Technical appendix to
"How should access to antiretroviral treatment be measured?"
Published in the Bulletin of the World Health Organization

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This document provides a technical description of the models used to generate the results presented in the article "How should access to antiretroviral treatment be measured?", published in the Bulletin of the World Health Organization in 2011.

Model used to estimate ART access in Figure 1

Variables are defined as follows:

$U(t)$ = number of untreated ART-eligible individuals at time t
$P(t)$ = number of individuals becoming eligible to receive ART for the first time in year t (i.e between times t and $t + 1$)
$D(t)$ = number of deaths in untreated individuals who are eligible to receive ART, in year t
$S(t)$ = number of individuals starting ART in year t
μ = mortality rate in untreated ART-eligible individuals

The mortality rate in untreated ART-eligible individuals can be calculated in year t as the number of deaths in untreated ART-eligible individuals in year t, divided by the average number of untreated ART-eligible individuals over the course of the year. If it is assumed that entrants to and exits from the untreated ART-eligible state occur uniformly over year t, then this is equivalent to stating that

$$\mu = \frac{D(t)}{U(t) + 0.5P(t) - 0.5S(t) - 0.5D(t)}.$$

From this it follows that

$$\frac{1}{\mu} = \frac{U(t) + 0.5P(t) - 0.5S(t)}{D(t)} - 0.5$$

and solving for $D(t)$:

$$D(t) = U(t)\left(\frac{2\mu}{\mu+2}\right) + P(t)\left(\frac{\mu}{\mu+2}\right) - S(t)\left(\frac{\mu}{\mu+2}\right).$$

We obtain a recursive relation for $U(t)$ as follows:

$$\begin{aligned} U(t+1) &= U(t) + P(t) - S(t) - D(t) \\ &= U(t)\left(1 - \frac{2\mu}{\mu+2}\right) + P(t)\left(1 - \frac{\mu}{\mu+2}\right) - S(t)\left(1 - \frac{\mu}{\mu+2}\right) \\ &\approx U(t)\exp(-\mu) + (P(t) - S(t))\exp(-0.5\mu) \end{aligned}$$

If we define q to be the annual *probability* of death in untreated ART-eligible individuals, then

$$q = 1 - \exp(-\mu),$$

and hence the recursive relation can be re-expressed as

$$U(t+1) \approx U(t)(1-q) + (P(t) - S(t))(1-q)^{0.5}. \quad (1)$$

Based on South African estimates of mortality rates in untreated patients with CD4 counts less than 200,[1] we set μ at 0.27, from which it follows that q = 0.237. Hence we are able to calculate the number of untreated ART-eligible individuals at the start of each year from the specified numbers of individuals progressing to ART eligibility and starting ART in each year.

In order to estimate the change in the number of individuals receiving ART, we need to define $N(t)$ as the number of individuals receiving ART at time t. As described previously,[2] we assume that the probability of remaining on ART for the first 6 months on ART is 0.895, and thereafter the annual probability of remaining on ART is 0.935, based on data from a public sector programme in South Africa.[3] If we assume that individuals starting ART in year t start ART, on average, at time t + 0.5, then

$$N(t+1) \approx N(t) \times 0.935 + S(t) \times 0.895. \quad (2)$$

Hence we have a further recursive relation for calculating the number of individuals on ART at the start of each year from the specified numbers of individuals starting ART in each year. (It is also possible to calculate $S(t)$ as a function of $N(t)$ if only the $N(t)$ values are known, by using this equation.)

The model estimate of ART coverage in year t, according to the standard UNGASS definition, is

$$\frac{N(t)}{U(t) + N(t)}. \quad (3)$$

The enrolment ratio is the ratio of the number of patients starting ART to the number becoming eligible to receive ART, i.e.

$$\frac{S(t)}{P(t)}. \quad (4)$$

Model used to estimate ART access in South African provinces

A more sophisticated model is used to estimate ART access in South Africa's provinces. This model has been described in detail elsewhere.[2] Briefly, a multi-state model is used to characterize the progression of HIV infection in infected adults. ART-naive adults are categorized into seven states, defined in terms of CD4 count and AIDS diagnosis:

- Pre-AIDS, CD4 > 900 cells/μl
- Pre-AIDS, CD4 700-900 cells/μl
- Pre-AIDS, CD4 500-699 cells/μl
- Pre-AIDS, CD4 350-499 cells/μl
- Pre-AIDS, CD4 200-349 cells/μl
- Pre-AIDS, CD4 < 200 cells/μl
- Untreated AIDS

Individuals can move between the pre-AIDS CD4 states as their CD4 counts fall and rise. The untreated AIDS state is an absorbing state, i.e. individuals cannot move back to the pre-AIDS states after having developed AIDS-defining illness. The rates of transition between these states have been set at values estimated in an untreated HIV cohort in Amsterdam over the period 1990-1996.[4] Using these assumptions, the model produces estimates of total survival times similar to those estimated in South Africa prior to the availability of ART, and the model also estimates CD4 distributions in infected adults similar to those observed in cross-sectional surveys in South Africa.

Estimates of the annual number of new HIV infections in adults, in each of the two provinces, have been obtained from the ASSA2003 AIDS and Demographic model.[5] The number of untreated adults in each of the seven states is projected at monthly intervals, based on the assumed rates of transition. The annual numbers of patients starting ART in each province have been estimated based on a synthesis of data from the public, private and NGO sectors,[2] and the method used to obtain cross-sectional estimates of numbers of adults on ART from the number newly enrolled in each year is the same as the method used in the previous model (equation 2). In line with the South Africa ART guidelines that were in place up to the end of 2009, adults are assumed to initiate ART only if they are in the untreated AIDS state or if they have a CD4 count below 200. Movement out of these two states therefore occurs as ART enrolment increases.

Based on the same equation used in the previous model, we calculate the numbers progressing to ART eligibility in year t, $P(t)$, from the level of unmet need at the start and end of the year ($U(t)$ and $U(t + 1)$ respectively), the number of deaths in the year in untreated individuals ($D(t)$) and the number starting ART in year t, $S(t)$:

$$P(t) = U(t+1) - U(t) + S(t) + D(t) .$$

The parameters $P(t)$, $U(t)$ and $D(t)$ are calculated differently depending on whether ART eligibility is defined in terms of CD4 < 200 or CD4 < 350. The UNGASS definition of ART coverage and the enrolment ratio are calculated in the same way as in the previous model (equations 3 and 4 respectively).

A limitation of this model is that it relies on CD4 data from a Western cohort, although the model is applied in an African context. CD4 distributions and rates of CD4 decline are likely to vary between populations,[6, 7] and we have therefore conducted a sensitivity analysis to assess the extent to which the model results change when seven different sets of CD4 transition estimates are entered into the model.[4, 8-10] However, all seven of the sets of transition estimates are from developed countries in which HIV-1 subtype B is dominant, and this sensitivity analysis may therefore fail to capture the true variation in results. Although we have shown that the results from the Amsterdam cohort are reasonably consistent with empirical data from South Africa,[2] it would be ideal to make use of local CD4 data. Further work is required to parameterize models of CD4 decline in the African context.

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