Supplementary material to the manuscript:

 “Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention and eligibility criteria for antiretroviral therapy initiation”

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## Brief description of HIV Synthesis Heterosexual Transmission Model for South Africa

The HIV Synthesis Heterosexual Transmission Model is an individual-based stochastic model of heterosexual transmission, progression and treatment of HIV infection. The aim of this model is to capture all the elements (e.g. sexual risk behaviour, testing, primary infection, viral load, CD4 cell count, use of ART, adherence, resistance, drug failure, drug interruption, loss to follow-up, occurrence of AIDS, non-AIDS death, etc.) that we have a reasonable understanding of due to extensive data sets, although not always from subSaharan African setting.

The model simulates the life course of individuals in 3 month step (all variables are updated in 3 month periods). It includes an age-structure and sexual risk behaviour is modelled as the number of condomless-sex short term (e.g. casual) partners and presence of a condomless-sex long-term (e.g. primary) partner in each period. It is assumed that HIV transmission only takes place via condom-less sex, therefore only partners with whom subjects have sex without using a condom are taken into account.The HIV infection, diagnosis and ART status of long-term condomless sex partners is tracked over time. In any given period, the probability of an uninfected person having a condomless-sex partner who is infected with HIV depends on their number of partners and on the prevalence of HIV amongst partnerships formed by those of the opposite gender, accounting for patterns of age mixing. Given exposure to an infected partner, the probability of transmission depends on the viral load level of the partner (obtained by sampling from the distribution of viral load levels in partnerships formed by HIV infected people, accounting for gender and age), on the estimated risk of transmission at that viral load, presence of a concurrent sexually transmitted infection and on gender (higher susceptibility for women and lower for men circumcised).

For HIV infected people the main variables modelled are: primary infection (a period of raised infectivity of 3 months duration), viral load, CD4 cell count, presence of specific resistance mutations, HIV diagnosis, whether the person has been linked to care and retained in pre-ART care and after initiating ART, the antiretroviral regimen the person is currently on, adherence to ART and risk of AIDS and death.

Figures 1-4 show the value assumed in the Synthesis model (median across simulation in black dotted line [brown for women in ] and uncertainty range black line [brown for women in ]) and observed (data) on the ground (dots in different colors).

The first step in the cascade of care is being tested for HIV. HIV testing became available in 1990 in antenatal clinics (ANC) and in 1996 for the general population and has increased dramatically in South Africa. The proportion of people ever tested was 21.4% in 2002 which increased to 30.3% in 2005 and to 50.8% in 2008(Shisana et al. 2009) and the percentage of people who reported having had an HIV test and received the result in the last 12 months was 25% in 2008.In the Synthesis model these rates have been chosen by fitting to observed data on the proportion of adults ever tested, gender-specific(Shisana et al. 2009) (see ).

Figure . Proportion of adults (15-65 years old) ever tested

UR: uncertainty range; LL: lower limit; UL: upper limit; SA National HIV: South Africa National HIV surveys conducted in 2002, 2005 and 2008

Once diagnosed with HIV, people can be lost at different stages before or after starting ART. In South Africa, the proportion of people who received a CD4 count or clinical staging to determine whether a person is eligible to be initiated on treatment (“staged”), after being diagnosed varies from 35% (although within 3 months of diagnosis)(Larson et al. 2010b) to 78%(Govindasamy et al. 2011) (see ); shows the proportion of people who were staged from 1998, when a significant number of people were tested for HIV and ART was available. The color dots represent estimates from different studies and they are positioned in terms of calendar year, approximately half way through when the study was conducted. The studies indicated in the are those summarized in the review by Rosen et al.(Rosen & Fox 2011) conducted in South Africa.

Two of the estimates reported in the graph come from the same study(Bassett et al. 2010; Losina et al. 2010). They followed people presenting for HIV testing at two sites offering HIV testing and CD4 cell count measurement and HIV care in Durban. In Losina et al. (Losina et al. 2010) (patients recruited between November 2006 and May 2007) they evaluated how many received a CD4 cell count within 8 weeks of diagnosis,they estimated it to be 55%, while in Bassett et al.(Bassett et al. 2010)(patients recruited between November 2006 and October 2008) the focus was on how many initiated ART by 12 months but they reported that 69%underwent CD4 cell count testingwithin 3 months.

The study conducted by Larson et al. (Bassett et al. 2010) estimated the proportion who complete CD4 testing by 12 weeks after diagnosis in patients tested in a hospital in Johannesburg, they estimated 35% linked to care by 3 months (conducted a CD4 and collected the results). A randomized controlled trial conducted in a urban primary health care clinic in Johannesburg (Faal et al. 2011), evaluating the impact of providing immediate CD4 results at diagnosis, rather than after 1 week, as is standard of care, found that the proportion of patients enrolled for further care within 1 month for pre-ART care were: 33.6%in the standard of care arm and 47.6% in the arm were patients received their CD4 result at diagnosis.

The highest estimate comes from a study(Govindasamy et al. 2011)which evaluated how many of those who received an HIV test from mobile testing unit in the Cape MetropolitanRegion, Western Cape received their CD4 results. In this study patients were given, at the moment of HIV testing, a referral letter to take to a health care provider and when CD4 counts became available (usually within72 hours), patients were contacted by phone and the CD4 results were communicated.Nevertheless 27% of them did not receive their CD4 results.

The studies conducted in Durban show that at 2 months around 50% received the CD4 result and this goes up to 70% by 3 months, similar to the median predicted by the model, although it should be noticed that the two analyses were not conducted exactly on the same number of patients. The estimates from the RCT (Faal et al. 2011) used 1 month as a time frame and therefore they are expected to be lower than what is predicted by the model.

Figure . Proportion linked to care by 3 months since diagnosis

Figure 3 shows the proportion of those who were not eligible at staging, who visit the clinic within the next year. has been found to vary from 31% (Larson et al. 2010a) to 46% (Luseno et al. 2008). This is well captured by the model; in fact most of the estimates are included within the 90% uncertainty range. The estimates which are not in this range are lower than predicted by the model. Nevertheless the observed data could potentially underestimate retention due to the fact that people go to different clinics. There is evidence from studies which investigated what happen to people who are considered lost to follow-up, that many of them have actually attended a different clinic in the last three months (Dalal et al. 2008; Geng et al. 2010; Tweya et al. 2013).

Figure . Proportion retained in care of those not eligible at staging

 shows the proportion initiated on ART of those who have been eligible to start ART for at least 12 months, starting from 2003 when ART became available. This has been estimated in studies, conducted mainly between 2003 and 2009 to be between 39% (Bassett et al. 2010) and 68% (April et al. 2009). The proportion of patients eligible for at least one year who initiated ART predicted by the model is lower than the estimates from the single studies, but this reflect the fact that those estimates come from areas/clinics where antiretroviral treatment was available, while the model reflects the situation in South Africa overall. In order for the model to reflect the number of people who have initiated ART(Johnson 2012), it was necessary to assume that by 2013 95% of those eligible for ART (CD4<350 cells/µl) were initiated on treatment.

Figure . Proportion initiated on ART among those identified as eligible for at least one year

ART is assumed to have been introduced in 2003 and the eligibility criteria for treatment initiation reflects national antiretroviral treatment guidelines for South Africa: <200 cells/mm3 or WHO stage 4 before mid-2010(South Africa National Department of Health 2004), CD4 counts ≤350 cells/mm3 irrespective of the WHO clinical stage after mid-2010(WHO 2010).In 2005, approximately 100,000 HIV-infected adults were receiving antiretroviral therapy in South Africa and this number increased to 1.6 million by mid-2011(Johnson 2012). Specific first and second line regimens follow those used in South Africa. The first line regimen consists of lamivudine (3TC), efavirenz (EFV) and stavudine (D4T), before June 2010(South Africa National Department of Health 2004), or tenofovir (TDF) afterwards(South Africa National Department of Health 2010b), with substitutions of D4T with TDF and EFV with nevirapine(NVP) if necessary for toxicity. Before June 2010, the second line regimen is assumed to consist of zidovudine (AZT), ddI and lopinavir/ritonavir (LPV/r). After mid-2010, second line ART is assumed to be TDF, 3TC and LPV/r if failing on a D4T- or AZT-based first-line regimen and AZT, 3TC and LPV/r if failing on a TDF-based first-line regimen, as recommended in 2010 national guidelines(South Africa National Department of Health 2010b).

Once on ART the need to switch people to second-line ART is assumed to be determined by VL monitoring: 6 monthly until mid-2010, from mid-2010 at 6 and 12 months and then annually afterwards. Before mid-2010 the criterion to switch people to second-line regimen is a detectable viral load measurement above 400 copies/ml followed by another above 5000 copies/ml(South Africa National Department of Health 2004). In the guidelines published in 2010 the recommended threshold for the confirmatory viral load has been modified to 1000 copies/ml (South Africa National Department of Health 2004; South Africa National Department of Health 2010b). At any time and therefore even when on ART they can be lost from care, it is estimated that the proportion retained on ART at 1 year since initiation varies from 80%(Cornell et al. 2010) to 93%(Boulle et al. 2008).

Figure . Proportion of people retained on ART at 1 year since ART initiation

For the remaining part, the model reflects the model for *HIV Synthesis Heterosexual Transmission Model for southern Africa,*for which full model details have been published elsewhere (Cambiano et al. 2013; Phillips et al. 2011; von, V et al. 2012). Full model details specific to South Africa are reported in the section “Full model details” on page 17.

## Calibration of the HIV Synthesis Heterosexual Transmission Model to South Africa

Heterosexual transmission is the predominant mode of HIV transmission in this country(Shisana et al. 2009)). The epidemic is assumed started in 1989, close to when the first reported heterosexual AIDS case in South Africa was reported (1988) and the model runs for 45 years, with variables updated every 3 months. Each run of the model simulates a cohort of 100,000 individuals, of which approximately 34,000 alive and aged between 15 and 65 years old in 1989. In order to fit our model to observed data and to produce output measures up to 2013, expressed in absolute terms, which are relevant for South Africa, this modelled population size needs to be multiplied by the ratio between the estimated adult population size in mid-2011(2010) and the size of the modelled population, which is 673.

To calibrate the model to the South African epidemic, we used Approximate Bayesian Computation (ABC) methods(Beaumont et al. 2002). In essence, this involves running multiple simulations which sample unknown parameter values from suitable distributions and then selecting those parameter sets where simulation outcomes produce model outputs most consistent with observed data best by assessing the fit using a summary statistic.

In our model, there are multiple parameter values describing various elements of the underlying progression of HIV and the effect of ART. The model has been shown to give a good fit to data on these processes and, for the purposes of fitting the model to the HIV epidemic in a given country, we hold these parameter values fixed. They, thus, become part of the model structure rather than parameters to be sampled from. The parameters for which values are sampled from distributions of plausible values are those which determine levels of condom-less sex and the rate of HIV transmission.

When sampling parameters which determine the HIV incidence and prevalence it is important to ensure that the parameter space sampled is chosen to be large enough to allow for extremities and that the parameterization is sufficiently flexible but also restricted enough to limit computation time. So for each run of the simulation model, we sampled at random a set of parameter values for those listedin section “Parameters values and distributions” with the distribution, and generate the HIV epidemic until the end of 2012. This is repeated 10,000 times in order to search for the best fitting parameter sets. For each run, the fit of the model to the observed data was assessed using a fit score; the sum of the deviances from the observed data (summed over the number of years data was available for, and for each type of data available), is quantified by |D – M| / D, where D is the observed data and M is the estimate produced by the Synthesis Model.

The data used to fit the model are:

* HIV prevalence among adults aged 15 to 49 years old (available for 2002, 2005, 2008 and 2011) (Shisana et al. 2009)
* HIV prevalence among young people, aged 15 to 25 years old (available for 2002, 2005, 2008) (Shisana et al. 2009)
* the proportion, gender-specific, of people who ever had an HIV test (available for 2002, 2005, 2008)(Shisana et al. 2009),
* the number, gender-specific, who started antiretroviral treatment (available from 2001 to 2011) (Adam & Johnson 2009)
* the proportion of new diagnoses with resistance (available from 2005 to 2010) (WHO HIV/AIDS Programme 2012).

Half weight was assigned to the deviance to the proportion of new diagnoses with resistance, because this estimate refers to southern Africa, rather than specifically South Africa and it may be not representative of all South Africa.

The 30 simulations with the best fit (out of 10,000), in terms of average deviance were selected (average deviance of less than 0.94)

## Analysis details

This analysis compares outcomes over 20 years from 2013 to the end of 2032.

Two potential scenarios regarding diagnosis and retention are considered. In one (“enhanced diagnosis and retention”) significant improvements in HIV testing, linkage to care and retention in pre-ART care are made so that 80% of people who become eligible for ART are in care, and retention on ART is improved so that 92% of patients are retained on ART one year after ART initiation (representing a 50% reduction in loss to follow-up while on ART). In the other scenario no change after 2012 in these factors is assumed.

Within each of these two scenarios, three different ART initiation policies are considered:

* continuation of the existing policy in South Africa of initiation at CD4 cell counts below 350 cells/mm3.
* at CD4 cell count below 500 cells/mm3 (currently recommended by WHO(World Health Organization 2013)),
* at time of diagnosis regardless of CD4 cell count,

The simulations from 2013 to the end of 2032 started from the epidemics (n=30) which provided a good fit to the observed data (see section Calibration of the HIV Synthesis Heterosexual Transmission Model to South Africa). The fact that it is stochastic means that each event modelled is the result of random processes, determined by probability distributions, therefore it is necessary to perform multiple runs and average the results to diminish the stochasticity in predictions. Multiple runs for each scenario and ART initiation policy have been generated and the median or the mean is presented. The median is presented with the uncertainty range: the 5th and 95th percentile across all simulations so it reflects the uncertainty in the parameters. The 95% confidence interval for the average reduction in incidence was calculated by calculating the 95% confidence interval of the ratio between the incidence in 2032 and in 2012 which reflects the stochastic variability.

## Parameters values and distributions

**Sexual behaviour**

As mentioned in the Brief description of HIV Synthesis Heterosexual Transmission Model, sexual risk behaviour is modelled as the number of short term (e.g. casual) partners (STPs) and presence of a long-term partner (LTP) in each 3 month period and, as for all variables modelled, is updated in 3 month periods. The status of the long-term partner, in terms of HIV infection, diagnosis and ART use, is tracked over time. It is assumed that HIV transmission only takes place via condom-less sex, therefore only partners with whom subjects have sex without using a condom are taken into account.

The values of the parameter that determine the sexual behaviour are listed below. If they were sampled from a distribution the distribution is reported.

Table . Parameters and distribution on sexual behaviour

|  |  |
| --- | --- |
| **Parameter (variable name in the program)** | **Value (or distribution)** |
| Sexual behaviour |
| Sexual behaviour model structure | 60% base structure, 40% alternative structure (with no sex workers; see model details) |
| Factor to change overall average level of condomless sex with short term partners (newp\_factor) | lognormal(ln10,0.3), if fold\_tr\*<=1 and tr\_rate\_primary\*<=0.2;lognormal(ln4,0.3), if fold\_tr> 1 and tr\_rate\_primary> 0.2;lognormal(ln6,0.3), otherwise; |
| Poisson mean for highest short term partner group (see model details) (swn) | Gamma(20,2) (mode=19/2=9.5) if fold\_tr\*<=1 and tr\_rate\_primary\*<=0.2;Gamma(8,2) (mode=7/2=3.5) if fold\_tr> 1 and tr\_rate\_primary> 0.2;Gamma(14,2) (mode=13/2=6.5)otherwise; |
| Change in propensity to have a long-term condom-less sex partner (“risk”) after HIV diagnosis (i.e. mainly reflects the chance of starting to adopt 100% condom use or cease sexual intercourse) (ch\_risk\_diag) | Beta (8,10) (mode=7/16=0.44)  |
| Change in propensity to have short term (“new”) condom-less sex partners after HIV diagnosis (ch\_risk\_diag\_newp) | Beta(6,2) (mode=5/6=0.83) |
| Date at which population level reduction in condomless sex with short-term and long-term partners started (date\_ch\_risk\_beh) | Uniform (1991,1998.75) |
| Date at which the slope in the population level reduction in condomless sex behaviour with short term-partners changes (date\_ch\_risk\_beh\_2)  | Uniform (1999,2005.75) |
| Date at which the population level reduction in condomless sex behaviour with short term-partners stops (date\_ch\_risk\_beh\_3) | Uniform (2006,2009.75) |
| Annual reduction in propensity to have condomless sex (“risk behaviour”) with short term-partners in the period between date\_ch\_risk\_beh and date\_ch\_risk\_beh\_2 (rate\_ch\_risk\_beh) | Lognormal(ln0.065,0.75) |
| Annual reduction in propensity to have condomless sex (“risk behaviour”) with short term-partners in the period between date\_ch\_risk\_beh\_2 and date\_ch\_risk\_beh\_3 (rate\_ch\_risk\_beh\_2)  | lognormal(ln0.025,0.5) |
| This parameter is the fold increase in the proportion who do not have condom-less sex, of those who had condom-less sex at the time before, relative to before date\_ch\_risk\_beh (ch\_risk\_beh\_ep) [This parameter applied after date\_ch\_risk\_beh] | 1/(Beta(10,2)) [Mean=1.2] |
| Pregnancy |
| Base probability of pregnancy per 3 months of condomless sex. It applies to women 35-45. (prob\_pregnancy\_base) | Uniform(0.035,0.075) |
| Multiplicative factor to the base probability of pregnancy for women 15 to 25 years old (fold\_preg1525) | Uniform(1.015,1.065) |
| Multiplicative factor to the base probability of pregnancy for women 25 to 35 years old (fold\_preg2535) | Uniform(1.005,1.055) |
| Multiplicative factor to the base probability of pregnancy for women 45 to 55 years old (fold\_preg4555) | Uniform(0.95,1.0) |
| Multiplicative factor to the base probability of pregnancy for women 55 to 65 years old (fold\_preg5565) | Uniform(0.9,0.95) |

\*fold\_tr is a multiplicative factor which change rate of transmission, tr\_rate\_primary is the rate of transmission in primary infection.

Swn and newp\_factor are sampled to be inversely correlated with a multiplicative factor which changes the rate of transmission (fold\_tr) and rate of transmission in primary infection (tr\_rate\_primary) to ensure that a high proportion of epidemics generate have a prevalence which fit to South Africa epidemic (without this factor we would generate many more epidemics where prevalence is very low, if fold\_tr, tr\_rate\_primary, swn and newp\_factor are all low, or very high, if all four values are high – the aim is to achieve good sampling efficiency without imposing too much constraint on epidemics generated).

**Transmission**

Table b. Parameters and distribution on parameters related to HIV transmission, transmission of resistant virus and persistence of ARV-drugs resistance mutations transmitted

|  |  |
| --- | --- |
| **Parameter (variable name in the program)** | **Value (or distribution)** |
| Fold difference in transmission rate for a given viral load (see Model details for base assumption on transmission rate by viral load) (fold\_tr) | Lognormal(ln1,0.5) |
| Rate of transmission in primary HIV infection (lasting 3 months) (tr\_rate\_primary) | beta(2,7) (mode=1/7=0.15) |
| Transmission rate when plasma viral load is < 500 cps/mL (tr\_rate\_undetec\_vl) | lognormal(ln0.0001,1) |
| Fold higher rate of acquisition for women compared to men (higher rate of transmission from men to women, compared with women to men) (fold\_change\_w) | lognormal(ln1.5,0.5)  |
| Fold higher rate of acquisition in young women compared with older women (fold\_change\_yw) | lognormal(ln3,0.4)  |
| Fold higher rate of acquisition in people with STI (fold\_change\_sti) | lognormal(ln3,0.3)  |
| Fold rate of acquisition in men circumcised (fold\_circ) | 0.5 |
| Fold lower transmission rate per 3 mths for short term partners compared with long term partners (reflecting average lower number of sex acts) (fold\_tr\_newp) | beta(5,10) (mode=4/13=0.31) |
| Adjustment to factor determining extent to which some transmitted resistance is effectively immediately lost (even from minority virus) (res\_trans\_factor) | lognormal(1,0.3) |
| Probability per 3 months of loss of persistence of transmitted mutations from majority virus to minority virus (same for each mutation) (rate\_loss\_persistence):  | lognormal(ln0.04,0.3)  |

**Natural progression**

For HIV infected people the variables modelled include: primary infection (a period of raised infectivity of 3 months duration), viral load, CD4 cell count, presence of specific resistance mutations, adherence to ART, risk of AIDS and death. The model of progression of HIV and the effect of ART has been shown to provide a generally close fit to observed data relating to natural progression of HIV infection, comparing the output of the model with data coming mainly from observational studies conducted in Europe for the natural history (incubation period) (Babiker et al. 2000; Phillips et al. 2007; Phillips et al. 2008; Phillips et al. 2011).

Table c. Parameters on natural history of HIV

|  |  |
| --- | --- |
| **Parameter (variable name in the program)** | **Value (or distribution)** |
| Initial CD4 count at infection (square root scale) (mean\_sqrtcd4\_inf) | 30 |
| Factor adjusting basic rate of natural cd4 decline (see model details) (fx)  | 0.9 |
| Factor adjusting basic rate of natural viral load change (see model details) (gx) | 1 |
| Fold increase in risk of WHO 3 condition, compared with risk of WHO 4 condition, for given level of CD4 count, viral load and age (fold\_incr\_who3) | 5 |
| Fold decrease in risk of HIV-related death, compared with risk of WHO 4 condition, for given level of CD4 count, viral load and age (fold\_decr\_hivdeath) | 0.25 |
| Increase in death rate in 3 months period in which a WHO 4 condition is present (incr\_death\_rate\_adc)  | 5 |
| Increase in death rate in 3 months period in which TB is present (incr\_death\_rate\_tb) | 2 |

**Circumcision, HIV testing, linkage to care and retention in pre-ART care and on ART**

Table d. Parameters and distributions on HIV care delivery (including circumcision)

|  |  |
| --- | --- |
| **Parameter (variable name in the program)** | **Value (or distribution)** |
| Circumcision |
| Baseline prevalence of circumcision (before medical circumcision was rolled out for HIV prevention) (prev\_circ) | 42% |
| Start date of medical circumcision roll out (mc\_int) | 2008 |
| Annual increase in probability of male circumcision per 3 months (incr\_anprob\_circ) | * 1. between date of starting rolling out and mid-2009

0.015 between 2009.5-2010.5 |
| HIV testing |
| Date of start testing for HIV in antenatal clinics | 1990 |
| Date of start of testing for HIV (date\_start\_testing) | 1996 |
| Annual rate of increase in testing probability over time (test\_increase\_rate) | Uniform(0.02,0.035) |
| Annual quadratic increase in the probability of being tested in antenatal clinics for pregnant women (rate\_testanc\_inc – only up to first trimester of 2013) (rate\_testanc\_inc) | 0.00195 |
| Probability per 3 months of being tested for HIV for those with WHO stage 4 condition (test\_rate\_who4) in 1996 | 0.2 |
| Absolute rate of increase per 3 months of test\_rate\_who4; up to 2015) (inc\_ test\_rate\_who4) | 0.008 |
| Probability per 3 months of being tested for HIV for those with TB (test\_rate\_tb) in 1996 | 0.1 |
| Absolute rate of increase per 3 months on test\_rate\_tb; up to 2015. (inc\_test\_rate\_tb) | 0.005 |
| Probability per 3 months of being tested for HIV for those with WHO stage 3 condition (test\_rate\_who3) in 1996 | 0.03 |
| Absolute rate of increase per 3 months on test\_rate\_who4; up to 2015. (inc\_ test\_rate\_who4) | 0.0012 |
| Proportion of the population resistant to HIV testing (no probability of testing unless with WHO 4 condition, in which case they will be tested) (rate\_noreached) | lognormal(ln0.25,0.12) |
| Linkage to care |
| Probability of being linked to care at 3 months since diagnosis (for people without WHO4, WHO3 events in the last 3 months or TB in the last 6 months) (prop\_linkedtocare\_diag) | 0.4 |
| Probability of being linked to care at 3 months since diagnosis for people with WHO4, WHO3 events in the last 3 months or TB in the last 6 months | 1 |
| Retention in pre-ART care and on ART |
| Rate of loss to follow-up per 3 mths among those not on ART (rate\_lost) in the first year since diagnosis, (actual probability also depends on average willingness to adhere – see model details); after 1 year since diagnosis the parameter is a quarter of rate\_lost: 0.075 | 0.3 |
| Probability (per 3 mths) of return to care for person lost within 1st year from diagnosis, if no WHO 4 condition present. | 0 |
| Probability (per 3 mths) of return to care for person lost after at least 1 year since diagnosis, if no WHO 4 condition present (rate\_return) (actual probability also depends on average willingness to adhere – see model details) | 0.04 |
| Probability (per 3 mths) of return to care for person lost if WHO 4 condition occur | 0.8 |
| Probability (per 3 mths) of simultaneously being lost to follow-up amongst those stopping ART (prob\_lost\_art) (actual probability also depends on average willingness to adhere – see model details - see for probability of ART interruption) | 0.3 |
| Base probability (per 3 mths) of restart of ART in those remaining under care who have stopped/interrupted ART (this is also influenced by presence of WHO 3 or 4 conditions) (rate\_restart) | 0.4 |

**ART**

The model of progression of HIV and the effect of ART has been shown to provide a generally close fit to observed data relating to the effect of ART, comparing the output of the model with data coming mainly from Europe and South Africa (Morgan et al. 1997; Post et al. 2001; Todd et al. 2007).

Table e. Parameters determining ART roll-out and effect of ART on progression

|  |  |
| --- | --- |
| Parameter (variable name in the program) | Value (or distribution) |
| Delivery of ART care |
| ART introduction date (ART\_intro\_date) | 2002 |
| PMTCT introduction date with single dose nevirapine (date\_sd\_nvp) | 2004 |
| Annual rate of increase in use of PMTCT in pregnant women attending ANC (rate\_sd\_nvp - up to a maximum of 97.5) | 0.25 |
| Probability (per 3 months) of switching to second line treatment, given first line failure (by whatever definition is being used) (pr\_switch\_line) | 0.25 |
| Adherence to antiretroviral therapy |  |
| Pattern of underlying adherence across individuals, expressed as proportion of doses taken (adhav) | 15% adhav=0.49 15% adhav=0.7950% adhav=0.9020% adhav=0.95 |
| Reduction in adherence resulting from presence of TB or a WHO 4 condition (red\_adh\_tb\_adc) | 0 |
| Average reduction in adherence resulting from current toxicity (the actual reduction varies by individual person) (red\_adh\_tox\_) | 0 |
| Additional "effective" adherence for people on NNRTI regimens due to longer half life (add\_eff\_adh\_nnrti) | 0.1 |
| Average (amount differs by individual) increase in adherence in patients who have a measured VL in the last 6 months above 1,000 copies/ml (adh\_effect\_of\_vm\_pop) | 0.2 |
| Extent to which the average CD4 change is more favourable on a virologically failing PI/r-regimen compared with an NNRTI-regimen (poorer\_cd4\_rise\_on\_failing\_nnrti) | -10 |
| CD4 |
| Standard deviation for intra-subject variation in CD4 count and (sd\_cd4) | 1.2 |
| Standard deviation for the measurement error in CD4 count (sd\_measured\_cd4) | 2.0 |
| Standard deviation representing inter-patient variation in rate of CD4 rise - when CD4 is rising (patient\_cd4\_rise\_art) (after 2 years on ART is divided by 4) | Lognormal(0,0.5) |
| ART interruption |
| Underlying probability (per 3 mths) of interrupting ART (actual probability also depends on presence of current toxicity and average adherence – see model details) (rate\_int\_choice) | 0.02 |
| Probability (per 3 mths) of drug stock out, and hence ART interrupted (prob\_supply\_interrupted) | 0.01 |
| Probability (per 3 mths) that drug supply resumed after stock-out (prob\_supply\_resumed) [i.e 80% chance that stock-out lasts 3 months only] | 0.8 |
| Acquisition of ART resistance mutations |
| Risk of NNRTI resistance emergence due to stopping an NNRTI regimen (due to effective monotherapy due the long half-life) | 0.05 |
| Fraction of people who stop ART (and are still visiting the clinic) for whom the clinic is aware of the interruption. If they are not aware they treat the patient as if they were on ART (and hence may switch to the next line having wrongly classified them as virologically failing) (clinic\_aware\_int\_frac) | 0.5 |
| Probability of an NNRTI resistance mutation arising in the 3 months after having stopped NNRTI (risk\_res\_stopping\_nn) | 0.05 |
| Probability per pregnancy of NNRTI resistance emergence in pregnant women receiving single dose nevirapine for MTCT (prob\_nnresmaj\_sd\_nvp) | 0.35 |
| Probability per pregnancy of NNRTI resistance emergence in pregnant women receiving AZT during pregnancy, sdNVP + AZT during labour and TDF + FTC single dose after delivery(prob\_nnresmaj\_dual\_nvp) | 0.045 |
| Probability per 3 months of loss of NNRTI mutations, acquired due to PMTCT, from majority virus to become only in minority virus (rate\_loss\_nnres\_pmtct\_maj) | 0.25 |
| Probability per 3 months of loss of virus with NNRTI mutations acquired due to PMTCT, from minority virus to effectively be extinct altogether (rate\_loss\_nnres\_pmtct\_min) | 0.25 |

## Full model details

### Demographic model

The model runs for 45 years from 1989, with variables updated every 3 months. The first reported heterosexual AIDS case in South Africa was in 1988. Each run of the model simulates a cohort of 100,000 individuals, although only 34,300 alive and aged over 15 in 1989. In order to fit our model to observed data and to produce output measures, expressed in absolute terms, which are relevant for South Africa, this modelled population size needs to be multiplied by the ratio between the estimated adult population size in mid-2011(2010) and the size of the modelled population. Estimates of the South Africa adult (15-65 years old) population are similar across different sources (2010; Central Intelligence Agency 2012). By mid 2032, the World Bank estimates that 37 million people aged 15-65 are projected to be living in the Republic of South Africa(The World Bank 2011).

#### Determination of age in 1989 and general population death rates

The initial age and gender distribution is determined on the basis of the South African Census conducted in 1996(Statistics South Africa 1996), because this is the first SA census were information were collected for all South Africa. 48.2% of the population is assumed to be male and the table below shows the age distribution of people within gender.

|  |  |  |
| --- | --- | --- |
| **Age group** | **Probability of being in age group in 1989** | **Distribution of people aged 15-65** |
| Males |
| -30-14 | 0.733 |  |
| 15-24 | 0.091 | 0.34 |
| 25-34 | 0.072 | 0.27 |
| 35-44 | 0.067 | 0.20 |
| 45-54 | 0.053 | 0.12 |
| 55-64 | 0.019 | 0.07 |
| Females |
| -30-14 | 0.716 |  |
| 15-24 | 0.094 | 0.33 |
| 25-34 | 0.077 | 0.27 |
| 35-44 | 0.054 | 0.19 |
| 45-54 | 0.034 | 0.12 |
| 55-64 | 0.025 | 0.09 |

\* the actual age of a person in a given group in 1989 is determined by sampling from a Uniform distribution.

This distribution is chosen to reflect the growth in population seen in South Africa(2010; Statistics South Africa 1996; Statistics South Africa 2005). Thus over half of simulated people have an age below 15 in 1989 and a constant birth rate is assumed until the end of 2012.

The only variable that is modelled and updated up to reaching the age of 15 (when becoming potentially sexually active) is age itself. The “youngest” person in 1989 is age -30 (i.e. will be born in 2019 and reach age 15 in 2034, when the modelled period ends).

In each point in time, each individual has an underlying age and gender specific probability of dying. These underlying age and gender specific death rates are those estimated in South Africa in 1997(Statistics South Africa 2006), before the significant impact of HIV-related deaths.

Age specific death rates for uninfected people (per 1,000 person-years) are as follows:-

|  |  |
| --- | --- |
| **Age group** | **Annual death rate** |
| **Males** | **Females** |
| 15-19 | 2 | 1.5 |
| 20-24 | 3.2 | 2.8 |
| 25-29 | 5.8 | 4.0 |
| 30-34 | 7.5 | 4.0 |
| 35-39 | 8.0 | 4.2 |
| 40-44 | 10.0 | 5.5 |
| 45-49 | 12.0 | 7.5 |
| 50-54 | 19.0 | 11.0 |
| 55-59 | 25.0 | 15.0 |
| 60-64 | 35.0 | 21.0 |
| 65-69 | 45.0 | 30.0 |
| 70-74 | 55.0 | 38.0 |
| 74-79 | 65.0 | 50.0 |
| 80-84 | 100.0 | 70.0 |
| 85 or more | 400.0 | 150.0 |

HIV infected people will have an additional probability of dying from HIV related causes, as described in section “”.

### Model of sexual behaviour and risk of HIV acquisition

In this model risk behaviour is characterized by two variables representing, respectively, the number of “short-term” or “casual” partners a person has sex with without using condom from this point onwards called condom-less short-term (CLST) partners and whether the person has a current “long-term” or “main” partner the person has sex with without condom in each 3 month period, called condom-less long-term (CLLT) partner. This model does not distinguish on whether a person had sex with a person using condom effectively or did not had sex, because it assumes that if correctly used condom is 100% effective. Condom break can be treated as no condom use.

The risk behaviour is mainly determined by the level of condom-less sexual contacts required to produce an epidemic as described. Although some data on sexual behaviour for South Africa are available(Shisana et al. 2009), these data are often affected by social desirability bias and recall bias. Sexual risk behaviour tends to be under-reported particularly in women and higher levels of behaviour have to be assumed both to be consistent with levels of risk behaviour reported in men, and to generate an epidemic of the proportions observed (Shisana et al. 2005; Shisana et al. 2009). In addition, even if these data were not biased, it would be impossible to calibrate directly this model to these data because the number of sexual partner people have condom-less sex with is not collected.

In the South African national HIV prevalence, incidence, behaviour and communication survey(Shisana et al. 2009) information on age of sexual debut was collected among young people aged 15-24 and in all three surveys (in 2002, 2005, 2008) less than 10% had sex before the age of 15 years and no data are available on the age of first condom-less sex act. For simplicity the model assumes the minimum age of sexual debut is 15 years old. In the last two surveys(Shisana et al. 2005; Shisana et al. 2009) data on the age difference between sexual partners in people aged 15 to 19 years old were collected. In both surveys 98% of men had a partner within 5 years of their own age, while among women 81% in 2005 and 72% in 2008 had a sexual partner within 5 years of their age. In this model the CLLT partner is assumed to be in the same 10 years age-category, while CLST partners can belong to different age group, as illustrated in the age-mixing matrix (see Table 4).

The parameter values relating to sexual behaviour are therefore derived fitting the model outputs to observed data on HIV prevalence(Shisana et al. 2005; Shisana et al. 2009; South Africa National Department of Health 2010a).

In this model five parameters determine the sexual behaviour: the relative average sexual behaviour (x1), the skewness in the distribution of number of condomless sex partners (x2 and x3, with the former determining the most extreme numbers of sexual partners), the rate with which new CLLT partnerships are formed (x4), and the proportions of people who have a lifetime reduced likelihood of CLST partners (x5). Several risk behavioural model (combination of distribution of parameters) have been identified and the distributions indicated in section.

#### Determination of number of short term partners at period t

The numbers of condomless short-term (CLST) partners is assumed to depend on gender, age, propensity to be sexually active (x1), experiencing an AIDS defining condition, being diagnosed with HIV and change in risk behaviour in the general population.

In a given 3-month period it is generated at random, according to which of four risk behaviour groups the person was in for the previous period. The four groups are:

* zero CLST partners,
* one CLST partner,
* 2-10 CLST partners,
* 10 or more CLST partners

The initial distribution is sampled among the distributions indicated in Table 6. Each individual can pass from one of these categories to the other based on transition probabilities.

Transition probabilities *pgija* of moving from partner group *i* at time t-1 to partner group *j* at t in a person of gender *g* (0=males, 1=females) and age *a* are given by:

*pgija = fgij /(f­gi1 + Σj=2-4 (f­gij. rga))* for j=1 (0 casual partners)

*pgija = fgij. rga /(f­gi1 + Σj=2-4 (f­gij. rga))* for j=2-4

where *a* = 1-10 for age groups 15-, 20-, 25-, 30-, 35-, 40-, 45-, 50-, 55-, 60-, respectively. Values of rga, the factor determining relative level of sexual risk activity with short term partners(x1), gender and age-specific, are given in Table 1 (table 7 for alternative risk behavioural models[RBM]). Values of *f­gij*, the values determining probability of transitioning between short term partner risk behaviour groups are indicated in Table 2 (table 8 for alternative RBM).

Values of rga are modified at time t by the following factors:

* 0.01 if the subject belongs to that subset of people who experience only very low sexual risk activity in their life (Random 35% of men and 50% of women, *p\_rred\_p;* See table 9 for values of alternative RBM)
* 0.2 if the subject has a current AIDS defining disease,
* *0.*83 (the actual value is *ch\_risk\_diag\_newp*, sampled from the distribution indicated in the section “”) if the subject has been diagnosed with HIV in the last 6 months and by its square root afterwards.
* The change in risk behaviour with short term partners is assumed occurred in two phases: the first started between 1992 and end of 1998 (*date\_ch\_risk\_beh*, the value is sampled from the distribution indicated in the section “”) and finishes between 1999 and end of 2005 (*date\_ch\_risk\_beh\_2*, the value is sampled from the distribution indicated in the section “”)), the second phase finished between 2006 and end of 2009 (*date\_ch\_risk\_beh\_3*, the value is sampled from the distribution indicated in the section “”).

The rate of annual decrease in risk behaviour for the first (*rate\_ch\_risk\_beh*) and the second phase (*rate\_ch\_risk\_beh\_2*) are sampled from the distribution indicated in the section “”, up to a maximum reduction of 0.95. Afterwards no change in risk behaviour is assumed.

Actual transitions between groups for each individual followed are determined by random sampling. For the first two groups the number of partners in the period is given (i.e. no short term partners, 1 short term partner, respectively). When a person is in the 2-9 short term partners group the number of partners is determined by sampling from a Poisson(1.5), and when the transition is to > 10 short term partners the number of partners is determined by sampling from a Poisson(2) and multiplied by the parameter *swn* (the value is sampled from the distribution indicated in the section “) that determine the skewness of this distribution (x2).

#### Determination of having a long term (unprotected sex) partner at period t

As for short-term partners, only condom-less sex long-term partnerships are modelled. Thus if a person has a long-term partner but condoms are used on all occasions of sexual intercourse in a specific 3-month period then this is not counted as having a condomless long-term (CLLT) partner for that period.

In 1989, before any population level reductions in risk behaviour and without widespread availability of condom, around 60% of the population is assumed to have a CLST partner (See Table 10 for details). At the beginning of the epidemic, at each period, people with no current CLLT partner have an age-dependent probability of starting having sex without using condom with a LTP as indicated in table 9. This can be due to (re-)starting having condomless sex with an existing longer term partner or starting a new partnership which involves condomless sex.

At the time a CLLT partnership is started, it is classified into 3 duration groups, each with a different tendency to endure. The percent of people in each group is dependent on age and is shown in Table 3.At time period, t, for people with a long-term partner, the probability of the partnership continuing is 0.75 if duration category is 1, is 0.95 if duration category is 2, and 0.98 if duration category is 3.

At time period, t, for people with a long term partner, the probability of the condomless sex partnership continuing is:

* (1-(0.25\**ch\_risk\_beh\_ep*)) if duration category is 1,
* (1-(0.05\**ch\_risk\_beh\_ep*)) if duration category is 2,
* (1-(0.02\**ch\_risk\_beh\_ep*)) if duration category is 3,

The parameter *ch\_risk\_beh\_ep*assumes value 1 before*date\_ch\_risk\_beh,* which is the date when it is assumed a change in sexual behaviour in the population initiated (condom became more widely available). After *date\_ch\_risk\_beh,* the duration of these condom-less sex relationships is reduced, because *ch\_risk\_beh\_ep* (see distribution in section “Parameters values and distributions “) assumes value ≥1.This parameter represent the fold increase in the proportion who do not have condom-less sex, of those who had condom-less sex at the time before, relative to before date\_ch\_risk\_beh.

In addition the probability of having a CLLT partner is reduced by a factor *ch\_risk\_diag* in the 3 month period after a partner’s diagnosis, if a partner has HIV and is diagnosed. (see distribution in section “Parameters values and distributions “).

**Table 1. Values of rga (factor determining relative level of sexual risk activity)**

------------------------------------------------------------------------------------------

Age group Males females

(a=1,10) (g=1) (g=2)

------------------------------------------------------------------------------------------

15- 0.65 1.50

20- 0.65 1.50

25- 1.00 1.00

30- 0.80 0.80

35- 0.65 0.50

40- 0.50 0.35

45- 0.40 0.10

50- 0.35 0.05

55- 0.25 0.04

60- 0.15 0.02

------------------------------------------------------------------------------------------

**Table 2. Values of f­gij (values determining probability of transitioning between short term partner risk behaviour groups)**

--------------------------------------------------------------------------------------------------------------------

Short term partners Short term partners group in period t

group in period t-1

 0 1 medium high

 Poisson Poisson

 mean 1.5 mean 2

 x *swn\**

--------------------------------------------------------------------------------------------------------------------

**Males**

0 0.89 0.08 0.03 0.00

1 0.80 0.15 0.05 0.00

medium 0.35 0.27 0.38 0.00

high --- --- --- ---

**Females**

0 0.93 0.05 0.02 0.00025

1 0.86 0.11 0.03 0.0005

medium 0.54 0.08 0.38 0.001

high 0.05 0.05 0.10 0.800

-----------------------------------------------------------------------------------------------------------------------

The values reported in the table above refer to the RBM more often used. Different RBM have been considered (see table 7)

**Table 3. Percent of newly formed long term partnerships classified into each of three duration groups, each of which has a different tendency to endure (higher class, more durable).**

Age 1 2 3

-----------------------------------------------------------------------------------------------

15-44 30% 30% 40%

45-54 30% 50% 20%

55-64 30% 70% 0%

-----------------------------------------------------------------------------------------------

**Table 4. Sexual mixing by age and gender. The proportion of short term partnerships formed by men in age group am which are with females of age group af (za­m,af) and the proportion of short term partnerships formed by females in age group af which are with men of age group am (z af,a­m).**

 Females

 Age group (af)

Males

Age group (am) 15-24 25-34 35-44 45-54 55-64

----------------------------------------------------------------------------------------

15-24 0.865 0.11 0.025 0.00 0.00

25-34 0.47 0.43 0.10 0.00 0.00

35-44 0.30 0.50 0.20 0.00 0.00

45-54 0.43 0.30 0.23 0.03 0.01

55-64 0.18 0.18 0.27 0.27 0.10

----------------------------------------------------------------------------------------

 Males

 Age group (am)

Females

Age group (af) 15-24 25-34 35-44 45-54 55-64

----------------------------------------------------------------------------------------

15-24 0.43 0.34 0.12 0.10 0.01

25-34 0.09 0.49 0.30 0.10 0.02

35-44 0.03 0.25 0.34 0.25 0.13

45-54 0.00 0.00 0.05 0.25 0.70

55-64 0.00 0.00 0.00 0.10 0.90

----------------------------------------------------------------------------------------

**Table 5a and 5b. Sexual risk behaviour before introduction of HIV for one example epidemic using modal values for parameters (mean over 30 runs).**

**Table 5a.**

|  |  |
| --- | --- |
|  | **% with condomless sex partners (short or long term) in past year** |
| **Age group** | **≥1** | **≥2** | **≥5** | **≥10** | **≥1** | **≥2** | **≥5** | **≥10** |
| **Male** | **Females** |
| **15-** | 71% | 29% | 1.2% | 0.02% | 75% | 41% | 2.6% | 2.5% |
| **25-** | 85% | 46% | 2.0% | 0.02% | 82% | 36% | 1.8% | 1.8% |
| **35-** | 74% | 31% | 1.2% | 0.01% | 67% | 17% | 0.8% | 0.8% |
| **45-** | 65% | 21% | 0.8% | 0.01% | 54% | 4% | 0.1% | 0.1% |
| **55-** | 53% | 10% | 0.4% | 0.00% | 45% | 2% | 0.1% | 0.1% |

**Table 5b.**

|  |  |
| --- | --- |
|  | **% with long term condomless sex partner**  |
| **Age group** | **Males** | **Females** |
| **15-** | 48% | 48% |
| **25-** | 57% | 57% |
| **35-** | 48% | 47% |
| **45-** | 41% | 41% |
| **55-** | 35% | 34% |

#### Alternative sexual behavioural models

As mentioned, an alternative sexual behaviour structure has also been developed, the table below shows how it differs compared to the main one (referred to as RBM =17).

The main one is called the “asymmetric” model because it is asymmetric by gender, with the proportion of women having > 10 partners higher than for men, representing sex workers.

The probability of sampling a symmetric model was 0.4: 0.05 for respectively RBM 2 and 5, 0.1 for respectively RBM 7, 10 and 12. In the remaining 60% of cases an asymmetric RBM is sampled: 0.2 for RBM 17, 0.1 for respectively RBM 9, 11, 13 and 4.

**Table 6. Distribution of condom-less sex short term partners at time 0, at the beginning of the epidemic**

RBM Symmetric Asymmetric Symmetric Asymmetric (alternative) (alternative)

CLST partners Males (g=1) Females (g=2)

in period t

0 0.55 0.9 0.55 0.93

1 0.30 0.07 0.30 0.05

2-9 (Poisson(1.5)) 0.05 0.03 0.05 0.0185

> 10 (Poisson(2) x *swn)* 0 0 0 0.0015

There is a 5% chance that the symmetric RBM is sampled, 95% that the asymmetric is sampled

**Table 7. Values of f­gij (values determining probability of transitioning between CLSTP risk behaviour groups) for different risk behavioural mode (RBM)**

Table 7a. Values of f­gij for RBM 4,9,11,13,17 (Probability of these RBM being sampled 0.6)

--------------------------------------------------------------------------------------------------------------------

CLST partners CLST partners in period t

in period t-1

 0 1 2-9 > 10\*

 Poisson Poisson

 mean 1.5 mean 2 x X2

--------------------------------------------------------------------------------------------------------------------

Males

0 0.89 0.08 0.03 0.00

1 0.80 0.15 0.05 0.00

2-9 0.35 0.27 0.38 0.00

> 10 0.00 0.00 0.00 0.00

Females

0 0.93 0.05 0.02 0.00025

1 0.86 0.11 0.03 0.0005

2-9 0.53 0.08 0.38 0.001

> 10 0.005 0.00 0.00 0.995

--------------------------------------------------------------------------------------------------------------------

Table 7b. Values of f­gij for RBM 10,12 (Probability of these RBM being sampled 0.2)

--------------------------------------------------------------------------------------------------------------------

CLST partners CLST partners in period t

in period t-1

 0 1 2-9 > 10\*

 Poisson Poisson

 mean 1.5 mean 2 x X2

--------------------------------------------------------------------------------------------------------------------

Males

0 0.8 0.17 0.03 0.00001

1 0.9 0.08 0.02 0.00001

2-9 0.15 0.35 0.5 0.00001

> 10 0.25 0.05 0.20 0.5

Females

0 0.8 0.17 0.03 0.00025

1 0.9 0.08 0.02 0.00025

2-9 0.15 0.35 0.50 0.001

> 10 0.04 0.03 0.03 0.9

--------------------------------------------------------------------------------------------------------------------

Table 7c. Values of f­gij for RBM 2,7 (Probability of these RBM to be sampled 0.15)

--------------------------------------------------------------------------------------------------------------------

CLST partners CLST partners in period t

in period t-1

 0 1 2-9 > 10\*

 Poisson Poisson

 mean 2.3 mean 2 x X2

--------------------------------------------------------------------------------------------------------------------

Males and Females

0 0.77 0.13 0.10 0.00

1 0.55 0.32 0.13 0.00

2-9 0.15 0.70 0.15 0.00

> 10 0.01 0.00 0.00 0.99

--------------------------------------------------------------------------------------------------------------------

Table 7d. Values of f­gij for RBM 5 (Probability of these RBM to be sampled 0.05)

--------------------------------------------------------------------------------------------------------------------

CLST partners CLST partners in period t

in period t-1

 0 1 2-9 > 10\*

 Poisson Poisson

 mean 1.5 mean 2 x X2

--------------------------------------------------------------------------------------------------------------------

Males

0 0.8 0.17 0.03 0.00

1 0.9 0.08 0.02 0.00

2-9 0.15 0.35 0.5 0.00

> 10 0.00 0.00 0.00 0.00

Females

0 0.8 0.17 0.03 0.00025

1 0.9 0.08 0.02 0.00025

2-9 0.15 0.35 0.5 0.001

> 10 0.005 0.005 0.00 0.99

--------------------------------------------------------------------------------------------------------------------

## The value for the factor X2 is indicated as *swn* in the section “Parameters values and distributions”.

**Table 8. Values of rga (factor determining relative level of sexual risk activity)**

RBM 2,7 4,9, 17 5,10,12 2,7 4,9, 17 5,10,12 11,13 11,13

Age group Males (g=1) Females (g=2)

(a=1,10)

15- 0.75 0.65 0.35 0.85 1.15 1.5 3.2 1.5

20- 0.75 0.65 0.45 1 1.15 1.5 3.5 1.5

25- 1 1 1.3 1.4 1 1 3 1.3

30- 1 0.8 0.5 1.2 0.85 0.8 1.5 1

35- 0.65 0.65 0.35 1 0.55 0.5 0.7 0.8

40- 0.45 0.5 0.3 0.8 0.35 0.35 0.7 0.6

45- 0.35 0.4 0.3 0.6 0.2 0.1 0.7 0.5

50- 0.23 0.35 0.15 0.5 0.15 0.05 0.6 0.4

55- 0.18 0.25 0.25 0.4 0.08 0.04 0.4 0.3

60- 0.10 0.15 0.15 0.3 0.04 0.02 0.3 0.2

**Table 9. Proportion of the population who experience only very low sexual risk behaviour (*p\_rred\_p*) and reduction in sexual behaviour in these subsamples**

RBM Males (g=1) Females (g=2) Reduction in sexual behaviour

2 0.2 0.2 0.01

4 0.35 0.5 0.1

5,7 0.2 0.35 0.01

9-13, 17 0.35 0.5 0.01

**Table 10. Proportion with a condom-less sex long-term partner(CLLT) and probability of starting a CLLT partnership, in 1989, at the beginning of the epidemic**

RBM 2,4,5,7, 17 2,5,7 4,9, 17

 9-13 10,12 11,13

**Age group Proportion with a CLLT Probability of starting a CLLT partnership**

15- 0.4 0.42 0.15 0.10 0.07

25- 0.5 0.65 0.10 0.07 0.09

35- 0.5 0.65 0.05 0.05 0.035

45- 0.5 0.58 0.01 0.01 0.035

55- 0.5 0.45 0.005 0.005 0.02

#### Determination of number of short term partners who are HIV infected at time t

For each short term partner that a subject has at time t, the probability that the partner is infected is calculated. This is dependent on the prevalence of HIV in those of the opposite gender, taking consideration of age mixing. If the subject is of gender *g* and age group *a*, then for each short term partner the first step is to determining by random sampling the age group, *a’*, of the short term partner (in fact, for simplicity, all short term partners at time t are assumed to be in this same age group). The gender and age mixing probabilities (i.e. the proportion of short term partnerships formed by men in age group am which are with females of age group af (zam,af) and the proportion of short term partnerships formed by females in age group af which are with men of age group am (zaf1,am)) used to determine this are given by values of in Table 6.

Then, for the given partner (of gender 1-g and age group a’), the risk that the partner is infected is then given by

ha,g(t) = Σ a’,1-g L1(t-1)/ Σa’,1-g L(t-1)

where Σ a’,1-gis the sum over all subjects of age group a’ and gender 1-g, L1(t-1) is the number of infected short term partners at time t-1, and L(t-1) is the number of short term partners at time t-1.

Since we assume that all short term partners at time t are in this same age group, the total number of infected short term partners that the subject has at time t, L1(t), is then given by

L1(t) = Min ( Poisson (ha,g(t).L(t) ) , L(t) )

The distribution of numbers of partners by age and gender, before introduction of HIV, is illustrated for one example epidemic in Table 5.

#### Determination of probability that a long term partner is HIV infected at time t

E1(t) indicates whether the subject has a long term (condomless sex) partner who is infected (E1(t) =1 if infected, else E1(t) = 0). A long term partner at time t can be infected either because:

1. a new long term partnership has been formed and the partner was already infected,
2. because a long term partner at t-1, which has remained a long term partner at time t, has become infected, or
3. because a long term infected longer partner has remained as a long term partner.

For (i):E1(t) = 1 if L1(t-1) > 1 (i.e. if the subject had a short term partner at time t-1 who was

infected then it is assumed that the long partner at time t is infected)

For (ii):The probability that a long term partner of a subject of age group a and gender g becomes

infected is derived from the HIV incidence at t-1 for age group a (i.e. the same age group) and gender 1-g, ia,1-g(t-1) (which is given by the number of subjects newly infected in age group at time t-1 / number of HIV-uninfected subjects in age group at t-1)

E1(t) = 1 if a sampled random variable from Uniform(0,1) <ia,1-g(t-1), else E1(t) = 0

In order to maintain balance, for each gender, between the number of uninfected people with a long term partner who is infected, and the number of infected people with a long term partner who is uninfected, this incidence ia,1-g(t-1) is modified at time t dependent on the degree of balance at time t-1.

For (iii):If E1(t-1) = 1 and E(t) > 1 then we assign E1(t) = 1

#### Determination of the risk of infection from a short term partner

For each HIV infected short term partner of a subject of gender *g* and age group *a* the viral load group, *v*, of the partner is obtained by sampling from the viral load distribution of those of the opposite gender. Thus we sample from Uniform(0,1), where the probability of the partner having viral load in group v is given by:

Σv L1(t-1)/ ΣL1(t-1)

where Σv is the sum over all HIV-infected subjects in viral load group v and Σ is the sum over all HIV-infected subjects.

The table below shows the viral load groups, *v*, of the infected partner and the rate of transmission per 3 month, tv, of the subject being infected by the partner.

 --------------------------------------------------------------------------------------------------------------------------

Group Viral load groups of the partner (v) tv

 --------------------------------------------------------------------------------------------------------------------------

< 2.7 log cps/mL Normal (*tr\_rate\_undetec\_vl*,0.000025)

2.7-3.7 log cps/mL Normal (0.01,0.0025)

3.7-4.7 log cps/mL Normal (0.03,0.0075)

4.7-5.7 log cps/mL Normal (0.06,0.015)

> 5.7 log cps/mL Normal (0.1,0.025)

primary infection Normal (*tr\_rate\_primary*,0.075)

 --------------------------------------------------------------------------------------------------------------

## These are based on (Hollingsworth et al. 2008) and are the rate of transmission per 3 months from a long term partner, by viral load. The transmission rate for a short term partner are multiplied by the parameter *fold\_tr\_newp* (See distribution in section “Parameters values and distributions”) due to the assumed lower number of sex acts. The probabilities of getting infected with HIV are increased by *fold\_change\_w*fold (See distribution in section “Parameters values and distributions”) for female subjects aged > 20, by *fold\_change\_yw*fold forwomen aged < 20 years old, by *fold\_change\_sti*-fold (See distribution in section “Parameters values and distributions”) if the person has an existing STI and by*fold\_circ*fold if the subject is a man who is circumcised. The risk of a new STI in any one three month period is given by the number of short term condom-less sex partners / 20 (or 1 if > 20 short term partners))(Cohen 1998; Nicolosi et al. 1994; Yang et al. 2010). The reduction in HIV acquisition in men circumcised in heterosexual relationship is based on the RCT which evaluated the efficacy of male circumcision in reducing HIV acquisition(Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007).

Male circumcision is assumed to be prevalent in *prev\_circ*(See distribution in section “Parameters values and distributions”) of men, as reported(WHO & UNAIDS 2012), and it is assumed medical circumcision is rolled out between *mc\_int*(See value in section “Parameters values and distributions”) and end of 2012, with an annual increase probability of circumcision of *incr\_anprob\_circ*, in men not diagnosed with HIV, to give a number of male circumcision as planned(WHO & UNAIDS 2012).

Uncertainty in the transmission rate for different viral load groups (except for the rate of transmission in primary infection, and the arte of transmission when plasma viral load is < 500 cps/mL ) is incorporated by sampling for each epidemic (run of the model program) the parameter *fold\_tr*(See distribution in section “Parameters values and distributions”), by which the transmission rate is multiplied. Uncertainty in the rate of transmission in primary HIV infection is incorporated by sampling a value of the parameter *tr\_rate\_primary* for each epidemic (See distribution in section “Parameters values and distributions”), and uncertainty in the transmission rate when plasma viral load is < 500 cps/mL is included by sampling the value for parameter *tr\_rate\_undetec\_vl* (See distribution in section “Parameters values and distributions”)

We assume that super-infection can occur(i.e. a person can be re-infected with HIV with consequent risk of acquiring new mutations), in the same way as HIV infection occurs in the first place.

Realization of whether the subject is infected by each short term partner is determined by sampling from Uniform(0,1).

####  Determination of the risk of infection from a long term partner

Infected long term partners at time t are classified by whether they are in primary infection (if infection occurred at t-1), whether they are diagnosed with HIV, whether they are on ART, and whether their current viral load is < 2.7 cps/mL or not.

The proportion of subjects with HIV who are diagnosed at time t-1, TD(t-1) / T1(t-1), is compared to the proportion of long term partners with HIV who have HIV diagnosed at time t-1, pDe(t-1) and the differenceis calculated, dDe(t-1):

dDe(t-1) = TD(t-1) / T1(t-1) – pDe(t-1)

where TD(t-1) is the total number of subjects diagnosed with HIV at time t-1and T1(t-1) is the total number of subjects with HIV (diagnosed and undiagnosed) at time t-1. If the difference is above 0, then the proportion of long term partners with HIV who have HIV diagnosed at time t, pDe(t) is assumed the same as the difference, dDe(t-1).

The proportion of those diagnosed who are on ART, and the proportion of those on ART who have viral load < 2.7 log cps/mL are determined in a similar manner. In this way the proportions diagnosed with HIV, on ART, and with current viral load is < 2.7 cps/mL are kept similar for the long term partners as in the simulated subjects themselves.

Risk of infection from a long term infected partner is determined by Normal (*tr\_rate\_primary*, 0.075) if the existing partner is in primary infection (i.e. infected at t-1), Normal (*tr\_rate\_undetec\_vl*, 0.000025) if the existing partner has viral load < 2.7 cps/mL, and Normal (0.05, 0.0125) otherwise.

#### Transmitted resistance

The viral load group of the person who infected the subject is known, as indicated above. For a subject infected by a person in viral load group *v* the probability of a resistance mutation being present in the infected person is given by

Σv,r=1 L1(t-1)/ Σv L1(t-1)

where Σv, r=1 is the sum over all HIV-infected subjects in viral load group *v* for whom a resistance mutation is present in majority virus and Σvis the sum of all HIV-infected subjects in viral load group v. Again, realization of whether the subject is infected by a person with at least one resistance mutation in majority virus is determined by sampling from Uniform(0,1).

For subjects infected from a source partner with a resistance mutation, the probability that a specific mutation, m, is present in the source is given by

Σr=1,m=1 L1(t-1)/ Σr=1 L1(t-1)

where Σr=1,m=1 is the sum over all HIV-infected subjects with mutation *m* present in majority virus and Σr=1 is the sum over all HIV-infected subjects with at least one resistance mutation in majority virus.

If a given resistance mutation, *m*, is present in the source partner, the probability that the mutation is both transmitted and survives in the subject (i.e. that its presence will affect future response to drugs for which the mutation confers reduced sensitivity) is mutation specific, as shown in Table 11.

We consider uncertainty in the extent to which transmitted resistance mutations are effectively immediately lost (even from minority virus) by sampling from a distribution for the parameter *res\_trans\_factor* (See distribution in section “Parameters values and distributions”).

**Loss from majority virus of transmitted mutations**

There is a probability per 3 months of loss of persistence of transmitted mutations from majority virus to minority virus (same for each mutation) *rate\_loss\_persistence*(See distribution in section “Parameters values and distributions”).

#### Example results from epidemics simulated used modal values of parameter distributions

To illustrate some features of the epidemics generated, Table 12 shows the proportion of people with at least one (at least two) condomless sex partners in the past year by HIV status and year using modal values for parameters. Table 13 shows the proportion of new infections that have been acquired from a person in primary HIV infection by year, and the proportion of new infections that have been acquired from a long term partner by year. Table 14 shows HIV prevalence by age and gender and calendar year.

**Table 11. Table of probabilities that for a given mutation present in the source partner the mutation is both transmitted and survives in the subject (based on evidence from studies comparing distribution of resistance mutations between treated and antiretroviral naïve populations; e.g. (Corvasce et al. 2006; Turner et al. 2004))**

Mutation Probability that for a given mutation present in

the source partner the mutation is both transmitted and survives in the subject

----------------------------------------------------------------------------------------------------------------------------------------

M184V 0.2

K65R 0.2

L74V 0.5

Q151M 0.5

Thymidine analogue mutations (TAMS) 0.5

NNRTI mutation 0.6

PI (lopinavir) mutations 0.5

(30,32,33, 46,47,48,50L,50V,54,76,82,84,90)

----------------------------------------------------------------------------------------------------------------------------------------

**Table 12. Proportion of people with at least one condomless sex partner in the past year 3 months by HIV status (mean over 30 runs).**

 1990 1995 2000 2005 2010

----------------------------------------------------------------------------------------------------------------------------------------

All pop 24% 24% 18% 15% 13%

HIV+ 59% 41% 28% 20% 16%

HIV + --- 40% 23% 17% 14%

diagnosed

----------------------------------------------------------------------------------------------------------------------------------------

## Table 13. Origin of new infections for the median over the simulations which provide a good fit as defined in section “Calibration of the HIV Synthesis Heterosexual Transmission Model to South Africa”. This shows the proportion of new infections that have been acquired from a person in primary HIV infection by year, and the proportion of new infections that have been acquired from a long term partner by year. For infections from people with primary infection, there are little data from sub-Saharan Africa to our knowledge. For proportion of people infected by a long term partner, compare with (Dunkle et al. 2008).

 Status of source partner

 Primary infection Long term partner

 1990 2000 2010 1990 2000 2010

-----------------------------------------------------------------------------------------------------------------------------

Overall 88% 43% 33% Male 0% 21% 41%

 Female 45% 60% 68%

-----------------------------------------------------------------------------------------------------------------------------

**Table 14. Median HIV prevalence (%) by gender and age using the simulations which provide a good fit as defined in section “Calibration of the HIV Synthesis Heterosexual Transmission Model to South Africa”.**

 Males Females

1990

----------------------------------------------------------------------------------------------------------------------------------------

Age group

15- 0.2 0.2

25- 0.4 0.2

35- 0.3 0.1

45- 0.2 0.05

55- 0.00 0.00

1995

----------------------------------------------------------------------------------------------------------------------------------------

Age group

15- 4.8 5.5

25- 7.5 7.0

35- 5.5 4.5

45- 3.9 2.5

55- 2.4 0.7

----------------------------------------------------------------------------------------------------------------------------------------

2000

----------------------------------------------------------------------------------------------------------------------------------------

Age group

15- 7.3 12.8

25- 14.5 17.8

35- 11.8 13.3

45- 7.7 6.8

55- 4.7 2.0

----------------------------------------------------------------------------------------------------------------------------------------

2005

----------------------------------------------------------------------------------------------------------------------------------------

Age group

15- 7.1 12.7

25- 18.7 25.2

35- 15.9 21.2

45- 9.4 10.7

55- 5.1 3.6

2010

----------------------------------------------------------------------------------------------------------------------------------------

Age group

15- 5.8 10.7

25- 18.7 27.8

35- 18.3 28.0

45- 11.2 14.7

55- 5.7 5.5

----------------------------------------------------------------------------------------------------------------------------------------

### Natural history of HIV infection

## The model of the natural history of HIV and the effect of antiretroviral therapy has been derived previously and validated (see (Phillips et al. 2007; Phillips et al. 2008), and associated supplementary material). Below we set out the structure of the model and explain what parameters represent. There is uncertainty associated with many of the values (see parameter distributions in section “Parameters values and distributions”).

#### Initial viral load and CD4 count

Initial log10 viral load (Vset) is sampled from Normal(4.0,0.5)

The maximum viral load ‘set point’ is defined to be 6.5.

This viral load (Vset) is assumed to be that reached after primary infection. It is not used to determine the risk of transmission in primary infection itself.

Initial CD4 count, modelled on the square root scale, is partially dependent on initial viral load and given by

Square root CD4 count = *mean\_sqrtcd4\_inf* - (2 x Vset) + Normal(0,2)

Or equivalently, the CD4 count (not on square root scale) is approximately distributed as follows:

The minimum and maximum initial CD4 count is defined to be 324 and 1500 respectively.

Initial virus is assumed to be R5-tropic. Shift to presence of X4 virus is assumed to depend on viral load. Probability of a shift per 3 months is given by 10v x 0.0000004, where v is the current log10 viral load.

**Comment:** This translates into a rate of 5% per year in a person with viral load 30,000 cps/mL and 16% per year in a person with 100,000 copies/mL, which are broadly consistent with observed data (Koot et al. 1993a).

#### Determination of changes in viral load and CD4 count

Viral load change (vc) from period t-1 to period t (i.e. in 3 months) is given by sampling from a Normal distribution N ( gx x 0.02275, 0.05)(see value and distribution of gx in section “Parameters values and distributions”).

CD4 count changes from period t-1 to t are dependent on the current viral load (i.e. viral load at time t-1) and are given by sampling from a Normal distribution with standard deviation *sd\_cd4* and mean *fx* (see value and distribution of fx in section “Parameters values and distributions”) times the values as follows:

-----------------------------------------------

Viral load Change in

at t-1 square root

 CD4 count

 (per 3 mths)

-----------------------------------------------

< 3.0 -0.03

3-0 -0.08

3.5- -0.15

4.0- -0.20

4.5- -0.50

5.0- -1.00

5.5- -2.00

6.0- -2.50

-----------------------------------------------

The change additionally is affected by the current age as follows:

----------------------------------------------------------------------

Age Additional change in

 square root CD4 count

----------------------------------------------------------------------

< 20 +0.15

20- +0.09

25- +0.06

30- +0.0

35- +0.0

40- -0.06

45- -0.09

50- -0.15

60- -0.20

----------------------------------------------------------------------

People with X4 virus present experience an additional change in square root CD4 count of -0.25.

These estimates are derived based on synthesis of evidence from natural history studies (Henrard et al. 1995; Hubert et al. 2000; Koot et al. 1993b; Lyles et al. 2000; Mellors et al. 1997; O'Brien et al. 1998; Pantazis & Touloumi 2005; Sabin et al. 2000; Touloumi et al. 2004) and were selected in conjunction with other relevant parameter values to provide a good fit to the incubation period distribution. Differences that have been found in initial viral load by sex and age are not currently incorporated in the model.

**Table 15.** Incubation period by age. Kaplan-Meier percent with WHO 4 Event. Using median over the simulations with a good fit. Compare with (Babiker et al. 2000; Darby et al. 1996).

------------------------------------------------------------------------------------------------

Age at infection Years from infection

 1 3 5 10 15 20

------------------------------------------------------------------------------------------------

15- 0.3% 3% 10% 43% 75% 91%

25- 0.8% 5% 15% 55% 84% 95%

35- 0.9% 9% 22% 64% 91% 98%

45- 1.4% 11% 26% 74% 93% 99%

55- 1.8% 11% 30% 75% 96% 100%

------------------------------------------------------------------------------------------------

### HIV testing and diagnosis of HIV infection

HIV testing is assumed became available in 1990 in antenatal clinics and in *date\_start\_testing*(1996) for the rest of the population.

The basic probability of someone testing for HIV in any 3 month period, if he/she has not been tested in the last year, is assumed to increase linearly by *test\_increase\_rate* (see distribution in section “Parameters values and distributions”). This probability of testing is independent of presence of WHO stage 3 or 4 conditions and it applies only if the person did not test in the last year; in other words HIV testing is assumed to occur with a frequency no more than annual.

A proportion of the population (*rate\_noreached*) is assumed to be “impossible to reach” and can never be tested for HIV unless symptoms occur (WHO stage 4 disease). In addition those who did not have condom-less sex since last HIV test are assumed to have a 10-fold reduction in the probability of being tested for HIV.

In addition some individuals experience an additional probability of being tested for HIV based on their condition in the previous 3 months:

|  |  |  |
| --- | --- | --- |
| Situation | Probability of HIV testing in 1996 | Rate of increase per 3 months (Up to a probability of 0.95) |
| Current AIDS defining condition | *test\_rate\_who4* | *inc\_ test\_rate\_who4* |
| Current TB, but not an AIDS defining condition | *test\_rate\_tb* | *inc\_ test\_rate\_tb* |
| Current WHO stage 3 disease, but not TB nor an AIDS defining condition | *test\_rate\_who3* | *inc\_ test\_rate\_who3* |

## The result of the HIV test is assumed to be available immediately and to be 100% sensitive and specific, except during the primary infection (assumed to last 3 months) therefore people who are infected with HIV for at least 3 months and who get tested are diagnosed with HIV. From 2013 onwards the probability of being tested for HIV are assumed constant. These parameters have been chosen to reflect the situation in South Africa(Shisana et al. 2009). See section Brief description of HIV Synthesis Heterosexual Transmission Model for South Africa.

Among those who are not “impossible to reach” (determined by *rate\_noreached),* the proportion of HIV positive people who are linked to care and therefore received a CD4 measurement and result to evaluate whether they are eligible to initiate ART is determined as the sum of *rate\_noreached* and *prop\_linkedtocare\_diag* (See the value and distribution of these two parameters in section“Parameters values and distributions”).

#### HIV testing in antenatal clinics

The reason why pregnancies are included in this modelis mainly to be able to simulate HIV testing in antenatal clinics, and therefore a higher rate of testing in women overall, and to capture the impact of receiving antiretrovirals to prevent of mother to child transmission on the development of resistance. Vertical transmissions are not modelled.

Given a woman had condom-less sex with a long term partner in a 3 month period, and did not give birth in the last 9 months, in the model the probability that they get pregnant is age dependent. The probability for a woman aged 25 to 35 years old is determined by the parameter *prob\_pregnancy\_base*(See distribution in section “Parameters values and distributions”). For the other age groups (15 to 25 years old up to 55 to 66 years), the following multiplicative factors, respectively *fold\_preg1525*, *fold\_preg2535*, 1, *fold\_preg4555*, *fold\_preg5565*(See distribution in section “Parameters values and distributions”) are multiplied by *prob\_pregnancy\_base,* to determine the probability of pregnancy in women who had condom-less sex in the previous 3 months. If they had condom-less with short term partnersthe probability of transmission from each of the short term partner is multiplied by the factor *fold\_tr\_newp*, to take into account of the lower number of sex acts per short term partner than per long-term partner.

These parameters have been chosen to reflect the cumulative average number of children ever born per woman, for the age group 15-24 up to 45 to 49 years old, estimated in a community survey in South Africa conducted in 2007(Statistics SouthAfrica 2010).

In pregnant women, who are not “impossible to reach” the probability per pregnancy of attending an antenatal clinic and receiving an HIV test (for women not diagnosed yet with HIV) is assumed to increase over time. This probability from 1990 to 2013,is given by:

 (current calendar year – 1990)2x *rate\_testanc\_inc*

See distribution of *rate\_testanc\_inc*in section “Parameters values and distributions”.

The maximum for the probability of attending and ANC is assumed to be 0.975.

Pregnant women who are diagnosed with HIV, since *date\_sd\_nvp*, the year when prevention of mother to child transmission (PMTCT)with use of single dose nevirapine is assumed to be introduction date are assumed to have an increasing chance of receiving PMTCT. This is determined as the product of the difference between calendar year and the year of introduction of single dose NVP (*date\_sd\_nvp*) and the parameter *rate\_sd\_nvp*, up to a maximum of 0.975.

With this parameter choice 90% of pregnant women receive PMTCT by 2011, as has been estimated for South Africa(UNAIDS 2012).

### Use of ART

#### Initiation of ART

In the base model ART initiation in diagnosed people before 2010, starting from 2003 when it is assumed ART was introduced, it is determined by a CD4 count < 200 cells/mm3or the development of a WHO stage 4 event, as recommended by the South African guidelines (South Africa National Department of Health 2004). From mid-2010 this is determined by a CD4 count < 350cells/mm3, irrespective of the WHO clinical stage(South Africa National Department of Health 2010b; WHO 2010)

#### Interruption of ART

The basic rate of interruption due to patient choice is *rate\_int\_choice* (See distribution in section “Parameters values and distributions”). This rate depends on the person’s underlying tendency to adhereand whether they have current toxicity. The table below shows by how much *rate\_int\_choice* is multiplied for different levels of adherence and presence of toxicity:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

 Current presence of toxicity

Underlying tendency No Yes

to adhere

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

≥80% 1 2

50-79.9% 1.5 3

<50% 2 4

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

These rates are reduced by half for people who have been continuously on ART for two years.

If ART is interrupted because of patient choice the probability per 3 month period that the interruption coincides with the interrupting/stopping visits to the clinic (i.e. lost to follow-up) is determined by the parameter *prob\_lost\_art* for patients with adherence average of 80% or more.

Patients with average adherence between 50 and 80% experience a 50% higher probability of being lost per 3 month during ART interruption, while those with adherence average less than 50% a double probability of being lost compare to those with high average adherence (>80%).

The rate of interruption due to choice and therefore the retention of people on ART are likely to vary by setting. The above rates were derived to be consistent with data from South Africa (Boulle et al. 2008; Cornell et al. 2010).

The basic rate of interruption per 3 months due to interruption of the drug supply is the parameter *prob\_supply\_interrupted*  (See distribution in section “Parameters values and distributions”)

#### Interruption of ART without clinic/clinician being aware

It is known that in some instances people on ART have such poor adherence that they have in fact interrupted or stopped ART entirely but, in the same way that the clinician is not always aware of the true adherence level, they are also not always aware when the person has completely interrupted ART. This means that the clinician may think a patient is virologically failing, because viral load is high, when in fact this is due to interruption rather than resistance. This can be seen from studies on people with virologic failure in which a proportion have no identified resistance mutations(Hamers et al. 2012; Hoffmann et al. 2009; Wallis et al. 2010). Thus, when a person interrupts ART (but remains under care) we introduce a variable that indicates whether the clinician is aware, *clinic\_aware\_int\_frac*(See distributionin section “Parameters values and distributions”). If a patient has interrupted ART with the clinician unaware then not only is the patient (wrongly) classified (by the clinician) as virologically failing, but a switch to second line can potentially occur.

#### Re-initiation of ART after interrupting in patients still under follow-up

For patients who have interrupted ART due to choice but are still under clinic follow-up, the probability of restarting ART per 3 months in the base model is *rate\_restart* (See distributionin section “Parameters values and distributions”). This probability is increased 3-fold if a new WHO 3 condition has occurred at t-1, and 5-fold if a new WHO 4 condition has occurred at t-1.

In addition, if VL monitoring is introduced, a measured VL above 1,000 copies/ml in the last 6 months, triggers an adherence intervention which can increase the rate of restart. This will be discussed in more detail in section5.7.

This was derived from consideration of estimates of the proportion of people who had started ART who were on ART (e.g. (Cambiano et al. 2010)). This will likewise vary by setting.

For patients who have interrupted ART due to interruption of supply the probability of restarting ART per 3 months in the base model is *prob\_supply\_resumed* (See distributionin section “Parameters values and distributions”).

#### Switch to second line after failure of first line ART

Whatever the criterion for the need to switch to second line ART is determined, the probability of switching per 3 month period after the criterion is met is *pr\_switch*\_line (See distribution in section “Parameters values and distributions”). (See (Fox et al. 2012; Johnston et al. 2012))

#### Loss to follow-up while off ART

The probability per 3 months of interrupting/stopping clinic visits (i.e. being lost to follow-up) is *rate\_lost*in the first year since diagnosis (See distribution in section “Parameters values and distributions”) for people with willingness to adhere (See section 5.7) of 80% or above. After one year since diagnosis, the probability of being lost to follow-up is a quarter of *rate\_lost*.

This is increased by 1.5 fold if willingness to adhereis between 50 and 80% and by 2-fold if the willingness to adhere is below 50%. Concept of adherence average is described in section5.7.

## This applied to people ART-naïve and to people ART experienced and the values have been chosen to reflect the proportion retained in pre-ART care (see section “Brief description of HIV Synthesis Heterosexual Transmission Model for South Africa” and (Govindasamy et al. 2011; Ingle et al. 2010; Kranzer et al. 2010; Larson et al. 2010a; Luseno et al. 2008)) and in people initiated on ART (see section “Brief description of HIV Synthesis Heterosexual Transmission Model for South Africa” and (Boulle et al. 2008; Cornell et al. 2010).

For people lost to follow-up who are asymptomatic, the probability of returning to clinic per 3 months is *rate\_return* (See distribution in section “Parameters values and distributions”) if the willingness to adhere is 80% or above. This is decreased by 2-fold if the underlying tendency to adhereis between 50 and 80% and by 3-fold if the willingness to adhere is below 50%. If a person develops a new WHO 3 or 4 event then they are assumed to return to the clinic with probability 0.8. These will vary by setting (Anaky et al. 2010; Charurat et al. 2010; Larson et al. 2010a).

#### Adherence to antiretroviral treatment

There are two components to the adherence. Each patient has a fixed “tendency to adhere” but their actual adherence varies from period to period, both at random and according to the presence of symptoms. Adherence is measured on a scale of 0 to 1 (sometimes reported as between 0 and 100%).

There is a component which is fixed over time for a given patient, referred to as adherence average (*adhav*), which is a measure of the patient’s tendency to adhere, a fixed value for a patient, with a certain period-to-period variability (adhvar). Adherence at any one period is determined as follows (although with modifications explained below): adh(t) = adhav + Normal(0,advar).

if adh(t) > 1 then adh(t)=1.

|  |  |  |
| --- | --- | --- |
| **Proportion of the population** | **Adhav** | **Adhvar** |
| 0.15 | 0.49 | 0.2 |
| 0.15 | 0.79 | 0.2 |
| 0.5 | 0.90 | 0.06 |
| 0.2 | 0.95 | 0.05 |

These estimates are based partially on observed adherence data (Bangsberg et al. 2004; Mills et al. 2006), but also on adherence levels required to produce observed estimates of rates of resistance development and virologic failure and also data on the proportion of patients at first virologic failure who have no resistance mutations present (Hamers et al. 2012; Hoffmann et al. 2009; Mackie et al. 2010; Wallis et al. 2010). It is clear from such data in more recent years that the great majority of patients who started ART with 3 or more drugs are sufficiently adherent that virologic failure rates (and so resistance accumulation is likely to have been slow also) are low (El-Khatib et al. 2010; Fox et al. 2012).

**Effective adherence**

We also considered the concept of effective adherence, which reflects predicted adequacy of drug levels, whereby for those on regimens that do not include an NNRTI the effective adherence is as the adherence, but for those on NNRTI-containing regimens the effective adherence is the adherence + *add\_eff\_adh\_nnrti* (See distribution in section “Parameters values and distributions”), reflecting the long half-life of these drugs (Cheeseman et al. 1993). Additionally, it is assumed that patients on ART are susceptible to occasional (rate 0.02 per year) severe temporary drops in drug level (i.e. effective adherence level), leaving them susceptible to viral rebound (but with low risk of resistance as the effective adherence drop is so profound). This phenomenon is assumed to be 3 times more frequent among those on protease inhibitor regimens. This latter assumption is the only plausible means (at least within our model framework), together with the fact that the patient interrupt treatment without the clinician knowing it (see section 5.3) to explain why virologic failure occurring on boosted protease inhibitor regimens often occurs in the absence of resistance.

**Effect of viral load measurement above 1000 cps/mL on adherence**

Studies have indicated that viral load frequently returns to undetectable after a measured value > 1000 cps/mL, largely attributable to targeting of adherence support(Hoffmann et al. 2009; Orrell et al. 2007; Orrell et al. 2011). Adherence is assumed to be incremented by an average *adh\_effect\_of\_vm\_pop* (by an amount that varies by individual) when the viral load has been measured to be above 1000 copies/mL in the past 6 month period (it can apply only once for each individual). In addition in 50% of the population there is a 0.2 probability of a one-off increase in adherence sampled from a Uniform distribution with extremes 0 and 0.8, up to a maximum of 1 for the adherence.

Having a measured VL above 1,000 copies/ml in the last six months is assumed to have an effect on the probability of restarting ART in people who have interrupted. In particular this is multiplied respectively by 1.5, 2, 3 and 5 if the individual increase in adherence due to this effect is respectively 0.05, between 0.05 and 0.10, 0.10 and 0.25 and above 0.25.

### Effect of ART on viral load, CD4 count, resistance development and drug toxicity

#### Determination of viral load, CD4 count and acquisition of new resistance mutations while on ART

The viral load, CD4 count, acquisition of new resistance mutations between t-1 and t (variable “newmut(t)”) of patients on ART, is assumed to depend on the effective adherence between t-1 and t, number of active drugs (nactive(t-1)), time on the current regimen and the current viral load itself. The way the values are generated is detailed on the following pages (see Table 16). For those on NNRTI regimens the new mutations risk is assumed to be that for the effective adherence category of 0.5 – 0.8 (i.e. maximal) even if the effective adherence is below 0.5, reflecting the fact that NNRTI resistance develops easily, even when drug exposure is very low.

The changes in viral load and CD4 count are based on observed data and observational studies (and to some extent randomized trials, although responses tend to be better in trial participants), and provide long term estimates of virologic failure rates and CD4 count increases in ART which are broadly consistent with observed. Values of the “new mutation risk” (*new\_mut*) parameter have been chosen in conjunction with the translation of presence of mutations into reduce drug activity to provide estimates of resistance accumulation consistent with those observed in clinical practice (Blackham et al. 2005; Gallant et al. 2004; Harrigan et al. 2005; Johannessen et al. 2009; Ledergerber et al. 1999; Phillips et al. 2001; Staszewski et al. 1999a; Staszewski et al. 1999b; van Leth et al. 2004).

**Table 16a.** Viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk in first 3 months. For 0 active drugs, these are the changes regardless of time from start of regimen.For viral load this is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5\*normal(0)) and the CD4 count change given here is multiplied by this factor. For the new mutation risk, this is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting number ("newmut") is used when assessing whether a new mutation or mutations have arisen (see below).

 Effective Number of active drugs

 adherence

 between

 t-1 & t 3 2.75 2.5 2.25 2.0 1.75 1.5 1.25 1 0.75 0.5 0.25 0

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Viral load > 0.8 -3.0 -2.6 -2.2 -1.8 -1.5 -1.25 -0.9 -0.8 -0.7 -0.55 -0.4 -0.3 -0.3

(log change > 0.5, < 0.8 -2.0 -1.6 -1.2 -1.1 -0.9 -0.8 -0.6 -0.5 -0.4 -0.25 -0.1 -0.05 -0.1

from vmax) < 0.5 -0.5 -0.4 -0.3 -0.25 -0.2 -0.15 -0.0 +0.05 +0.1 +0.1 +0.1 +0.1 -0.0

CD4 count > 0.8 +50 +45 +40 +35 +30 +25 +20 +17 +13 +10 +5 -2 -15

change > 0.5, < 0.8 +30 +30 +23 +20 +15 +13 +10 +8 +5 +3 +0 -7 -17

(t-1 to t) < 0.5 +5 +4 +3 +2 +1 -1 -3 -6 -10 -11 -12 -13 -18

new mutation > 0.8 0.002 0.01 0.03 0.05 0.1 0.15 0.2 0.3 0.4 0.45 0.5 0.5 0.5

risk > 0.5, < 0.8 0.15 0.15 0.2 0.25 0.3 0.3 0.3 0.35 0.4 0.45 0.5 0.5 0.5

(x log viral load)< 0.5 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

**Table 16b.** Summary of viral load (mean absolute value or mean change from viral load max) between 3-6 months, and after 6 months if viral load at t-1 > 4 logs. This is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled.

Effective adherence Effective adherence Number of active drugs

between between

t-2 & t-1 t-1 & t 3 2.75 2.5 2.25 2.0 1.75 1.5 1.25 1 0.75 0.5 0.25

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

> 0.8 > 0.8 0.5 0.8 1.2 1.4 2.0 2.7 -1.7 -1.15 -0.9 -0.75 -0.6 -0.4

> 0.5, < 0.8 > 0.8 1.2 1.2 1.2 1.4 -2.0 -1.6 -1.2 -1.05 -0.9 -0.7 -0.5 -0.35

< 0.5 > 0.8 1.2 1.2 1.2 1.4 -2.0 -1.6 -1.2 -1.0 -0.9 -0.7 -0.5 -0.2

> 0.8 > 0.5, < 0.8 1.2 1.6 1.8 2.2 2.4 -2.4 -1.5 -0.9 -0.7 -0.55 -0.4 -0.3

> 0.5, < 0.8 > 0.5, < 0.8 2.5 2.5 2.5 2.5 -1.2 -1.1 -0.8 -0.65 -0.5 -0.35 -0.2 -0.05

< 0.5 > 0.5, < 0.8 -2.0 -1.8 -1.5 -1.35 -1.2 -1.1 -0.8 -0.65 -0.5 -0.2 -0.2 -0.05

> 0.8 < 0.5 -0.5 -0.4 -0.3 -0.25 -0.2 -0.15 -0.10 -0.05 +0.0 +0.0 +0.0 +0.0

> 0.5, < 0.8 < 0.5 -0.5 -0.4 -0.3 -0.25 -0.2 -0.15 -0.10 -0.05 +0.0 +0.0 +0.0 +0.0

< 0.5 < 0.5 -0.5 -0.4 -0.3 -0.25 -0.2 -0.15 -0.10 -0.05 +0.0 +0.0 +0.0 +0.0

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

**Table 16c.** Summary of CD4 count change (mean change between t-1 and t) between 3-6 months, and after 6 months if viral load at t-1 > 4 logs. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5\*normal(0)) and the CD4 count change given here is multiplied by this factor. Once the mean of the underlying CD4 count is obtained, to obtain the (underlying) CD4 count, variability (SD = 1.2) is added on the square root scale

Effective adherence Effective adherence Number of active drugs

between between

t-2 & t-1 t-1 & t 3 2.75 2.5 2.25 2.0 1.75 1.5 1.25 1 0.75 0.5 0.25

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

> 0.8 > 0.8 +30 +28 +25 +23 +21 +19 +3 -5 -9 -10.5 -12 -14

> 0.5, < 0.8 > 0.8 +30 +28 +25 +23 +7.5 +1.5 -4.5 -7 -9 -11 -13 -14.5

< 0.5 > 0.8 +30 +28 +25 +23 +7.5 +1.5 -4.5 -7.5 -9 -11 -13 -16

> 0.8 > 0.5, < 0.8 +15 +13 +10 +8 +7 +13.5 +0 -9 -11 -12.5 -14 -15

> 0.5, < 0.8 0.5, < 0.8 +15 +13 +10 +8 -4.5 -6 -10 -11.5 -13 -14.5 -16 -17.5

< 0.5 > 0.5, < 0.8 +7.5 +4.5 +0 -2 -4.5 -6 -10 -11.5 -13 -16 -16 -17.5

> 0.8 < 0.5 -13 -14 -15 -15.5 -16 -1 -17 -17.5 -18 -18 -18 -18

> 0.5, < 0.8 < 0.5 -13 -14 -15 -15.5 -16 -16.5 -17 -17.5 -18 -18 -18 -18

< 0.5 < 0.5 -13 -14 -15 -15.5 -16 -16.5 -17 -17.5 -18 -18 -18 -18

------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

**Table 16d. Summary of new mutation risk between 3-6 months, and after 6 months if viral load at t-1 > 4 logs.**This is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting number ("newmut") is used when assessing whether a new mutation or mutations have arisen (below).

Effective adherence Effective adherence Number of active drugs

between between

t-2 & t-1 t-1 & t 3 2.75 2.5 2.25 2.0 1.75 1.5 1.25 1 0.75 0.5 0.25

---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

> 0.8 > 0.8 0.002 0.01 0.03 0.05 0.05 0.1 0.2 0.3 0.4 0.45 0.5 0.5

> 0.5, < 0.8 > 0.8 0.002 0.01 0.03 0.05 0.05 0.1 0.2 0.3 0.4 0.45 0.5 0.5

< 0.5 > 0.8 0.05 0.05 0.03 0.05 0.05 0.1 0.2 0.3 0.4 0.45 0.5 0.25

> 0.8 > 0.5, < 0.8 0.10 0.15 0.2 0.2 0.3 0.3 0.3 0.35 0.4 0.45 0.5 0.5

> 0.5, < 0.8 > 0.5, < 0.8 0.10 0.15 0.2 0.2 0.3 0.3 0.3 0.35 0.4 0.45 0.5 0.5

< 0.5 > 0.5, < 0.8 0.10 0.15 0.2 0.2 0.3 0.3 0.3 0.35 0.4 0.45 0.5 0.25

> 0.8 < 0.5 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05

> 0.5, < 0.8 < 0.5 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05

< 0.5 < 0.5 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05

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**Table 16e.** Summary of viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk after 6 months, where viral load at t-1 < 4 logs. For viral load this is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by sampling from exp(0.5\*normal(0)) and the CD4 count change given here is multiplied by this factor. For the new mutation number, this is a number that is multiplied by the viral load (mean of values at t-1 and t). The resulting probability ("newmut") is used when assessing whether a new mutation or mutations have arisen (see below).

 Effective Number of active drugs

 adherence

 between

 t-1 & t 3 2.75 2.5 2.25 2.0 1.75 1.5 1.25 1 0.75 0.5 0.25

-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Viral load > 0.8 0.5 0.9 1.2 1.6 -2.5 -2.0 -1.4 -1.15 -0.9 -0.75 -0.6 -0.3

(absolute value > 0.5, < 0.8 1.2 1.2 1.2 1.4 -1.2 -1.0 -0.7 -0.6 -0.5 -0.4 -0.3 -0.1

or log change < 0.5 -0.5 -0.4 -0.3 -0.25 -0.2 -0.2 -0.1 -0.1 -0.1 -0.1 -0.1 -0.0

from vmax)

CD4 count > 0.8 +30 +28 +25 +23 +21 +19 +3 -5 -9 -10.5 -12 -12

change > 0.5, < 0.8 +15 +13 +10 +8 -4.5 -7.5 -10 -12 -13 -14 -15 -15

 (t-1 to t) < 0.5 -13 -14 -15 -15.5 -16 -16.5 -17 -17 -18 -17 -17 -17

new mutation > 0.8 0.002 0.01 0.03 0.08 0.10 0.15 0.2 0.3 0.4 0.45 0.5 0.5

(x viral load) > 0.5, < 0.8 0.15 0.18 0.2 0.25 0.3 0.3 0.3 0.35 0.4 0.45 0.5 0.5

< 0.5 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05

-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

#### Additional effects on CD4 count rise while on ART

**Tendency for CD4 count rise on ART**

For scenarios in the above table in which the CD4 count change is positive the CD4 count change is modified by the factor patient\_cd4\_rise\_art.

Reduced CD4 count rise if CD4 is increasing fast(more than what stated in the table above) after 2 continuously years on ART is included, to reflect the fact that the rate of CD4 count increase on ART tends to diminish with time(Staszewski et al. 1999b).

**Accelerated rate of CD4 count loss if PI not present in regimen**

The rate of change in CD4 count in people on failing regimens is largely based on data from the PLATO collaboration, for which patients were mainly on regimens containing a PI. If the regimen does not contain a PI the change in CD4 count per 3 months is modified (in the base model) by the additive factor *poorer\_cd4\_rise\_on\_failing\_nnrti (*See distribution in section “Parameters values and distributions”) cells/mm3. This applies regardless of viral load level, so PIs are assumed to lead to a more beneficial CD4 count change than NNRTIs (Ledergerber et al. 2004).

**Variability in individual (underlying) CD4 counts for people on ART**

Once the mean of the underlying CD4 count is obtained as described above for people on ART, to obtain the CD4 count, variability is added on the square root scale by sampling for each patient a value from a Normal distribution with mean 0 and standard deviation *sd\_cd4*. The estimate was based on unpublished analyses.

#### Viral load and CD4 count changes during ART interruption

During ART interruption, viral load returns to previous maximum viral load (vmax) in 3 months and adopts natural history changes thereafter.

CD4 rate of decline returns to natural history changes (i.e. those in ART naïve patients) after 9 months, unless the count remains > 200 above the CD4 nadir.

Before returning to the natural history, the rate of CD4 count decline depends on current viral load.

|  |  |  |  |
| --- | --- | --- | --- |
| **If (circumstance)** | **Then v(t)** | **If v(t)=** | **Then cc(t-1)** |
| TOA\* is 3 months or(TOA> 3 months and CD4 in previous period is > 300 above the minimum CD4 count to date) | vmax(t-1)  | > 5 | N(-200,10)  |
| 4.5 - 5 | N(-160,10) |
| < 4.5 | N(-120,10) |
| TOA is 6 months  | - | > 5 | N(-100,10)  |
| 4.5 - 5 | N(-90,10)  |
| < 4.5 | N(-80,10)  |
| TOA is 9 months | - | > 5 | N(-80,10)  |
| 4.5 - 5 | N(-70,10)  |
| < 4.5 | N(-60,10)  |

\*TOA = time off ART

If this leads to c(t) < cmin(t) (CD4 nadir) then c(t) is set to cmin(t)

This is broadly based on evidence from a number of analyses of the effects of ART interruption (Achenbach et al. 2005; Boschi et al. 2004; d'Arminio et al. 2005; Fischer et al. 2003; Lawrence et al. 2003; Li et al. 2005; Mocroft et al. 2001; Skiest et al. 2004; Tebas et al. 2002; Thiebaut et al. 2005; Wit et al. 2005; Youle et al. 2000).

#### Incidence of new current toxicity, continuation of existing toxicity and switching due to toxicity

Toxicities including gastrointestinal symptoms, rash, hepatoxicity, CNS toxicity, lipodystrophy, hypersensitvity reaction, peripheral neuropathy and nephrolithiasis can occur with certain probability on certain specific drugs. These probabilities are based broadly on evidence from trials and cohort studies, although there are no common definitions for some conditions which complicates this.

**Table 17.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Toxicity** | **Drug** | **Risk of development****per 3 months** | **Probability of continuation if pre-existing** |
| nausea | LPV, ddI, AZT | 0.03 | 0.5 |
| diarrhoea | LPV | 0.03  | 0.2 |
| ddI | 0.05 | 0.2 |
| rash | EFV | 0.03 (this is a one-off risk in 1st 3 months) |  |
| NVP | 0.1 (ditto) |  |
| CNS | EFV | 0.1 (in 1st year, 0 after) | 0.8 (in 1st year)0.9 (after 1st year) |
| Lipodystrophy | d4T | 0.05 | 1.0 |
| AZT | 0.015 | 1.0 |
| PeripheralNeuropathy | d4T | 0.02 (1.5 fold higher in 1st year) | 1.0 if remain on d4T, 0 otherwise |
| DdI | 0.01 (1.5 fold higher in 1st year) | 1.0 if remain on ddI,0 otherwise |
| acute hepatitis | NVP | 0.019 (one off risk in first and 2nd 3 month periods) |  |
| Anaemia | AZT | 0.03 (1.5 fold higher in 1st year) | 0.2 |
| headache | AZT | 0.1 (1.5 fold higher in 1st year) | 0.4 |
| pancreatitis | ddI, d4T | 0.001 |  |
| lactic acidosis | AZT, ddI, d4T | 0.0002 |  |

LPV: lopinavir; EFV: efavirenz; NVP: nevirapine

**Switching of drugs due to toxicity**

If toxicity is present then individual drugs may be switched due to toxicity. In most cases, the switch is to another in the same class, if such a drug (that has not been previously failed nor stopped due to toxicity) is available. This will vary by setting and availability of alternative drugs.

#### First line ART failure definition

The definition for first line failure depends on the availability of CD4 count and viral load measures.

## As mentioned in section “Brief description of HIV Synthesis Heterosexual Transmission Model for South Africa “, for South Africa it is assumed people on ART are monitored using viral load measurements. The frequency of viral load for people in care is assumed 6 monthly until mid-2010, while from mid-2010 at 6 and 12 months since ART initiation and then annually. Before mid-2010 the criterion to switch people to second-line regimen (i.e. failure definition) is a detectable viral load measurement above 400 copies/ml followed by another above 5000 copies/ml (South Africa National Department of Health 2004). In the guidelines published in 2010 the recommended threshold for the confirmatory viral load has been modified to 1000 copies/ml (South Africa National Department of Health 2004; South Africa National Department of Health 2010b), so the failure definition is a VLabove 400 copies/ml followed by another above 1000 copies/ml.

**Table 18**. Kaplan-Meier estimates of percent with viral load failure (> 500 copies/ml after at least 6 months on ART(a), two consecutive VL, the 1st>400 copies/ml, followed by a value above 1000 copies/ml), resistance (predicted susceptibility < 50%) to at least one drug, CD4 count rise of > 200/mm3, using parametervalues which provided the best fit, assuming no ART interruption and restricting to people with no transmitted drug resistance and assuming no super-infection with resistant virus, in the context of CD4 at ART initiation of 270 cells/mm3. Compare, for example, with (Anaky et al. 2010; Cozzi-Lepri et al. 2010; Fox et al. 2012).

 Years from start of ART

 1 3 5 10 20

--------------------------------------------------------------------------------------------------------------------------

Viral load failure (a) 13% 21% 27% 32% 40%

Viral load failure (b) 9% 19% 25% 31% 39%

Resistance 12% 19% 24% 29% 45%

CD4 count rise of 12% 61% 80% 93% 96%

> 200/mm3

CD4 count rise of 46% 82% 91% 97% 98%

> 100/mm3

--------------------------------------------------------------------------------------------------------------------------

**Table 19**. Kaplan-Meier estimates of percent interrupting ART, percent lost to follow up after starting ART, and percent dead, using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cell/mm3. Both restricting to those in care and including those lost to care.

-------------------------------------------------------------------------------------------------

 Years from start of ART

 1 3 5 10 20

-------------------------------------------------------------------------------------------------

Interruption of ART 14% 33% 45% 67% 88%

Loss to care 5% 12% 18% 30% 46%

Death (in those under care) 3% 7% 10% 18% 40%

Death (incl in those lost) 4% 8% 14% 28% 56%

-------------------------------------------------------------------------------------------------

**Table 20.** Cumulative risk of death and returning to care after first being lost to follow up after starting ART using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cell/mm3. Competing risk approach.

 Years from first lost

 (after starting ART)

 1 3 5 10

-----------------------------------------------------------------------------------------------------------------------

Death while lost 9% 30% 50% 69%

Return after loss to care 16% 43% 55% 63%

**Table 21.**Median and interquartile range (IQR) in change in CD4 cell count in people exposed to ART (i.e. ever started on ART) and in those on ARTusing parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cell/mm3.

|  |  |
| --- | --- |
|  | Years from start of ART   |
| 1 | 3 | 5 | 10 |
| Change in CD4 count(ART exposed)            | 71 (1,143)       | 121 (-27,238)    | 220 (-42,367)     | 304 (97,478)      |
| Change in CD4 count(on ART)            | 81 (17,143)      | 151 (88,308)      | 261(89,375)   | 356 (182,498)  |

**Table 22.**Cross sectional analysis at 1, 5, 10 and 20 years since ART initiation of status of patients initiated on ART, using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cell/mm3.

|  |  |
| --- | --- |
|  | Years from start of ART   |
| 1 | 3 | 5 | 10 |
| On ART  | 86%       | 78%    | 74%     | 63%     |
| Off ART, attending the clinic | 2%      | 2%      | 2%   | 3%  |
| Off ART, lost from care      | 7% | 8% | 9% | 9% |
| Dead | 5% | 12% | 15% | 26% |

### Emergence of specific resistance mutations and their effect on drug activity

#### Accumulation of resistance mutations

*newmut* (see Table 16 above) is a probability used to indicate the level of risk of new mutations arising in a given 3 month period. If this chance comes up in a given 3 month period (determined by sampling from the binomial distribution) then the following criteria operate.

**Table 23.**

Drug on Mutation Probability of arising (given newmut=1)

-------------------------------------------------------------------------------------------------------------------------

3TC M184V 0.80

d4t or AZT new TAM if not on 3TC

 increase by 1: 0.20

 increase by 2: 0.01

if on 3TC

 increase by 1: 0.12

 increase by 2: 0.01

ddI L74V 0.01

ddI or d4t or TDF 65R if on zidovudine 0.01

 If not on zidovudine 0.04

ddI or d4t or AZT Q151M 0.02

NVP or EFV NNRTI mutation 0.80

LPV/r 32 0.04

 47 0.04

 82 0.04

-------------------------------------------------------------------------------------------------------------------------

These values are chosen, in conjunction with values of *newmut*, to provide estimates of accumulation of specific classes of mutation consistent with those observed in clinical practice (Harrigan et al. 2005; Johannessen et al. 2009; Sigaloff et al. 2012). They reflect a greater propensity for some mutations to arise than others. This probably relates to the ability of the virus to replicate without the mutations (e.g. probably very low in the presence of 3TC for virus without M184V) as well as the replicative capacity of virus with the mutations. Over time as more data accumulate it may be possible improve these estimates of rates of accumulation of specific mutations.

#### Accumulation and persistence of resistance mutations in pregnant women receiving prevention of mother to child transmission

As described in section 4.1, the model simulates pregnancies in women who engage in condom-less sex, whether they are tested in ANC and whether they receive antiretrovirals for prevention of mother to child transmission.

As mentioned, it has been reported that in South Africa single dose nevirapine became available in clinical care in 2004 for pregnant women(UNAIDS 2008). Since 2010 the South African guidelines have been recommending the use of AZT from 14 weeks, sdNVP and AZT 3hrly during labour, and TDF and FTC single dose after delivery(South Africa National Department of Health 2010b).

Single dose nevirapine and the most recent regimen have been associated with different risk of NNRTI resistance emergence(Arrive et al. 2007): the first is assumed to be determined by the parameter *prob\_nnresmaj\_sd\_nvp* and the second by *prob\_nnresmaj\_dual\_nvp* (See distribution in section “Parameters values and distributions” and (Arrive et al. 2007)).

There is evidence that even if NNRTI mutations are acquired in women receiving PMTCT, they tend to be lost and this does not seem to affect their immunological response when in the future they start ART for their own health(Hauser et al. 2012). It is assumed in women we have acquired NNRTI resistance due to PMTCT, a rate of losing these mutations from majority virus of *rate\_loss\_nnres\_pmtct\_maj* per 3 months, and once they are present only in minority virus a rate of losing them completely, so that even if they start an NNRTI regimen, the mutations are not going to re-emerge of *rate\_loss\_nnres\_pmtct\_min.*

#### New resistance to NNRTI arising as a result of ART interruption

It is assumed that due to the long half-life of NNRTIs nevirapine and efavirenz, stopping of a regimen containing one of these drugs is associated with a probability *risk\_res\_stopping\_nn* (See distribution in section “Parameters values and distributions”) of an NNRTI resistance mutation arising (see, for example, (Fox et al. 2008)).

#### Loss of acquired mutations from majority virus

It is assumed that mutations acquired while on ART tend to be lost from majority virus with a certain probability from 3 months after stopping to take a drug that selects for that mutation. The probability of losing mutations per 3 months from majority virus (from 3 months after stopping) is as follows ((Birk et al. 2001; Deeks et al. 2003; Devereux et al. 1999; Devereux et al. 2001; Hance et al. 2001; Tarwater et al. 2003; Walter et al. 2002).

**Table 24.**

----------------------------------------

M184V 0.8

L74V 0.6

Q151M 0.6

K65R 0.6

TAMS (lose all) 0.4

NNRTImutation 0.2

Protease mutations 0.2

---------------------------------------

Mutations are regained in majority virus if a drug selecting for the mutation is again started.

#### Determination of level of resistance to each drug and calculation of activity level of each drug

The level of resistance conferred by each mutation to the certain drugs is displayed in the Table 25, where a value of 1 means full resistance, while a value of 0 means that the drug is fully active.

**Table 25.**

|  |  |  |
| --- | --- | --- |
| **Drug** | **Mutation** | **Level of resistance** |
| 3TC | M184V | 0.75 |
| AZT or d4t  | (no 3TC in regimen) | 1-2 TAMS | 0.5 |
| 3-4 TAMS | 0.75 |
| 5-6 TAMS | 1.00 |
| AZT or d4t  | (3TC in regimen- no M184V ever)  | 1-2 TAMS | 0.5 |
| 3-4 TAMS | 0.75 |
| 5-6 TAMS | 0.75 |
| AZT or d4t  | (3TC in regimen- M184V ever) | 1-2 TAMS | 0.25 |
| 3-4 TAMS | 0.5 |
| 5-6 TAMS | 0.75 |
| AZT or d4t | Q151M | 0.75 |
| d4T | K65R | 0.5 |
| TDF  | (no K65R ever, no 3TC in regimen) | 2-3 TAMS | 0.5 |
| >=4 TAMS | 0.75 |
| TDF  | (no K65R ever, 3TC in regimen,no M184V ever) | 2-3 TAMS | 0.5 |
| >=4 TAMS | 0.75 |
| TDF  | (no K65R ever, 3TC in regimen, M184V ever) | 2-3 TAMS | 0.5 |
| >=4 TAMS | 0.5 |
| TDF | K65R | 0.5 |
| ddI | > 3 TAMS | 0.5 |
| Q151M | 0.75 |
| K65R | 0.75 |
| L74V | 0.75 |
| NVP or EFV | NNRTI mutation | 1.00 |
| LPV/r | 1 from Pr 32,47, 76, 82 | 0.25 |
| 2 from Pr 32,47, 76, 82 | 0.5 |
| 3 from Pr 32,47, 76, 82 | 0.75 |
| 2-3 from Pr 46, 76, 82, 84, 90  | max(r\_lpr, 0.25) |
| 4 from Pr 46, 76, 82, 84, 90 | max(r\_lpr, 0.5) |

These rules approximately follow the interpretation systems for conversion of mutations present on genotypic resistance test into a predicted level of drug activity (or, equivalently, of resistance; e.g. (Liu et al. 2006; Liu & Shafer 2006; Meynard et al. 2002; Van et al. 2002). Currently interpretation systems differ to some degree in their prediction of activity for some drugs.

The activity level of each drug is given by 1-level of resistance (defined in the table above). For lopinavir/r (in base model) the activity level is given by 2 – (2 x level of resistance); i.e. assumed higher potency.

Activity levels of each drug in the regimen are summed to give the total number of active drugs.

### Risk of clinical disease and death in HIV infected people

#### Occurrence of WHO stage 4 event

Occurrence of WHO stage 4 diseases (see (Beral et al. 2004; Ledergerber et al. 2004; Phillips et al. 1991)) is assumed to depend on CD4 cell count (see Table 24), viral load, age, PCP prophylaxis and antiretroviral regimen.

### Independent effect of CD4 cell count

**Table 26.**Rate of WHO 4 diseases according to CD4 count

|  |  |
| --- | --- |
| **CD4 cell count** | **Rate of WHO 4 diseases per 3 months (per 100 person-years)** |
| ≥650 | 0.2 |
| [500-650) | 1.0 |
| [450-500) | 1.3 |
| [400-450) | 1.6 |
| [375-400) | 2.0 |
| [350-375) | 2.2 |
| [325-350) | 2.5 |
| [300-325) | 3 |
| [275-300) | 3.7 |
| [250-275) | 4.5 |
| [225-250) | 5.5 |
| [200-225) | 6.5 |
| [175-200) | 8 |
| [150-175) | 10 |
| [125-150) | 13 |
| [100-125) | 17 |
| [90-100) | 20 |
| [80-90) | 23 |
| [70-80) | 28 |
| [60-70) | 32 |
| [50-60) | 40 |
| [40-50) | 50 |
| [30-40) | 80 |
| [20-30) | 110 |
| [10-20) | 180 |
| [0-10) | 250 |

### Independent effect of viral load

The impact of viral load on the rate of experiencing WHO stage 4 disease is obtained by multiplying the cd4-specific rate by the factors indicated in the table below

|  |  |
| --- | --- |
| **Viral load level** | **Multiplicative factor** |
| < 3.0 log cps/mL | 0.2 |
| 3.0 - 4.0 log cps/mL | 0.3 |
| 4.0 - 4.5 log cps/mL | 0.6 |
| 4.5 - 5.0 log cps/mL | 0.9 |
| 5.0 - 5.5 log cps/mL | 1.2 |
| > 5.5 log cps/mL | 1.6 |

### Independent effect of age

To take into account the fact that the risk of experiencing WHO stage 4 increase as age increased the rate is multiplied by (age/38)1.2.

For example:

|  |  |
| --- | --- |
| Age | Multiply rate by |
| 20 | 0.46 |
| 30 | 0.75 |
| 40 | 1.06 |
| 50 | 1.39 |

### Independent effect of PCP prophylaxis

If the patient is on PCP prophylaxis, the rate of WHO stage 4 occurring is multiplied by 0.8.

From 1996, patients with a measured CD4 cell count below 350 cells/mm3have an 80% chance of starting PCP prophylaxis and those with a current WHO stage 3 or 4 condition 90% chance of starting it. They interrupt the use of PCP once they have a measured CD4 cell count above 350 cells/mm3, if CD4 cell count is measured, or if the patients has been continuously on treatment and did not experience WHO stage 4 or 3 in the last 6 months.

**Independent effect of being on ART**

For patients on a single drug regimen this risk is multiplied by 0.9, for patients on a two drug regimen it is multiplied by 0.85 and for patients on a 3 drug regimen it is multiplied by 0.8, to reflect the fact that being on ART has a positive effect on risk of AIDS and death independent of latest CD4 count and viral load.

#### Occurrence of WHO stage 3 event

To obtain the rate of WHO stage 3 diseases occurring, the rate of WHO stage 4 occurring is multiplied by*fold\_incr\_who3*(See distribution in section “Parameters values and distributions”).

#### Occurrence of HIV-related death

Risk of HIV-related death

To obtain the base rate of occurrence of an HIV related death, the rate of WHO stage 4 occurring is multiplied by*fold\_decr\_hivdeath* (See distribution in section “Parameters values and distributions”).

The base rate of HIV related death is then affected by presence of current TB and whether the patient has an AIDS defining condition. In the first case the rate is multiplied by *incr\_death\_rate\_tb*, in the second case by *incr\_death\_rate\_adc*

It is assume 15% of HIV-related deaths (i.e. not including deaths that arise due to background mortality rates) are classified as non-HIV-related.

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