of country-specific IRRs derived from country-specific DHS data and thus outcomes are unique at the country level.

Discussion

In the world of cause-specific modeling, UNAIDS' Spectrum/EPP is regarded as an advanced program for epidemic analysis and planning. The UNAIDS Reference group, a group of epidemiologists, demographers, statisticians and public health experts, meet several times a year to update modeling methods and discuss ways the modeling package can be more accessible to in-country policy makers.[31] Over the years the existing modeling infrastructure has been refined, new data has been added to drive assumptions, and different parts of the model have been tweaked. While countries are encouraged to add their own data to the modeling framework, in SSA countries with generalized epidemics, majority of the Spectrum assumptions used to generate country-year-age-sex-specific estimates of HIV/AIDS mortality from EPP's country-year-specific incidence estimates are based on inconsistent cohort studies with small sample sizes that are not necessarily representative of all SSA countries.

Scenario 1: Adjusting the proportion of new infections in CD4+ count categories

More research in particular needs to be conducted on the distribution of CD4+ counts at the time of HIV/AIDS seroconversion and how an HIV+ individuals progresses between decreasing CD4+ count categories in the absence of ARTs. The data on CD4+ counts at the time of seroconversion or among HIV negative individuals seems inconsistent when you look across cohort studies.[14,17–21,23,23] Much of this understanding might stem from confusion surrounding the definition of seroconversion; when individuals are first infected with the HIV virus their CD4+ count drops significantly and then rebounds to a slightly lower level than in HIV negative individuals (this obviously varies at the individual level).[32] It is unclear if Spectrum is attempting to capture new infections before or after this initial drop in CD4+ levels. While this initial drop in CD4+ levels is short lived, an individual's ability to bounce back to higher CD4+ count levels could influence their time spent in different CD4+ count categories. For example, a study by Panatazis *et al*[21] shows that although African individuals might have lower CD4+ counts at seroconverision they might also have a slower CD4+ count declines when compared to their non-African counterparts. There is also evidence that HIV+ individual with different viral subtypes progress between decreasing CD4+ count categories at varying rates.[33–35]

The analysis shows, however, that even when distributions of new infections in CD4+ count categories are modified, if parameters in the steady state model are calibrated to match the ALPHA network survivorship curves, age-sex patterns of Spectrum's HIV/AIDS mortality estimates will remain relatively unchanged. The distribution of HIV infections by CD4+ count categories is still important for any intervention analysis, but for Spectrum's estimates of HIV/AIDS mortality, survivorship data are the most important driver. The East African cohorts and South African miners cohort from the ALPHA network that are used to generate survivorship estimates over time are relatively small (1448 seroconverts, 4199 person-years and 1950 seroconverters, 11934 person-years respectively) and the data from the East African cohorts are pulled together instead of analyzed separately.[16] The Weibull distributions generated from these cohorts do not capture the variations in survivorship among the cohorts or among other potential cohorts not included in this analysis. A systematic review should be conducted to collect all available cohort data on survival in HIV positives pre-ARTs. Since survivor data appears to be a critical driver of Spectrum's estimates of age-sex specific HIV/AIDS mortality, uncertainty in this data should be properly propagated through the model so that the effect this has on Spectrum's age-sex-specific HIV/AIDS mortality estimates can be explored.

Scenario 2: Adjusting years spent in various CD4+ count categories

In fitting the ALPHA survivorship curves, Spectrum currently assumes a linear progression between CD4+ count categories and an exponentially increasing HIV/AIDS mortality rate by decreasing CD4+ count categories. Neither of these linear or exponential equations are based on any raw data; they are simply parameterized so the proportion of new infections over time matches the ALPHA network data. This calibration to ALPHA data results in inconsistent disease progression patterns by age group; for example, the linear equation for age group 15-45 has a negative slope while the other age groups have positive slopes (Table 1) . Data on years lived in CD4+ count categories are available from cohort studies and when the assumptions used in Spectrum are compared with this data the differences are significant (Appendix Figures 2a-2d). The data from the Lodi study, for example, shows a duration of 1.63 years in the CD4+ count category >500 for females under 25 while Spectrum assumes 8.53 years lived in this age-sex-specific category.[14] A systematic review of years lived in various CD4+ count categories pre-ARTs should be conducted to assess the range of estimates from other cohorts and more research in general should be conducted to understand how HIV positive individuals progress between decreasing CD4+ count categories. Real data on years lived in CD4+ count categories should be incorporated into the Spectrum model to generate more accurate estimates of age-sex-specific HIV/AIDS mortality. Research on progression rates by HIV viral subtype or by subpopulations would also be of particular interest as there is before mentioned believed variation here.

Scenario 3: Adjusting the non-AIDS mortality rate

In Spectrum's HIV/AIDS natural history model, the non-AIDS mortality rate is not country-specific, nor is it sex-specific, nor can it vary overtime. When GBD 2010's counterfactual non-AIDS mortality rates are evaluated by sex over time, they vary significantly by gender and with the rise and fall of the epidemic, Appendix Figures 3a-3d. Ideally Spectrum should be modified to incorporate these fluctuations overtime in background mortality rate; however, as demonstrated in this analysis, changes in background mortality appear to have little effect on Spectrum's estimates of HIV/AIDS mortality because of how much smaller these rates are in comparison to Spectrum's age and CD4+ count-specific HIV/AIDS mortality rates. Another area in Spectrum that does not incorporates changes over times and that might have a more significant effect on Spectrum's estimates of age-sex specific HIV/AIDS mortality are the age and sex-specific IRRs. These values, derived from the ALPHA network, remain constant throughout the model and consequently do not reflect how a country's epidemic might evolve based on age-specific increases in HIV awareness and modified behaviors. More research needs to be done and more methods need to be developed to explore changes in age and sex-specific HIV/AIDS IRRs over time.

Scenario 4: Adjusting the incidence rate ratios

HIV/AIDS epidemics are extremely difficult to measure across the globe because disease transmission and progression is dependent on local behaviors and treatment accessibility. While many SSA countries may suffer from significant HIV/AIDS epidemics, these countries are culturally distinct and thus age-sex patterns of HIV/AIDS mortality vary at the country level. In the EPP portion of UNAIDS' projection package, country-year DHS prevalence data is considered the gold standard and consequently prevalence trends generated using ANC data and other surveillance data are recalibrated to perfectly fit the DHS data. DHS prevalence data is also available at the age-sex-country-year level; however, Spectrum currently does not incorporate the granularity of this data in its modeling process. This paper shows how sensitive Spectrum's age-sex patterns of HIV/AIDS mortality are when adjustments are made to age-sex-specific IRRs that are currently applied for all countries with generalized epidemics. More country-level data needs to be incorporated into Spectrum so that estimates of HIV/AIDS mortality better reflect each country's unique epidemic.

Uncertainty in Spectrum

As before mentioned, the cohort studies from the ALPHA network that are selected to drive Spectrum's assumptions on survivorship and age-sex-specific IRRs are small and parameter values, especially at the

CD4+ category-specific and age-specific level, are very uncertain. There this is also wide variation in the progression rates between decreasing CD4+ count categories based on viral subtypes or subpopulations. The current Spectrum model does a poor job at incorporating uncertainty around these parameters. Spectrum uncertainty is fitted retrospectively using assumed standard deviations around input values and 1,000 incidence draws derived from the EPP portion of the modeling package. The standard deviations used in Spectrum are often smaller than variations in the observed data; for example, the standard deviation for average number of years lived in a CD4+ count category is only 0.05. As a result, uncertainty surrounding UNAIDS' estimates of HIV/AIDS mortality for SSA countries with generalized epidemics are implausibly small.[2,4] This is important because in the GBD 2010 study all-cause mortality adjustment, cause-specific estimates are adjusted based on their degree of uncertainty; thus estimate of HIV/AIDS mortality (when they do not exceed the GBD 2010 all-cause mortality estimates) are often adjusted less than other, more uncertain causes. While ignoring uncertainty in all these parameters allows the modeling package to run faster for policy makers in developing countries, it is important to properly propagate uncertainty through the Spectrum model as an academic exercise so that the effect this has on the package's overall HIV/AIDS mortality estimates can be explored.

Limitations

There are several limitations to this analysis that are important to note. Since the Lodi *et al* study[14] only had data on years lived in CD4+ count categories until the category of <200, I was unable to use study data to modify years lived in categories lower than this and explore the effect this has on Spectrum's age-sex specific estimates of HIV/AIDS mortality. Also, since the Lodi data was derived from a European cohort (CASCADE), majority of the infections were homosexual men. The heterosexual infections only accounted 24% of the total study population (4379 seroconverters), and when these are broken into sexes and four different age groups, sample sizes for the estimates I used on years lived in different CD4+ count categories were small and uncertainty intervals were large. My analysis did not account for the uncertainty surrounding these estimates and no regression was conducted to generate a smoothed progression rates between decreasing CD4+ count categories by age and sex. Other cohort studies that have data on CD4+ count progression were not incorporated in this analysis, but should be to help inform the range of uncertainty surrounding these Spectrum inputs. Values from the Lodi study were selected for this analysis because this was the same study the distributions of new infections in CD4+ count categories were derived from.

Similarly, uncertainty surrounding the DHS age-sex specific data was also not incorporated in this analysis, nor was uncertainty in the conversion of the DHS prevalence data to incidence data. Since the sample sizes for particular DHS age groups are small, the DHS prevalence estimates for these age groups are more uncertain, which results in fluctuations in the HIV/AIDS age-sex prevalence patterns. Age-sex prevalence pattern fluctuations were reflected in converted age-sex incidence data and thus the age-sex IRRs. In the future, these IRRs should be smoothed across age groups to reduce data fluctuations that results from uncertainty. The Hallet *et al* method[24] used in this analysis to convert DHS prevalence to incidence is also known for having important limitations.[36] The method relies on a number of large assumptions (for example, that incidence remains constant between DHS surveys and that survivorship data from the ALPHA network, which in itself has a large estimation uncertainty, can be generalized to all SSA countries). These issues undermine the validity of using this adjusted DHS data as a true reflection of country-year-age-sex specific incidence. The available Hallet *et al* method[24] can also only convert prevalence data to incidence data for five-year age groups between 15 and 49, while the revised method available to UNAIDS can generate incidence estimates for age groups 15-79. As a result, I had to leave Spectrum's default IRRs for age groups over 50 in my analysis.

Future research

Another part of the Spectrum model that could influence age-sex patterns of HIV/AIDS mortality estimates, but I did not get the chance to explore in this study, are the demographic assumptions inputted into the model. Currently Spectrum/EPP relies on model life tables and life expectancies from UNPOP, which vary significantly from those used in the GBD 2010 study. For GBD 2010, a new model life table system was developed that is more statistical than UNPOP's and based on a greater number of life tables, especially for developing countries.[9] It is possible that these differences in demographic inputs could partly be responsible for the discrepancies in the age-sex patterns of Spectrum's estimates of HIV/AIDS mortality and GBD 2010' estimates of all-cause mortality. A further investigation is necessary to explore this hypothesis in more detail.

While this exploration was useful at identifying how adjustments to important assumptions in Spectrum can influence the model's age-sex pattern of HIV/AIDS mortality, none of the results helped explain or narrow the age gap between GBD 2010's all-cause and UNAIDS' 2012 HIV/AIDS mortality estimates. The GBD demography team is currently working on modifications to their all-cause mortality models that potentially might shift the peak in all-cause mortality estimates to older age groups for SSA countries.

This paper may not have provided a solution to the problem of interest, but it did demonstrate how modifying Spectrum assumptions can influence Spectrum's estimates of age-sex-specific HIV/AIDS mortality and also demonstrated the significant variations in alternative data sources (country-level data, other cohort studies, and GBD data). Hopefully, moving forward, UNAIDS can continue to provide more details about the Spectrum/EPP modeling process and increase the accessibility of data sources used to drive model assumptions. Similarity, with the upcoming publication of the GBD mortality methods book, hopefully details of the all-cause mortality estimation process used in GBD 2010 will be clearer for a greater number of health researchers. Increased transparency on both ends could increase collaboration among researchers, improve methods and accessibility of scarce data, and result in even more precise age-sex-specific estimates of HIV/AIDS mortality that could be used for better epidemic planning and management.

Acknowledgements

A huge thank you goes out to John Stover at the Futures Institute for answering my many emails regarding the details of the Spectrum modeling process and taking the time to sit down with me and describe all the assumptions and methods used in Spectrum/EPP in great detail. I would also like to thank my advisors Christopher JL Murray, Theo Vos, Haidong Wang, and Geoff Garnett for their helpful insights and feedback throughout this investigation.

Figures

Figure 1. Age-specific mortality estimates for Zimbabwe in 2010, both sexes. Comparison of GBD 2010's estimates of all-cause mortality (green) and UNAIDS' estimates of HIV/AIDS mortality (red).

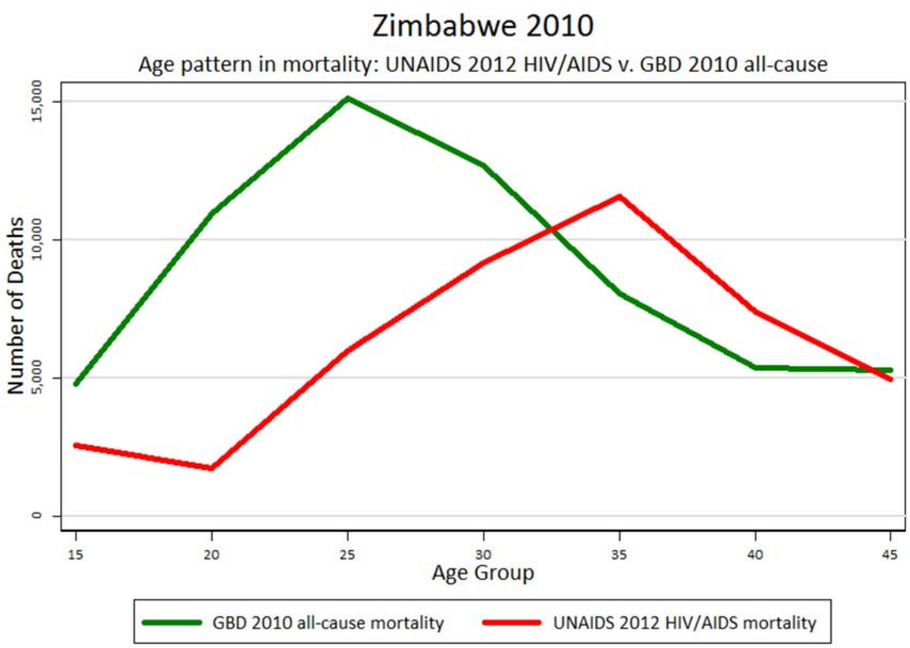


Figure 2. Spectrum's steady-state model for the natural history of HIV-infection in the absence of ARTs. New HIV infections are distributed into different CD4+ count categories by the proportions p_1 and p_2. These infections then progression between decreasing CD4+ count categories linearly (r_1-r_6), while the HIV/AIDS mortality rate increases exponentially (m_1-m_6) and the background non-AIDS mortality is held constant (x_c) between the CD4+ count categories.

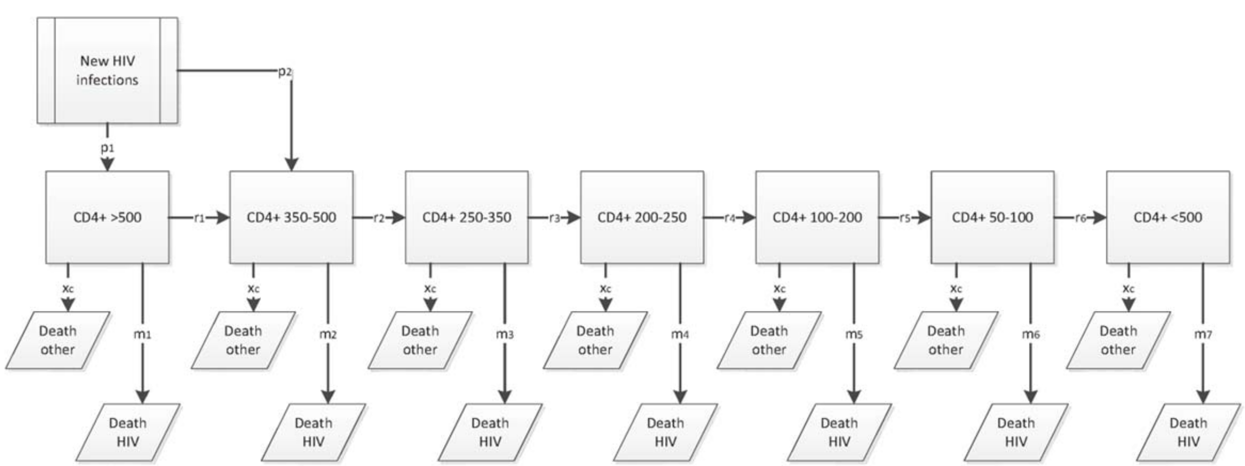
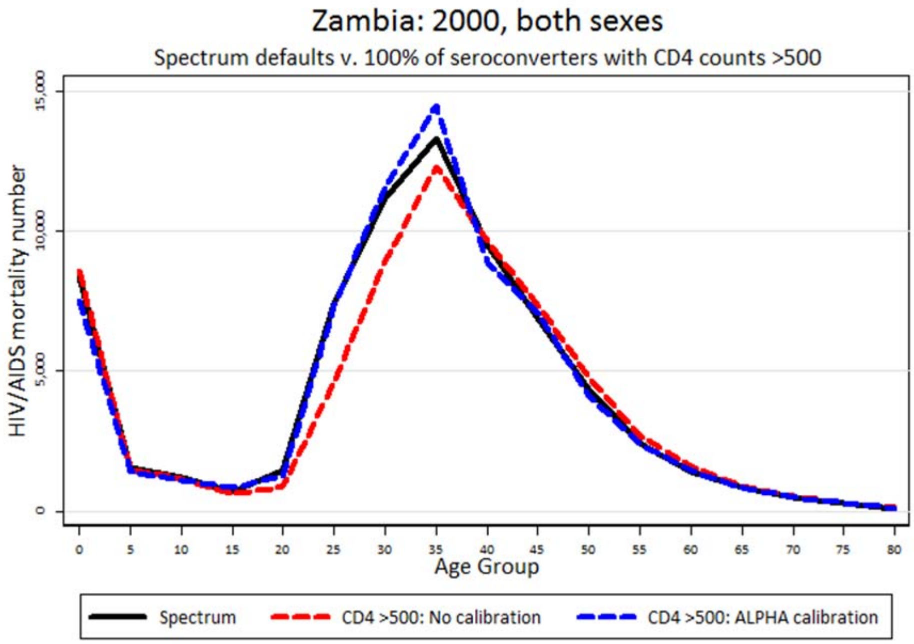
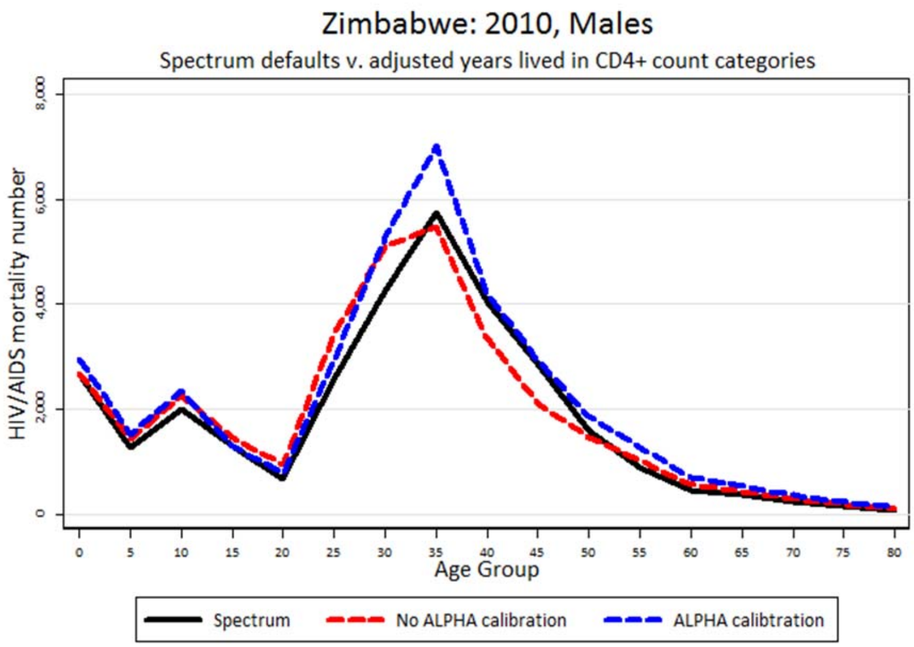


Figure 3. Estimates of HIV/AIDS mortality by age for Zambia in 2000, both sexes. Redistributing new infections that seroconvert with a CD4+ count >500: 100% seroconverters with CD4+ count >500 and no calibration to ALPHA survivorship curves (red), 100% seroconverters with CD4+ count >500 and calibration to ALPHA survivorship curves (blue), and Spectrum defaults (black).

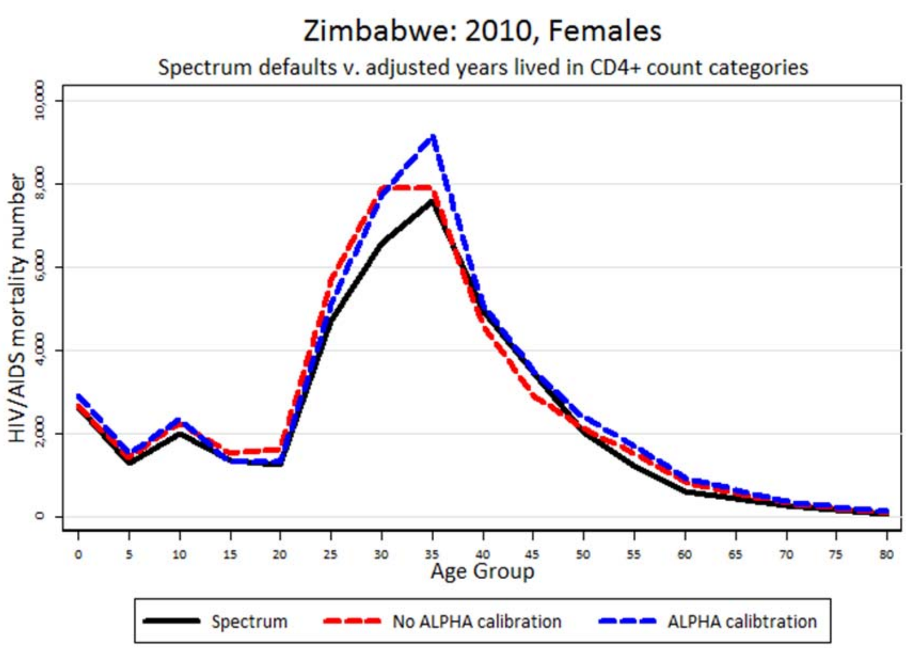


Figures 4a & 4b. Estimates of HIV/AIDS mortality by age for Zimbabwe in 2010, (a) males and (b) females. Age and sex-specific adjustments for years lived in different CD4+ count categories; adjusted years lived in CD4+ count categories and did not recalibrate survivorship to ALPHA network (red), adjusted years lived in CD4+ count categories and recalibrated HIV/AIDS mortality rate parameters so model survivorship matches the ALPHA network (blue), and Spectrum defaults (black).

(a)

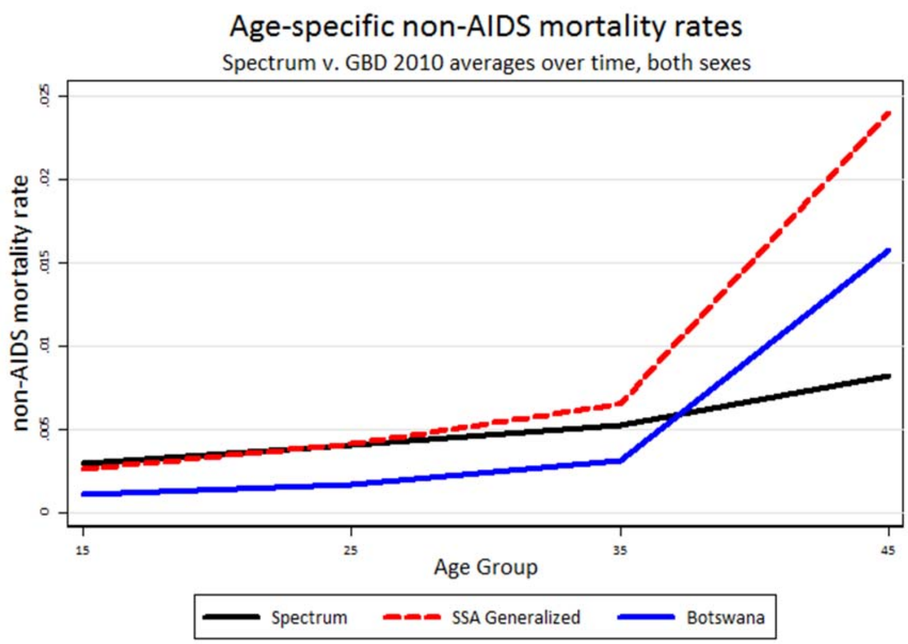


(b)



Figures 5a & 5b. (a) Non-AIDS mortality rates by age group, both sexes; Spectrum (black), SSA generalized (red), and Botswana (blue). (b) HIV/AIDS mortality by age for Botswana in 2005, both sexes; GBD 2010 SSA generalized non-AIDS mortality rate adjustments (red), GBD 2010 Botswana non-AIDS mortality rate adjustments (blue), and Spectrum defaults (black).

(a)



(b)

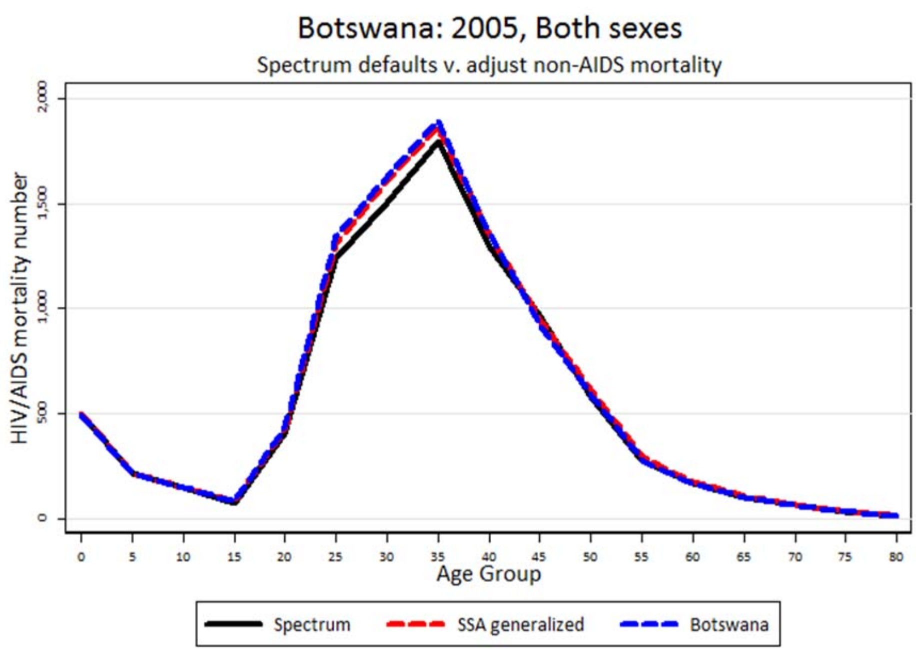
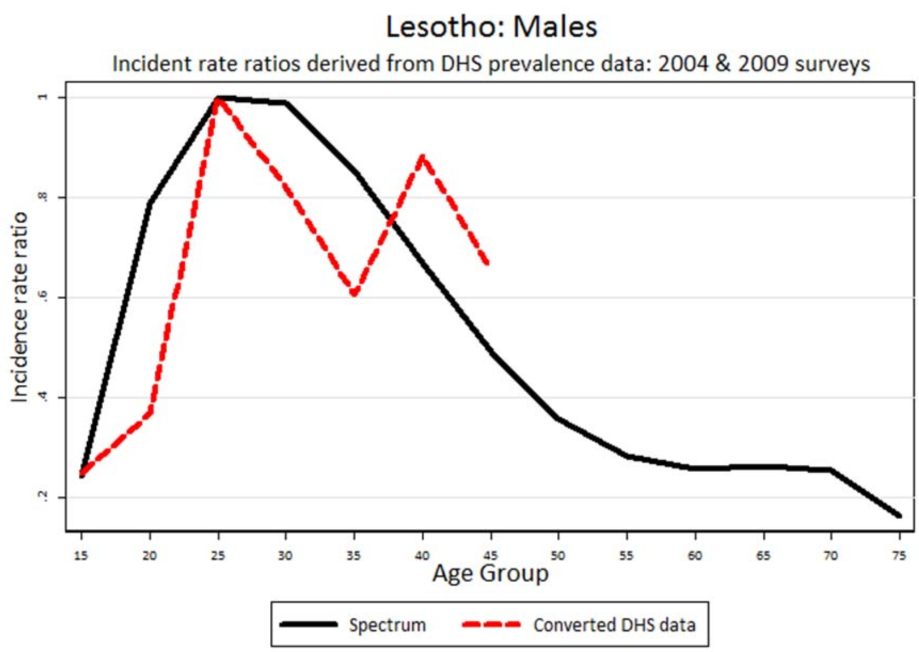
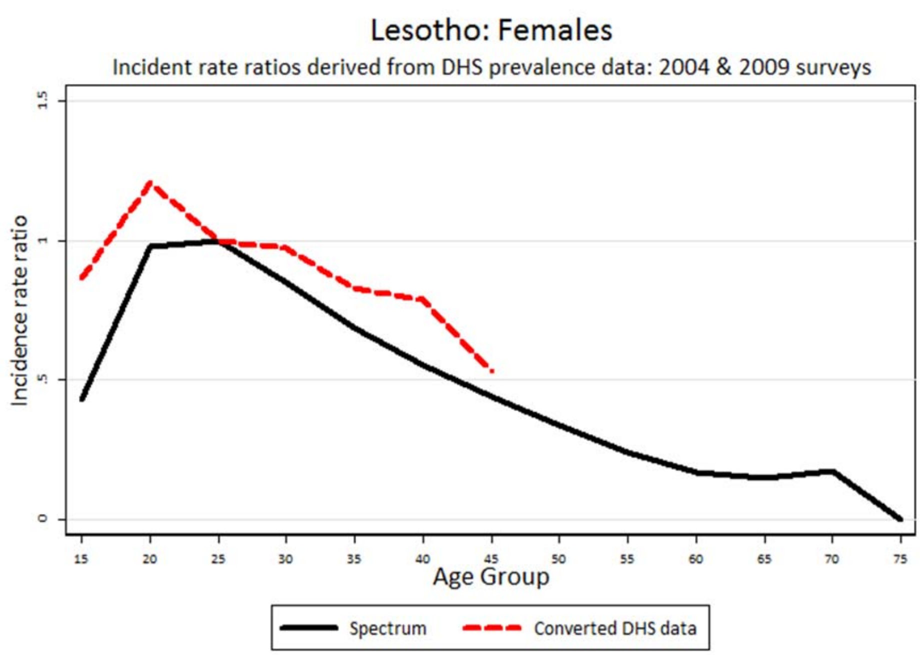


Figure 6a-6d. Age and sex-specific IRRs; DHS adjusted IRRs for Lesotho (red) compared to Spectrum's IRRs for generalized epidemics (black): (a) males and (b) females. Estimates of HIV/AIDS mortality by age for Lesotho in 2005, (a) males and (b) females; Spectrum defaults (black), Lesotho -specific female to male IRR and age and sex-specific IRR (red), and Lesotho -specific age and sex-specific IRR only (blue).

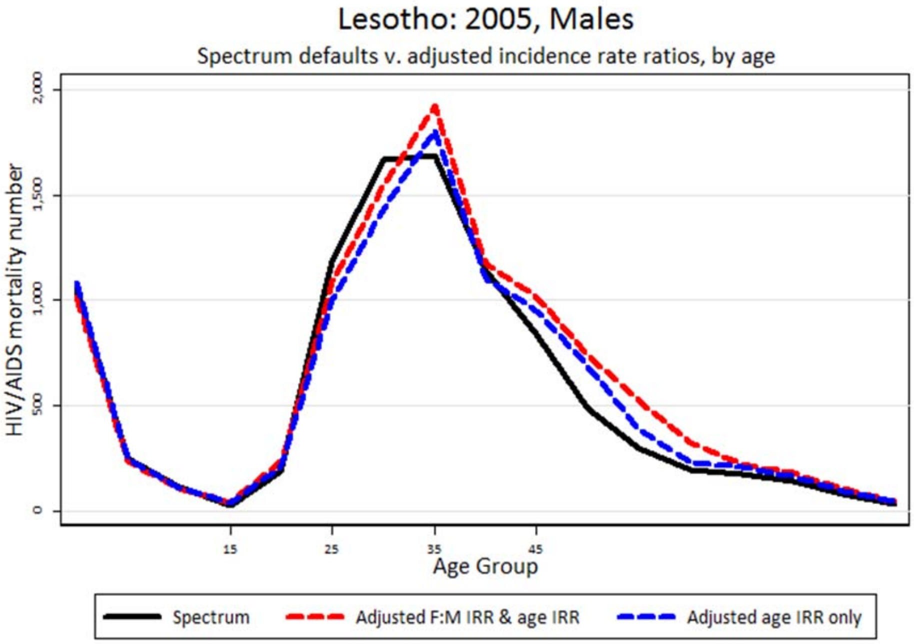
(a)



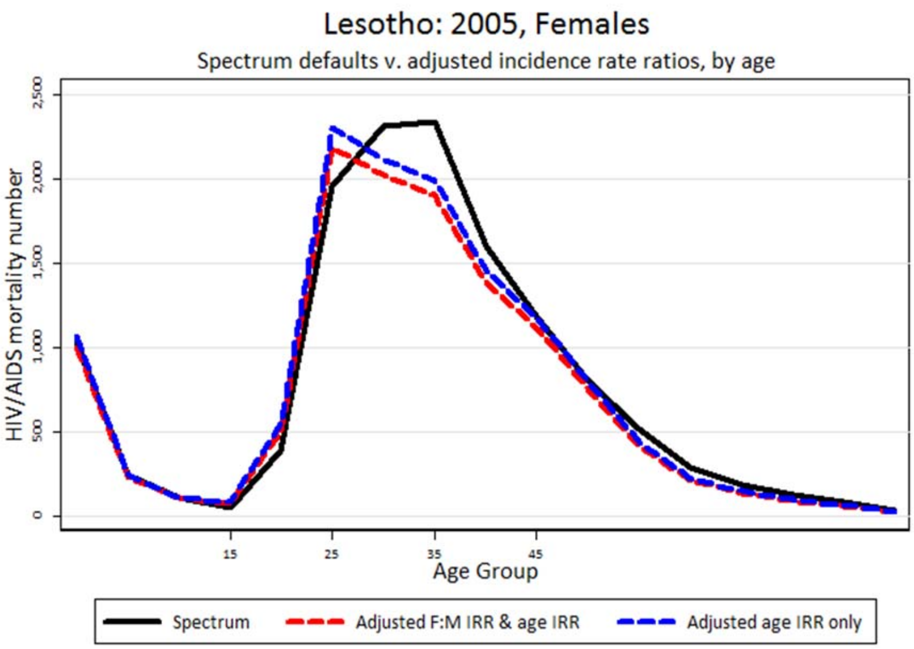
(b)



(c)


Lesotho: 2005, Males
Spectrum defaults v. adjusted incidence rate ratios, by age
HIV/AIDS mortality number
0
500
1,000
1,500
2,000
15
25
35
45
Age Group
Spectrum
Adjusted F:M IRR & age IRR
Adjusted age IRR only

(d)


Lesotho: 2005, Females
Spectrum defaults v. adjusted incidence rate ratios, by age
HIV/AIDS mortality number
0
500
1,000
1,500
2,000
2,500
15
25
35
45
Age Group
Spectrum
Adjusted F:M IRR & age IRR
Adjusted age IRR only

Tables

Table 1. Age-specific parameters used in Spectrum's steady state model				
Linear progression rate equation: *d+b*c*	**15 - 24**	**25 - 34**	**35 - 44**	**45+**
d-values	41.43	17.52	43.63	70.39
b-values	-4.00	9.24	4.80	5.00
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**	**45+**
a-values	0.002	0.001	0.002	0.002
r-values	0.832	0.990	0.986	0.926
Total error	8	12	29	71
				Note: c=CD4+ count categories 1-7

Table 2. Spectrum's distribution of new infections, by CD4 count and age group *(percentage)*				
CD4 count category	**15 - 24**	**25 - 34**	**35 - 44**	**45+**
> 500	64.3	60.7	58.5	55.2
350 - 500	35.7	39.3	41.5	44.8
250 - 349	0.0	0.0	0.0	0.0
200 - 249	0.0	0.0	0.0	0.0
100 - 199	0.0	0.0	0.0	0.0
50 - 99	0.0	0.0	0.0	0.0
< 50	0.0	0.0	0.0	0.0
Total	100	100	100	100

Table 3. Spectrum's average number of years in CD4 count category and HIV/AIDS mortality rate without ARTs, by CD4 count and age group

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 - 34	35 - 44	45+	15 - 24	25 - 34	35 - 44	45+
> 500	8.53	6.78	5.45	4.70	0.005	0.004	0.005	0.005
350 - 500	4.49	4.17	2.82	1.87	0.011	0.010	0.013	0.013
250 - 349	3.40	2.21	1.72	1.17	0.026	0.026	0.036	0.032
200 - 249	1.97	0.92	0.80	0.55	0.061	0.069	0.096	0.080
100 - 199	4.67	1.57	1.48	1.05	0.139	0.185	0.258	0.203
50 - 99	2.87	0.69	0.69	0.50	0.321	0.499	0.691	0.513
< 50	--	--	--	--	0.737	1.342	1.851	1.295

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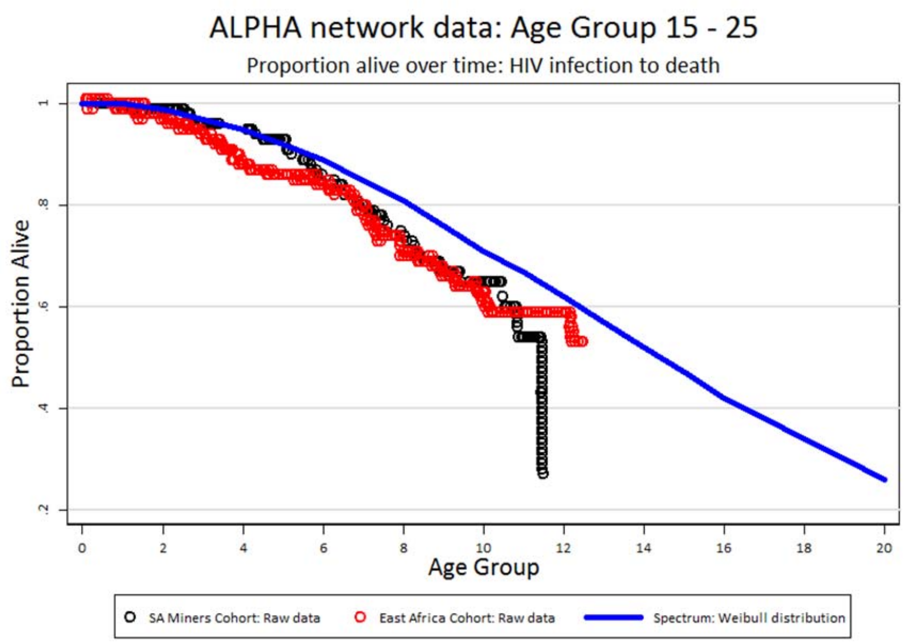
Appendix Figures

Appendix Figures 1a-1d. ALPHA network survivorship data. South African miners cohort (black), East African cohorts (red), and Weibull distributions (blue) for age groups (a) 15-25, (b) 25-35, (c) 35-45, and (d) 45 plus.[16]

(a)



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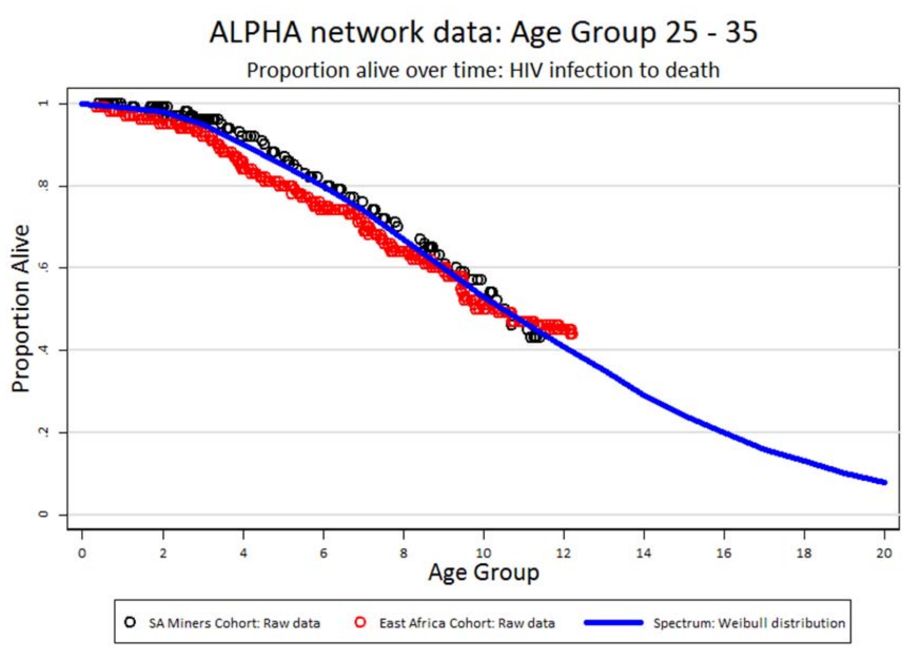

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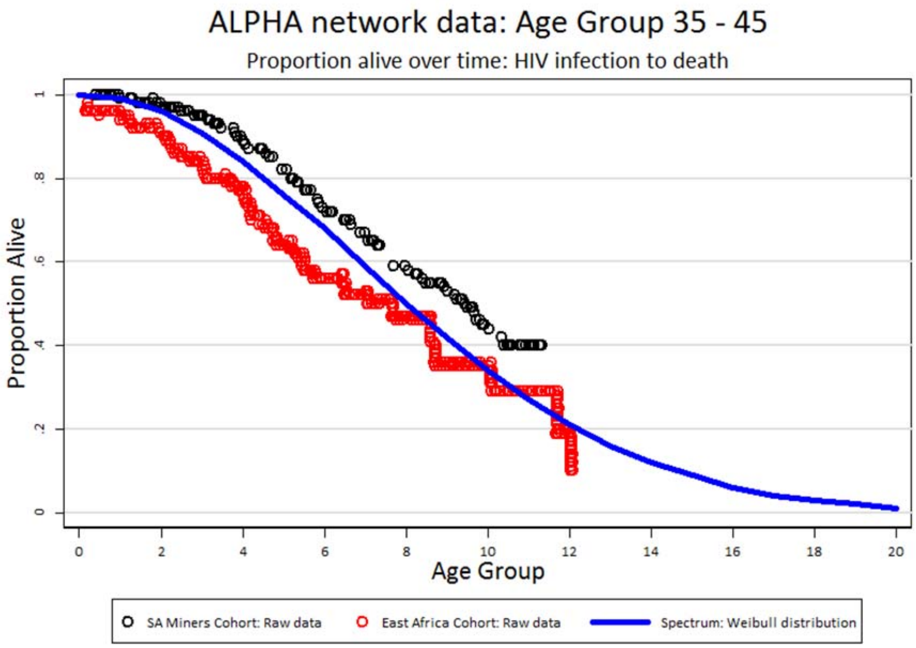
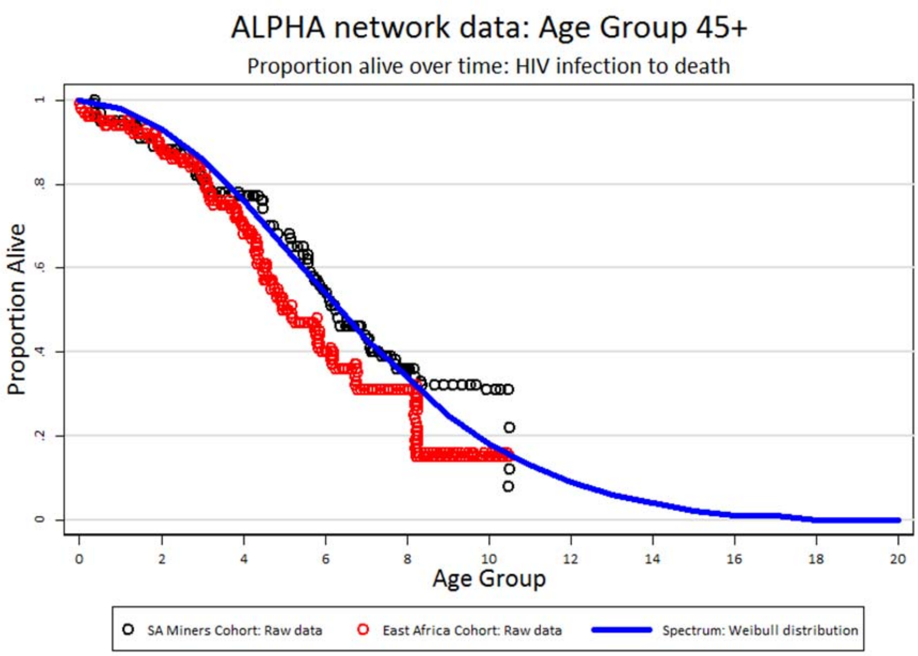
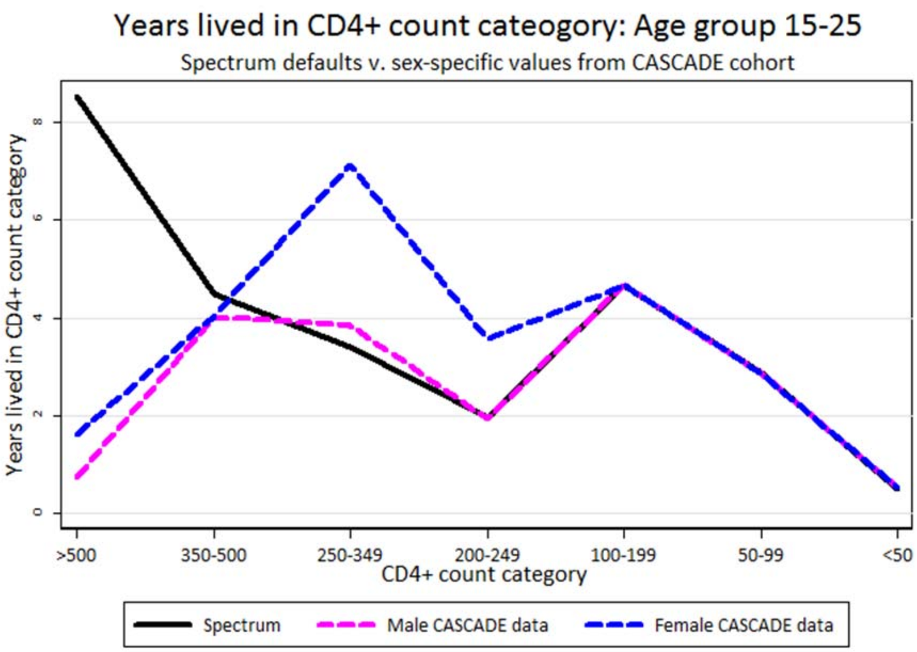

ALPHA network data: Age Group 35 - 45
Proportion alive over time: HIV infection to death
Proportion Alive
0
.2
.4
.6
.8
1
0
2
4
6
8
10
12
14
16
18
20
Age Group
SA Miners Cohort: Raw data
East Africa Cohort: Raw data
Spectrum: Weibull distribution

(d)


ALPHA network data: Age Group 45+
Proportion alive over time: HIV infection to death
Proportion Alive
0
.2
.4
.6
.8
1
0
2
4
6
8
10
12
14
16
18
20
Age Group
SA Miners Cohort: Raw data
East Africa Cohort: Raw data
Spectrum: Weibull distribution

Appendix Figures 2a-2d. Years lived in different CD4+ count categories by age groups (a) 15-25, (b) 25-35, (c) 35-45, and (d) 45 plus; Spectrum defaults (black), male data (MSW) from the CASCADE study (blue), and females data (MSW) from the CSACADE study (pink).

(a)



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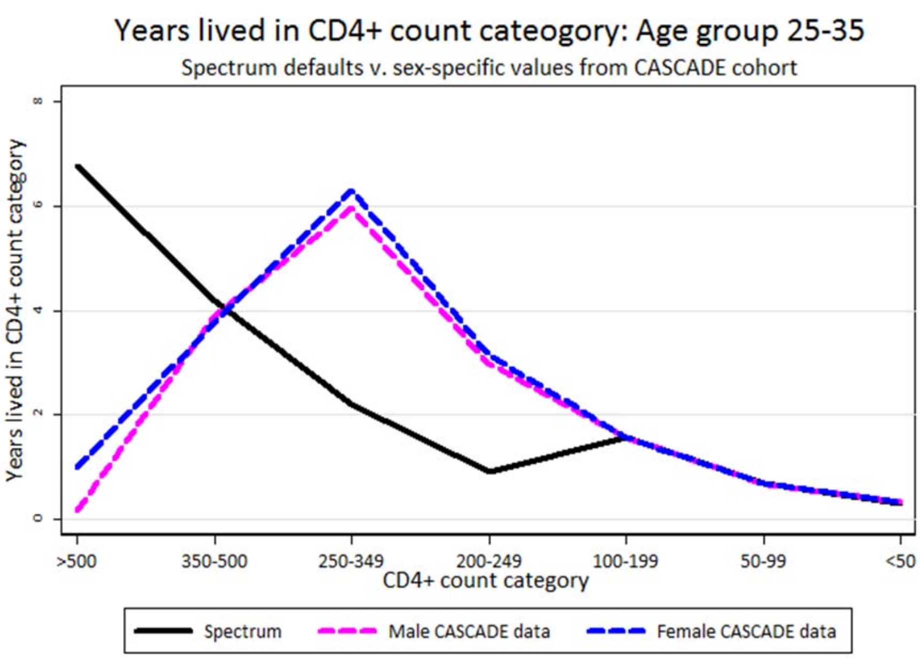

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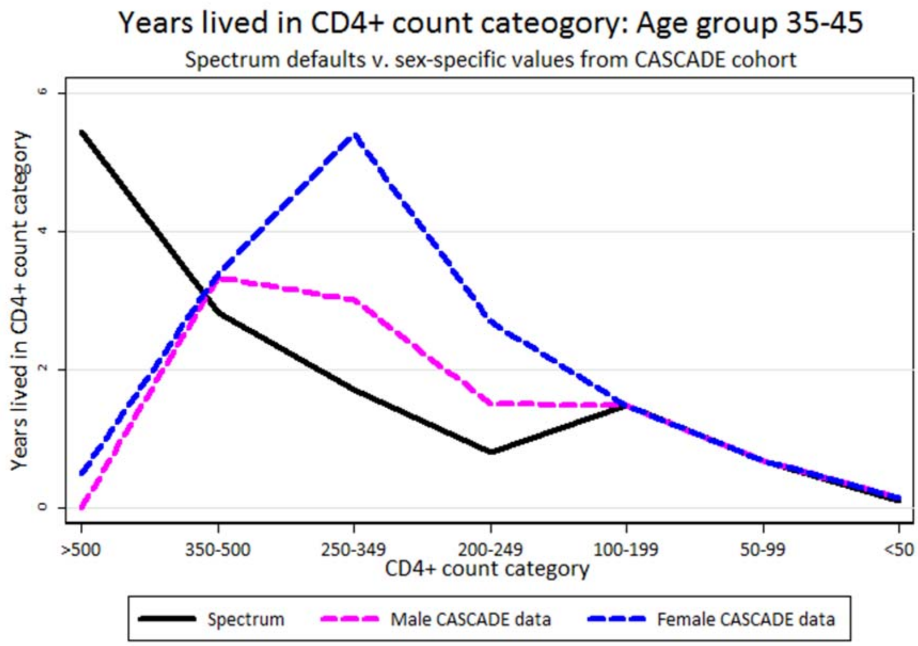
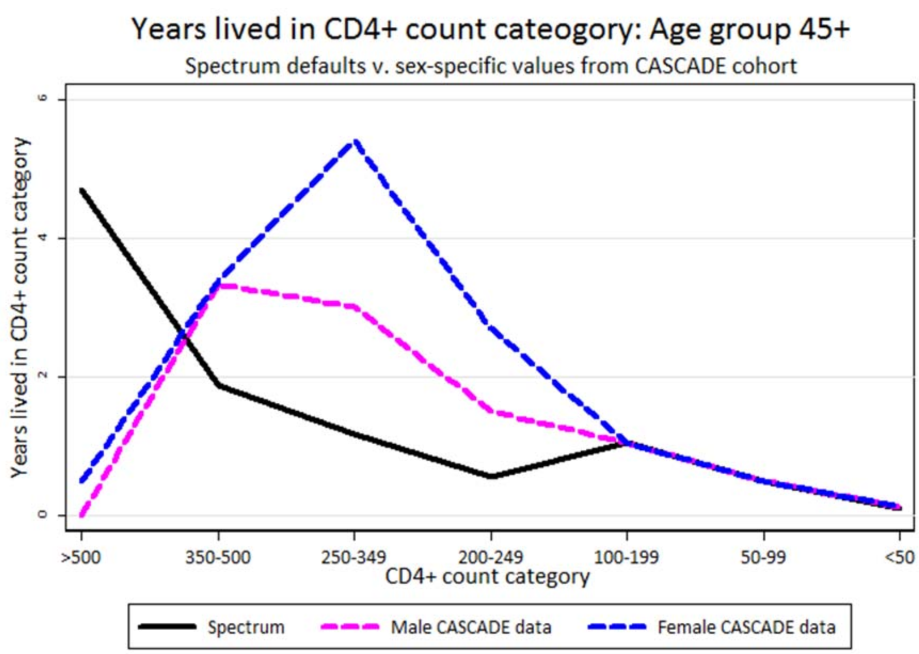

Years lived in CD4+ count cateogory: Age group 35-45
Spectrum defaults v. sex-specific values from CASCADE cohort
Years lived in CD4+ count category
0
2
4
6
>500
350-500
250-349
200-249
100-199
50-99
<50
CD4+ count category
Spectrum
Male CASCADE data
Female CASCADE data

(d)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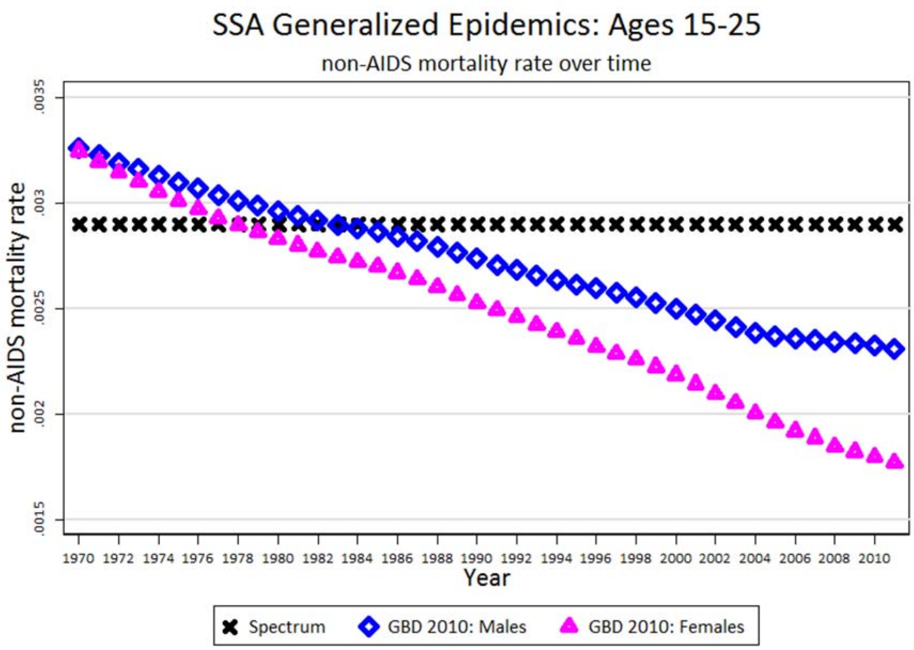
Years lived in CD4+ count category
0
2
4
6
>500
350-500
250-349
200-249
100-199
50-99
<50
CD4+ count category
Spectrum
Male CASCADE data
Female CASCADE data

Appendix Figures 3a-3d. Non-AIDS mortality rate from 1970-2010. GBD 2010 counterfactual non-AIDS mortality rates aggregated for all SSA countries with generalized epidemics, by sex (males in blue and females in pink), compared to Spectrum's default non-AIDS mortality rates (black) for age groups (a) 15-25, (b) 25-35, (c) 35-45, and (d) 45 plus.

(a)



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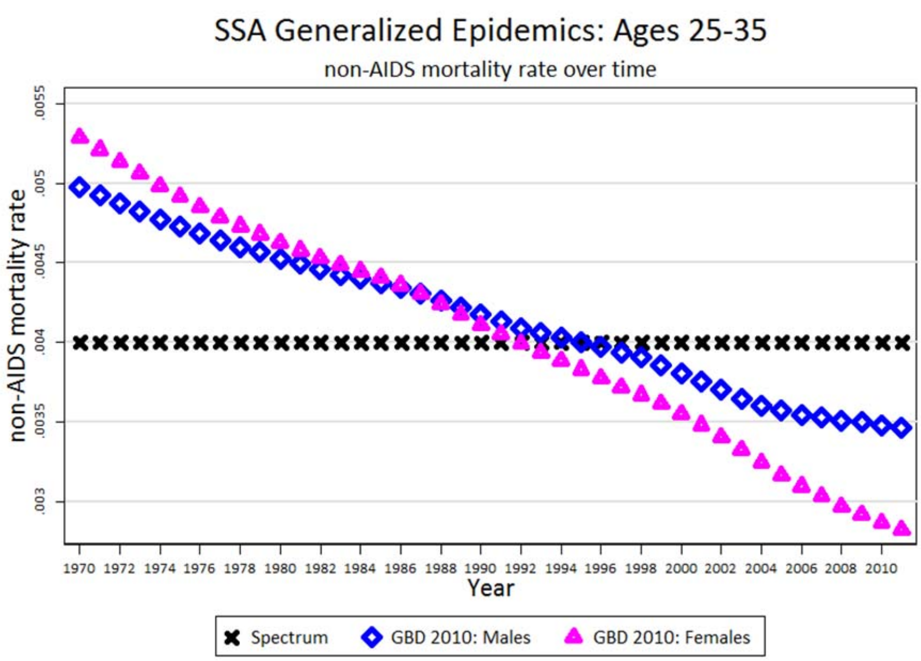

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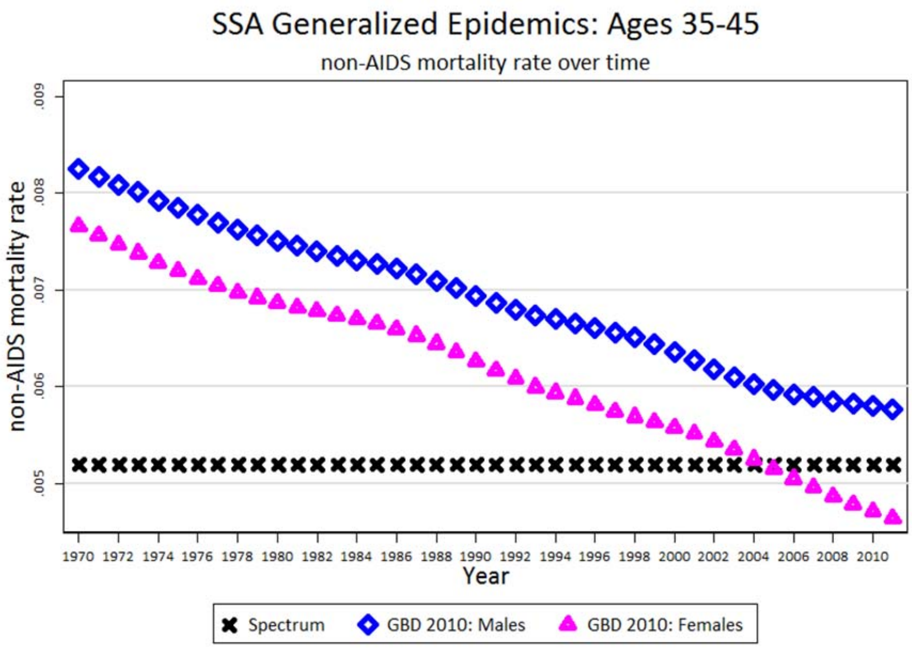
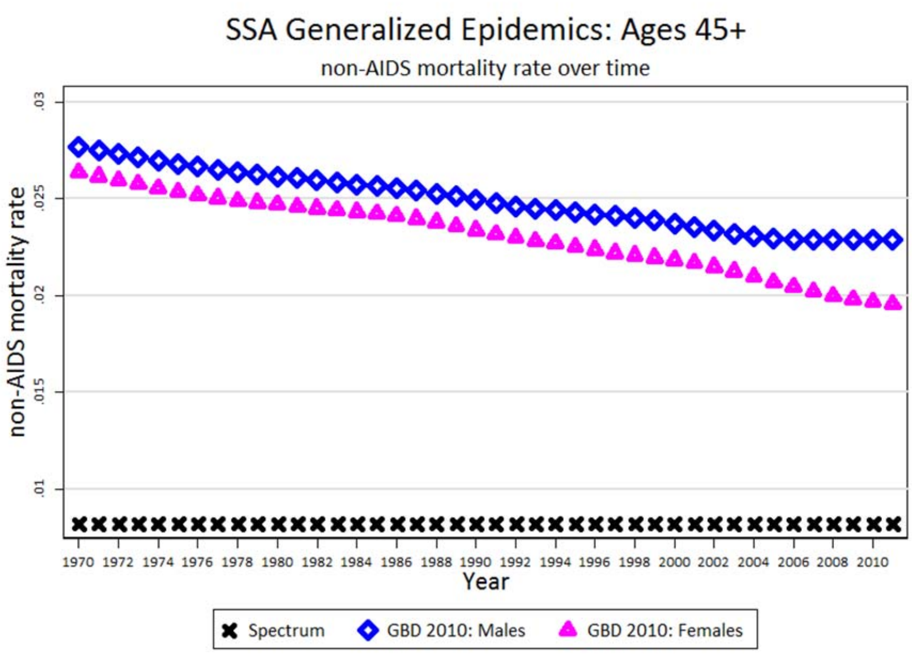
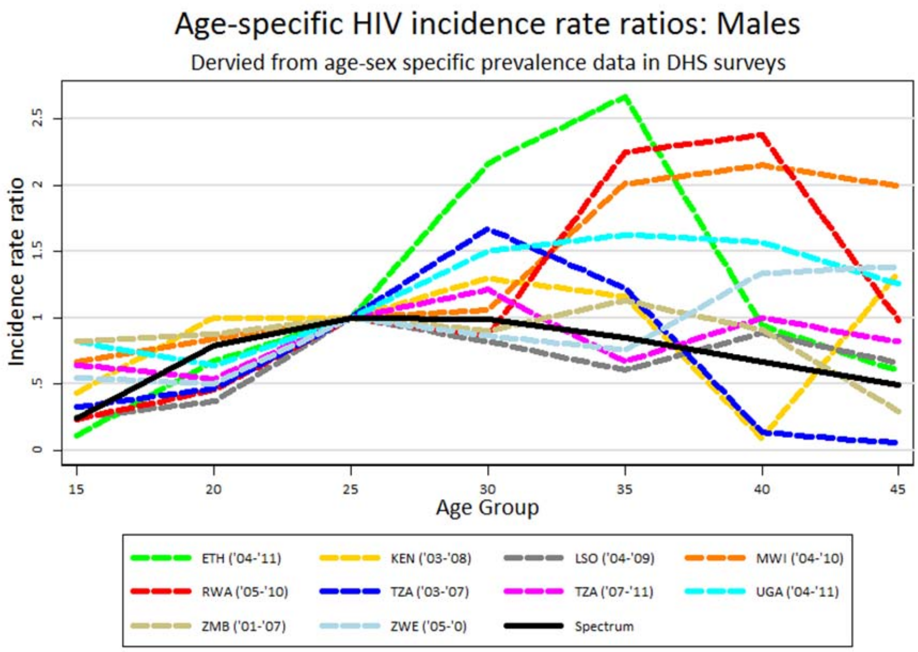

SSA Generalized Epidemics: Ages 35-45
non-AIDS mortality rate over time
non-AIDS mortality rate
.009
.008
.007
.006
.005
1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010
Year
Spectrum
GBD 2010: Males
GBD 2010: Females

(d)

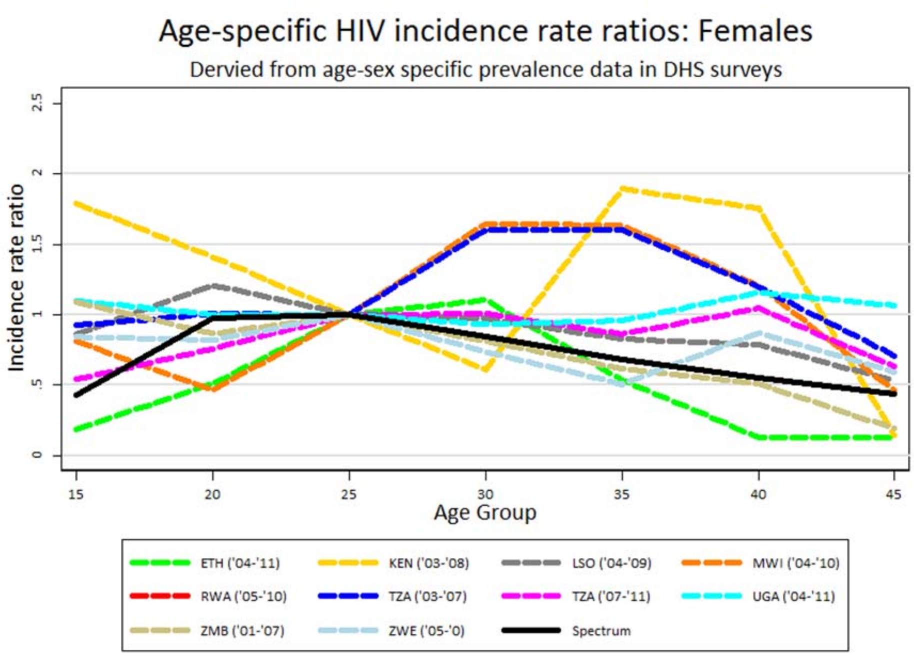

SSA Generalized Epidemics: Ages 45+
non-AIDS mortality rate over time
non-AIDS mortality rate
.03
.025
.02
.015
.01
1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010
Year
Spectrum
GBD 2010: Males
GBD 2010: Females

Appendix Figures 4a-4c. Sex and age specific incidence rate ratios derived from DHS prevalence data compared with Spectrum values (black) for generalized epidemics: (a) male age-specific IRRs, (b) female age-specific IRRs, and (c) female to male IRRs.

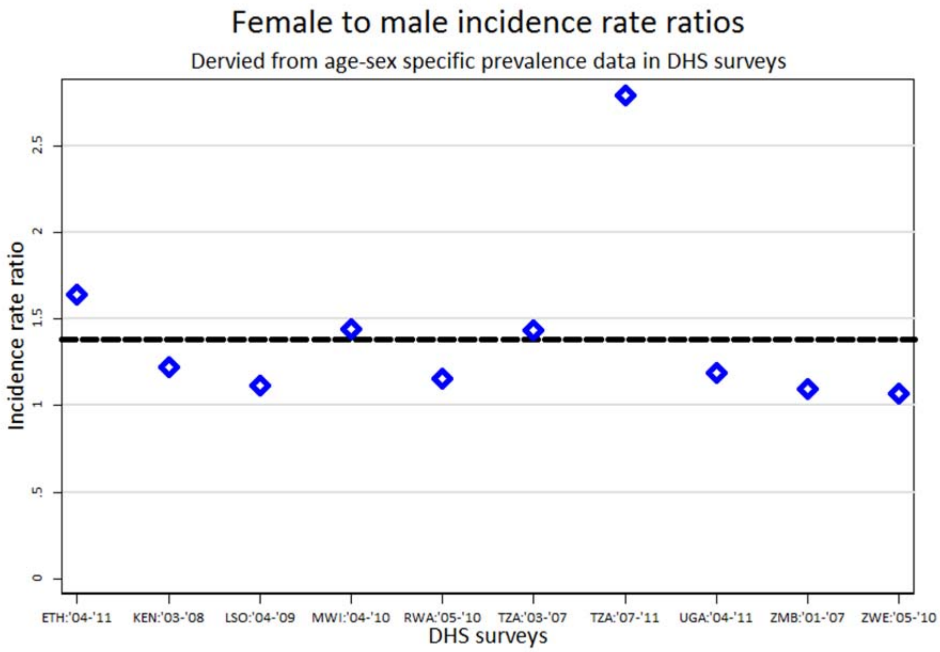
(a)



(b)

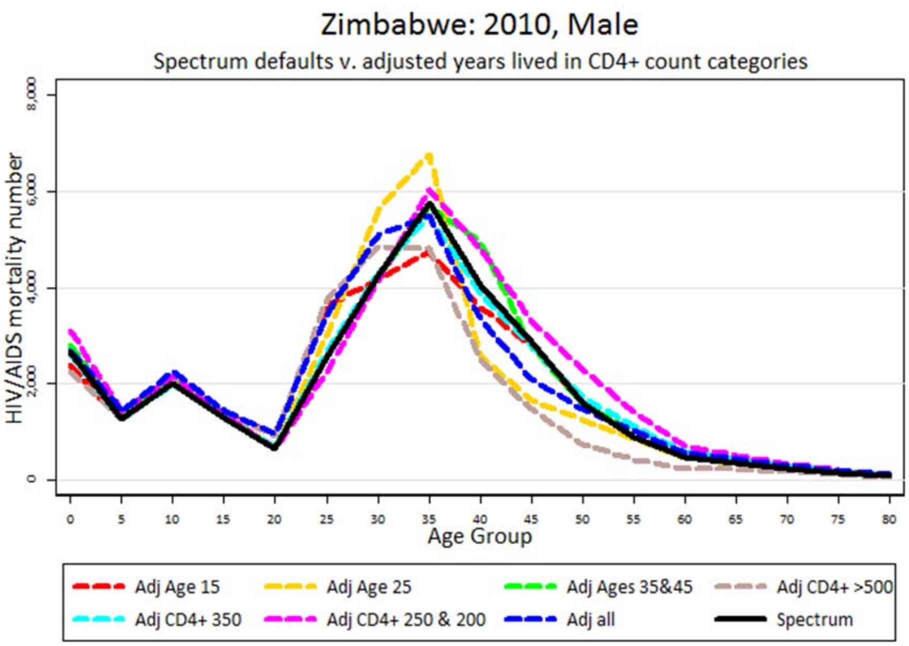


(c)

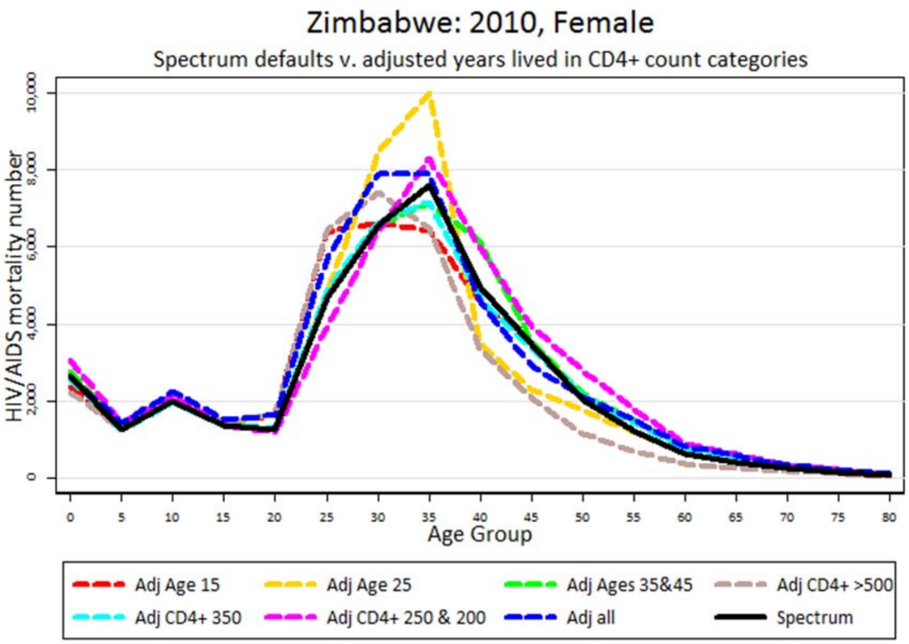

Female to male incidence rate ratios
Dervied from age-sex specific prevalence data in DHS surveys
Incidence rate ratio
0
.5
1
1.5
2
2.5
ETH:'04-'11
KEN:'03-'08
LSO:'04-'09
MWI:'04-'10
RWA:'05-'10
TZA:'03-'07
TZA:'07-'11
UGA:'04-'11
ZMB:'01-'07
ZWE:'05-'10
DHS surveys

Appendix Figures 5a & 5b. Estimates of HIV/AIDS mortality by age for Zimbabwe in 2010, (a) males and (b) females. Individually adjusted years lived by age groups and CD4+ count categories; no calibration of the HIV/AIDS mortality rate so survivorship matches the ALPHA network; adjusted age group 15-25 only (red), adjusted age group 25-15 only (gold), adjusted age group 35-45 and 45+ only (green), adjusted CD4+ count category >500 only (gray), adjusted CD4+ count category 350-500 only (light blue), adjusted CD4 + count categories 250-349 and 200-249 only (pink), adjusted all ages and categories (blue), and Spectrum defaults (black).

(a)



(b)


Zimbabwe: 2010, Female
Spectrum defaults v. adjusted years lived in CD4+ count categories
HIV/AIDS mortality number
0
2,000
4,000
6,000
8,000
10,000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
Age Group
Adj Age 15
Adj Age 25
Adj Ages 35&45
Adj CD4+ >500
Adj CD4+ 350
Adj CD4+ 250 & 200
Adj all
Spectrum

Appendix Tables

Appendix Table 1. Age-specific parameters used in Spectrum's steady state model; recalibrated to match ALPHA network survivorship after proportion of new infections adjusted so all begin with a CD4+ count >500

Linear progression rate equation: ***d+b*c***	**15 - 24**	**25 - 34**	**35 - 44**	**45+**
d-values	34.52	50.27	43.63	70.39
b-values	1.65	1.12	4.80	5.00
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**	**45+**
a-values	0.002	0.003	0.006	0.007
r-values	0.987	0.990	0.99	0.990
Total error	6	4	65	146

Note: c=CD4+ count categories 1-7

Appendix Table 2. Age-specific Spectrum inputs recalibrated to match ALPHA network survivorship after proportion of new infections adjusted so all begin with a CD4+ count >500 *(same for both sexes)*

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 - 34	35 - 44	45 -54	15 - 24	25 - 34	35 - 44	45 -54
> 500	8.53	6.99	5.86	5.05	0.005	0.008	0.018	0.020
350 - 500	3.97	2.86	2.82	1.87	0.013	0.021	0.048	0.054
250 - 349	2.53	1.86	1.72	1.17	0.036	0.057	0.129	0.145
200 - 249	1.22	0.91	0.80	0.55	0.097	0.154	0.348	0.390
100 - 199	2.34	1.79	1.48	1.05	0.260	0.416	0.936	1.049
50 - 99	1.13	0.88	0.69	0.50	0.697	1.119	2.520	2.823
< 50	0.53	0.33	0.15	0.13	1.870	3.011	6.781	7.599

Appendix Table 3a & 3b. Age-specific parameters used in Spectrum's steady state model. Mortality rate parameters calibrated so survivorship in the steady state model could match the ALPHA network, (a) males and (b) females.

(a) Males				
Linear progression rate equation: *d+b*c*	**15 - 24**	**25 - 34**	**35 – 44**	**45+**
d-values	41.43	17.52	43.63	70.39
b-values	-4.00	9.24	4.80	5.00
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**	**45+**
a-values	0.002	0.001	0.002	0.002
r-values	0.690	0.850	0.900	0.843
Total error	6	28	14	69
(b) Females				
Linear progression rate equation: *d+b*c*	**15 - 24**	**25 - 34**	**35 – 44**	**45+**
d-values	41.43	17.52	43.63	78.96
b-values	-4.00	9.24	4.80	5.00
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**	**45+**
a-values	0.002	0.001	0.002	0.002
r-values	0.730	0.910	0.960	0.837
Total error	6	29	7	61
				Note: c=CD4+ count categories 1-7

Appendix Tables 4a & 4b. Age and sex-specific Spectrum inputs for adjusting years lived in CD4+ count categories based on CASCADE data. Mortality rate parameters calibrated so that model survivorship matches the ALPHA network, (a) males and (b) females.

(a) Males

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 - 34	35 - 44	45 -54	15 - 24	25 - 34	35 - 44	45 -54
> 500	0.75	0.18	0.01	0.01	0.004	0.003	0.005	0.005
350 - 500	4.02	3.89	3.34	3.34	0.009	0.007	0.011	0.011
250 - 349	3.85	3.37	3.01	3.01	0.017	0.017	0.028	0.028
200 - 249	1.93	1.68	1.51	1.51	0.034	0.039	0.068	0.068
100 - 199	4.67	1.57	1.48	1.05	0.069	0.092	0.168	0.168
50 - 99	2.87	0.69	0.69	0.50	0.137	0.215	0.413	0.413
< 50	0.53	0.33	0.15	0.13	0.272	0.504	1.016	1.016

(b) Females

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 – 34	35 – 44	45 -54	15 - 24	25 – 34	35 - 44	45 -54
> 500	1.63	0.99	0.49	0.49	0.005	0.003	0.005	0.005
350 - 500	4.03	3.77	3.39	3.39	0.009	0.008	0.013	0.013
250 - 349	4.45	3.79	3.15	3.15	0.019	0.020	0.033	0.033
200 - 249	2.23	1.90	1.57	1.57	0.040	0.050	0.087	0.087
100 - 199	4.67	1.57	1.48	1.05	0.084	0.124	0.227	0.227
50 - 99	2.87	0.69	0.69	0.50	0.174	0.308	0.592	0.592
< 50	0.53	0.33	0.15	0.13	0.360	0.766	1.546	1.546

Appendix Table 5a & 5b. Age-specific parameters used in Spectrum's steady state model; recalibrated after adjustments to the background non-AIDS mortality rate, (a) SSA generalized epidemics and (b) Botswana

(a) SSA generalized epidemics			
Linear progression rate equation: ***d+b*c***	**15 - 24**	**25 - 34**	**35 - 44**
d-values	41.43	17.52	43.73
b-values	-3.99	9.24	5.00
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**
a-values	0.002	0.001	0.002
r-values	0.843	0.990	0.960
Total error	7	12	28
(b) Botswana			
Linear progression rate equation: ***d+b*c***	**15 - 24**	**25 - 34**	**35 - 44**
d-values	41.43	19.87	43.63
b-values	-3.99	8.36	4.80
Exponential HIV/AIDS mortality rate equation: $a*e^{rc}$	**15 – 24**	**25 – 34**	**35 – 44**
a-values	0.002	0.001	0.002
r-values	0.868	0.990	0.990
Total error	6	11	31

Note: c=CD4+ count categories 1-7

Appendix Tables 6a & 6b. Age-specific Spectrum inputs recalibrated after adjustments to the background non-AIDS mortality rate *(same for both sexes)*: (a) SSA generalized epidemics and (b) Botswana

(a) SSA generalized epidemics

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 - 34	35 - 44	45 -54	15 - 24	25 - 34	35 - 44	45 -54
> 500	8.53	6.78	5.45	4.70	0.005	0.004	0.005	0.005
350 - 500	4.49	4.17	2.79	1.87	0.012	0.010	0.013	0.012
250 - 349	3.40	2.21	1.70	1.17	0.027	0.026	0.034	0.027
200 - 249	1.97	0.92	0.78	0.55	0.063	0.069	0.090	0.063
100 - 199	4.66	1.57	1.45	1.05	0.146	0.185	0.235	0.146
50 - 99	2.87	0.69	0.68	0.50	0.338	0.499	0.614	0.338
< 50	1.27	0.75	0.62	1.27	0.786	1.342	1.606	0.785

(b) Botswana

CD4 count category	Years lived in CD4 count category				HIV/AIDS mortality rate without ART			
	15 - 24	25 – 34	35 – 44	45 -54	15 - 24	25 – 34	35 - 44	45 -54
> 500	8.53	6.80	5.46	4.70	0.005	0.004	0.005	0.005
350 - 500	4.49	4.10	2.82	1.69	0.012	0.011	0.014	0.012
250 - 349	3.40	2.22	1.72	1.06	0.028	0.029	0.038	0.027
200 - 249	1.96	0.94	0.80	0.51	0.068	0.077	0.103	0.062
100 - 199	4.66	1.62	1.48	0.96	0.161	0.208	0.278	0.142
50 - 99	2.86	0.71	0.69	0.46	0.384	0.559	0.747	0.328
< 50	1.09	0.66	0.50	1.32	0.916	1.505	2.012	0.758