ASSA HIV SUB-POPULATION MODEL

2023 model release

Actuarial Society of South Africa

Demography and Epidemiology Committee

ACTUARIAL SOCIETY
SOUTH AFRICA

1. Background

1.1 Purpose, intended model usage and professionalism

The Actuarial Society of South Africa (ASSA) Demography and Epidemiology committee (ASSA DEC) is releasing its 2023 HIV sub-population model (SPM), hereafter "ASSA SPM2023", to address limitations of previous ASSA SPMs (described in section 1.2) such as ASSASelect or PGN105 models (released in the early 2000s). The purpose of this document is only to provide high-level insights into the ASSA SPM2023. ASSA will be releasing the model together with comprehensive model documentation in Q3 2023 which will provide extensive model documentation. Previous SPMs are no longer deemed suitable in model design, assumed survival on anti-retroviral treatment (ART) and don't reflect modern ART clinical guidelines. The ASSA SPM2023 represents an improvement to previous SPMs that aims to enable actuaries and other users to generate projections of the future extra HIV-related mortality for a given sub-population that are more accurate and reflective of the current HIV epidemic. Like all models, future enhancements are possible and will be outlined in the model release.

The main intended application (use case) of the model remains unchanged from previous ASSA SPMs, namely to estimate extra HIV-related mortality rates for the purposes of deriving best estimates of all-cause mortality for life insurance pricing and valuation. The model is intended for application to both individual fully underwritten and non-underwritten business such as group life, funeral etc. A subset of such application is accounting for the impact of a cohort of individual life policy applicants that are selected to be HIV negative at policy application. The primary users of the model remain pricing and valuation actuaries involved in setting pricing and valuation assumptions.

ASSA SPM2023 is largely based on research (hereafter "authors' research") such as "*Survival of adults with HIV-1 infection or Type 2 diabetes in the South African private sector*" by Lee Sarkin (link) and "*Outcomes and cost-effectiveness of different models of delivery of antiretroviral therapy*" by Rory Leisegang (link). The authors' research has been published and peer reviewed through examination of the University of Cape Town Medicine Department and electronic journals. This research provides comprehensive literature review and primary research on extra-HIV mortality of HIV-positive South African adults starting ART. While advanced users may consider independently adapting the model for estimating all-cause mortality of an HIV-positive cohort, this application is beyond the intended scope of the ASSA SPM2023 and interested users are recommended to further consult the authors' research.

As per all previous ASSA SPMs, ASSA SPM2023 is calibrated to a specific population's survival (described in detail in section 2) and users continue to be expected to calibrate the model to reflect a sub-population's survival that's appropriate for their professional context. Further, users' attention is drawn to relevant ASSA professional guidance, namely Advisory Practice Note (APN) 105 (link) on deriving extra HIV-related mortality assumptions.

1.2 Why the update was necessary - limitations of existing ASSA SPMs

The following limitations of existing ASSA SPMs are addressed by ASSA SPM2023 and include changes in how survival on ART is modelled, both prior to and after initiating ART, the latter having the largest improvement in projected survival. This is justified with recent research clearly showing that existing ASSA ART-survival assumptions are prudent. The authors' research justifies that the following variables are highly prognostic of survival on ART yet are not considered by existing ASSA SPMs:

- **CD4 count-based multi-state disease system**: the current ASSA SPMs staging system does not consider CD4 count at all and instead uses only WHO stage (clinical symptoms) however current CD4 count is the most prognostic variable for future survival and is covered below in more detail.
- **Baseline CD4 count:** (CD4 count nearest to but prior to initiating ART). While current ART eligibility guidelines no longer use the baseline CD4 count to determine a patient's eligibility to start ART, the baseline CD4 count still has prognostic value for survival within the initial 3-5 years on ART. This is explained by noting that (1) many patients have historically started ART at lower (<200 cells/µl) CD4 counts, (2) this range of baseline CD4 count is associated with higher early mortality and (3) research suggests that if this group interrupts ART (non-adherent with clinical guidelines) this subgroup's current CD4 count returns to baseline levels, resulting in increased mortality risk.
- **Baseline HIV-1 viral load (VL):** (VL nearest to but prior to initiating ART) research has demonstrated prognostic value for survival within the initial years on ART when these data are available. Since baseline VL has never been a criterion for initiating ART, and VL testing is not available in all settings in low- and middle-income settings, the reporting and integration of baseline VL is seldom considered.
- **Baseline clinical stage of disease:** advanced symptoms at the time of starting ART are known to be independent predictors of survival on ART independent of baseline or current CD4 or HIV-1 viral load (VL). Examples include World Health Organization (WHO) stage 3 or 4 symptoms.
- **Current (time-updated) CD4 count and VL:** CD4 count or VL measured at subsequent time points after initiating ART, also known as time-updated or longitudinal measurements. Current CD4 count and VL are widely acknowledged (see authors research) as the most prognostic variables for mortality after starting ART. Three examples of models that considered current CD4 count were Goldie et al. 2006, Leisegang et al. 2012 and Rath-Meyer et al. 2014 and only two of Goldie and Leisegang considered the impact of VL on CD4 count changes. Models that include both current CD4 count and VL are necessary to appropriately model the impact of a suppressed VL on prevalence and survival given that (1) changes in CD4 count are a function of VL and (2) for generalizing the model into settings where the relative proportion of people with suppressed VL differs. Moreover, a model that does not consider VL suppression is also of limited value for assessing the impact of education and other interventions on VL suppression rates and thus HIV prevalence and mortality rates.
- **Time on ART:** mortality after starting ART is generally observed to reduce with increasing duration on ART. The extent of high mortality in the first year on ART varies by baseline CD4 count and/or WHO stage and is a significant feature observed in the authors' own data and other South African public-sector programmes as described in the authors' research.

- **Loss to follow up (LTFU) / ART interruption / ART discontinuance:** LTFU refers to patients becoming lost from care and is often associated with interrupting ART and stopping ART altogether. LTFU can lead to significant increases in mortality since the VL increases, resulting in decreasing CD4 count and increasing mortality. Further, LTFU is an important driver of mortality on ART given that some studies suggest that patients defaulting on ART quickly return to pre-ART CD4 levels and may therefore experience significant excess mortality (El-Sadr et al. 2006) in the case of low baseline CD4 counts. More often, LTFU is often regarded as an end-stage (Brinkhof et al. 2010, Johnson et al. 2013) whereas more detailed analyses show that a significant portion return to care (RTC) and restart ART (Ahonkhai et al. 2012, Leisegang et al. 2012). Therefore a LTFU model was considered similar to Leisegang et al. (2012) which allows for patients to become LTFU, mortality during periods of LTFU or RTC and restart ART (Figure 2).
- **Interaction of baseline and current variables:** The authors' research references relevant published literature and further supports this with primary research showing that when controlling for the effect of the response to ART (current CD4 count and VL at different durations on ART), baseline CD4 count only has prognostic value for mortality within the initial 3-5 years of ART.

Without accounting for these variables, existing ASSA SPMs are unable to model survival on ART realistically and have limited use for longer-term projections and scenario modelling. The details of the model methodology implemented are covered in section 3.

2 Data

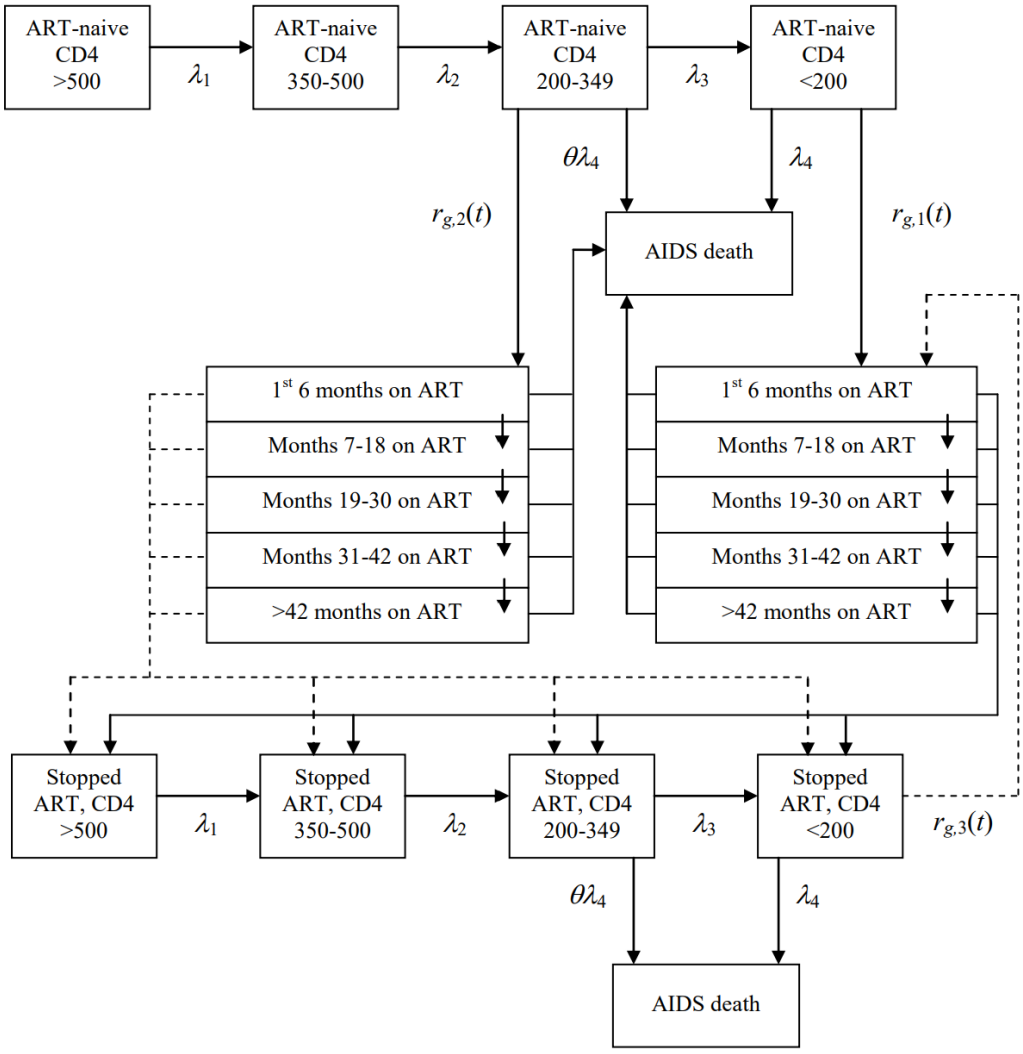
The authors' research is based on large cohorts of HIV-positive and HIV-negative lives that represent employed lives on medical schemes in South Africa which are a better proxy for insured populations than the general population. The data are ideal for informing the update to ASSA SPMs since they (1) contain large numbers of patients, (2), have long follow up times after starting ART, (3) include both baseline and current (time updated) CD4 counts and VL measurements, (4) have accurate mortality ascertainment achieved via the authors' access to the national death registry and (5) have significant relevant insights already published as peer-reviewed research. The authors developed methods for estimating HIV prevalence, non-HIV and HIV-related mortality from historic medical scheme claims data. Therefore, all key types of calibration data needed for calibrating the ASSA SPM2023 were available including HIV prevalence; mortality of HIV-negative, HIV-positive and all lives; and ART coverage. A phenomenal amount of work was necessary to process and clean source data from the HIV managed care programme and medical schemes, derive a valid cohort, derive calibration estimates and develop survival models. For more details on the data used, please refer to the full model documentation.

3 Model methodology

3.1 Baseline model considered

Leigh F. Johnson, Katharina Kranzer, Keren Middelkoop, Robin Wood published an SPM (hereafter "Masiphumelele model") in 2011 of the impact of HIV and ART in the Masiphumelele community of the Western Cape, under the UCT Centre for Infectious Disease Epidemiology and Research as a working paper (link). Given the absence of CD4 count from the multi-state model of survival in prior ASSA SPMs, the Masiphumelele model was of relevance for the ASSA SPM2023 update given its CD4-based multi-state model of survival (Figure 1). The Masiphumelele model has been adapted using a more recent formulation of HIV survival developed in the authors' research which is described in section 3.2.

Figure 1: Multi-state model of survival after ART initiation (Johnson et al, 2011). For simplicity, transitions due to non-HIV mortality and migration are not shown.

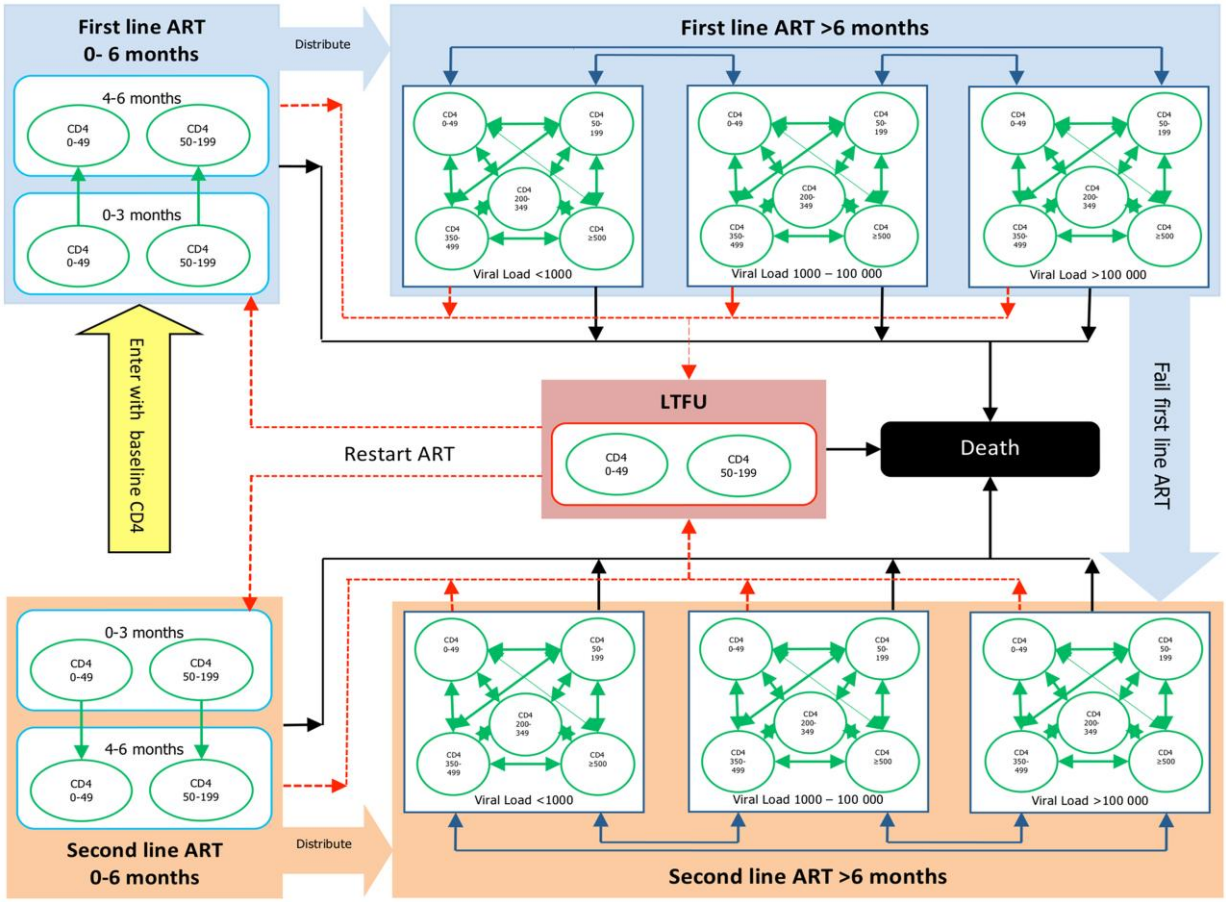


3.2 Recent models including current CD4 count and viral load

A newer SPM by Leisegang et al. (2013) accounts for dynamic changes in CD4 and VL status in addition to program LTFU and reentry, better reflecting changing dynamics over time (Figure 2). For example, GP-based care may be

associated with improved patient retention as demonstrated by Leisegang et al. (2013) and Mokhele et al. (2019), and the reduced mortality and morbidity associated with lower rates of LTFU over time can have a profound impact on outcomes and costs as demonstrated by Leisegang et al. (2013).

Figure 2: Model proposed by Leisegang et al. (2013) including loss to follow-up and return-to-care



3.3 Implementation of new model features

The ASSA SPM2023 is derived from the structure of the Liesegang et al. (2013) model with some changes in order to allow for the intended purpose. The Excel spreadsheet originated has its roots in the Masiphumelele model built by Johnson et al (2013). Although the state/staging structure has been completely overhauled some original assumptions have been changed.

The final model is a multi-state model that models transitions from an uninfected state to various stages of infection and treatment, using a monthly projection granularity. The monthly granularity is largely used in order to ensure that the probability of having multiple state transitions within a single time-step is small enough to be ignored which greatly simplifies the implementation.

3.3.1 Changes from the Liesegang et al. (2013) model

Several simplifications were made to enable practical implementation of the model in Excel:

- No distinction is made between first line and second line ART regimes
- Within the >6 months states, it is only possible to transition to adjacent states within a single timestep. For example, at VL 0-1000, CD4 ≥ 500 in one timestep it is only possible to transition to:
    - VL 1000-100000, CD4 ≥ 500
    - VL 0-1000, CD4 350-499

  It would not be possible to transition to VL 100000+ or to CD4 200-349. It is however possible to transition to one of the states outside of ART: death due to AIDS or otherwise, LTFU or exit from the population.
- Individual cohorts within each ART state are not tracked. In the Liesegang model these are used because duration on ART impacts transition rates. In order to approximate this detail the average duration on ART within each state is tracked instead.

Additional complexity that has been added to the model or changed in order to meet the intended purpose is:

- Within the first 6 months of ART and LTFU the CD4 states used are 0-199, 200-349, 350-500 and ≥ 500 as compared to the 0-49 and 50-199 used by Liesegang. This is in order to match the states used by lives not on treatment, but at the same time allow for treatment initiation at higher CD4 counts.
- Allowance for new entrants and population exits has been added. The modelling of this is currently handled in a relatively simple manner – although withdrawals and new entrants are allowed for in most states. New entrants are allocated between treated and untreated using a high-level assumption. A final scaling is applied to ensure that the population counts match assumptions for population sizes in each calendar year to be provided by the user.

4 Calibration, projections, user guide and reasonability checks

The comprehensive model documentation includes details coverage of this.

5 Research team

The project team consists of Lee Sarkin, Dr Rory Leisegang and Marc Burgess.

Lee Sarkin

Lee is the Chairperson of the ASSA Demography and Epidemiology committee which is responsible for maintaining the HIV and AIDS sub-populations used by the actuarial profession. Lee has been a member of this ASSA committee (previously “AIDS committee” since 2006) and has been modelling the impact of HIV and other chronic conditions on sub-populations in the Southern African public and private sectors for 18 years for insurers, companies, government departments, medical schemes, and financial services regulators. He has extensive experience working with HIV disease management programme data of South Africa’s largest medical scheme administrators and calibrating HIV sub-population models with this data and deriving extra-HIV mortality assumptions.

Lee completed an MSc in the University of Cape Town (UCT) medicine department on the insurability of South African HIV-infected adults initiating ART. The study involved a multi-stakeholder collaboration including South Africa's largest HIV managed care programme, UCT medicine department, medical scheme administrators and Munich Re. The research (link) received the best healthcare track award at the 2014 International Congress of Actuaries in Washington, D.C. The MSc analyzed the survival of a cohort of over 100,000 South African HIV-positive adults starting ART with long follow up times and included both baseline and current (time-updated) characteristics, the largest cohort to be receiving care in a private healthcare setting globally. His MSc research created an HIV underwriting guideline that contributed to insurers in South Africa widening insurability of HIV as a chronic condition through initial underwriting, consistent with other chronic conditions and reducing stigma.

In the last 10 years Lee specialized in AI and advanced analytics applications in insurance where he is now Regional Chief Analytics Officer for Munich Re covering APAC, Middle East and Africa (life and health).

RORY LEISEGANG

Rory is a chemical engineer, medical docto and holds a PhD in Clinical Pharmacology from UCT and a post-graduate diploma Certificate in Core Public Health Concepts through the University of North Carolina. He is skilled in several database and statistical software languages and has extensive experience working with large longitudinal datasets. His research within UCT has been presented at several international and local conferences, published in several papers, and earned him several internationally competitive grants.

Rory is an expert in modelling cost and outcomes of HIV and AIDS. He has worked extensively with healthcare providers (private, public-private, and public sectors including Aid for AIDS, Medscheme, Broachreach, and the Aurum Institute) in Southern Africa while working as a researcher within the Division of Clinical Pharmacology, UCT, with specific focus on HIV-care and non-communicable diseases. He has extensive experience as a qualified medical practitioner, having lead a private medical practice. He currently works for Gilead Sciences as a Director of Clinical Pharmacology within the Pediatric Centre of Excellence, Dublin, where he overseas clinical trials within the HIV sector.

Marc Burgess

Marc is an actuary at RGA who has been a primary contributor to the modelling work performed by both the ASSA Demography and Epidemiology Committee and Continuous Statistical Investigation Committee, including building the frameworks used for the ongoing new-generation mortality investigation and industry-wide COVID-19 reporting. He has experience building models and tooling in a wide range of programming languages, databases and actuarial platforms. Marc has 12 years of experience in the reinsurance market, beginning in valuations before taking on actuarial research and development, and now works as a health actuary and global project lead. He is currently completing an MSc in data science at the University of Cape Town.