ASSA HIV SUB-POPULATION MODEL

2023

Released by the

Actuarial Society of South Africa

Demography and Epidemiology Committee

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1. Background

1.1 Purpose, intended model usage and professionalism

The purpose of this document is to document the 2023 release of the Actuarial Society of South Africa's (ASSA) sub-population model (SPM) to provide users with sufficient background understanding to enable users to apply the model and understand its limitations and potential future enhancements.

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 required to test HIV at the time of policy application. The model is also able and intended to model extra HIV-related mortality for non-underwritten populations (e.g., group life, funeral, company workforce, etc.). The primary users of the model remain pricing and valuation actuaries involved in setting pricing and valuation bases (terms of trade).

While advanced users may consider independently adapting the model for estimating all-cause mortality of an HIV-positive cohort, this application of the model is not its intended purpose and is regarded as out of scope for this model release. For the latter purpose, users may refer to significant existing research (hereafter "authors' research") from the authors 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. This research provides comprehensive literature review and primary research on extra-HIV mortality of HIV-positive South African adults starting anti-retroviral treatment (ART). This research marks a material improvement in research into extra-HIV mortality of HIV-positive adults starting ART compared with that available at the time of release of current ASSA SPMs (e.g., ASSASelect or PGN105 models) released in the early 2000s. The 2023 ASSA SPM release is therefore critical as existing ASSA SPMs aren't suitable in model design, assumed survival on ART and don't reflect modern ART clinical guidelines.

As per all previous ASSA SPMs, the model 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 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 Limitations of existing ASSA SPMs informing enhancements

The following limitations of existing ASSA SPMs (ASSASelect and PGN105 models) are addressed in the 2023 update and include changes in how survival is modelled, both prior to and after initiating ART, the latter having the largest

improvement in estimated survival relative to existing ASSA models. This is justified with recent research clearly showing that existing ASSA ART-survival assumptions are prudent. The authors' research justified 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 WHO stage (clinical symptoms) only 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. Additionally, since many patients have historically started ART at lower (<200 cells/µl) CD4 counts and research suggests that if this group interrupts ART (non-adherence with clinical guidelines) that this subgroup's current CD4 count returns to baseline levels, resulting in increased mortality risk at longer durations of ART.
- **Baseline HIV-1 viral load (VL):** (VL nearest to but prior to initiating ART) research has demonstrated prognostic value for survival within the initial 3-7 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 predictors of survival on ART independently of baseline or current CD4 or 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 changing VL on CD4 count. 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. Further, complications from long-term use of ART (relevant for whole-of-life insurance) are suggested by some research, e.g. increased risk of non-communicable disease.
- **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 current CD4 counts of patients defaulting on ART quickly return to baseline levels. In the of the latter being at low levels, the result could be significant excess mortality (El-Sadr et al. 2006). 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). An LTFU model similar to Leisegang et al. (2012) was therefore implemented, allowing for patients to become LTFU, die while 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 in the 2023 ASSA SPM are covered in section 3.

1.3 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 over 17 years for insurers, companies, government departments, medical schemes, and financial services regulators. He has 18 years' experience in various actuarial roles both at primary insurers and reinsurers from pricing, product development, risk management and consulting to advanced analytics. 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 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 lead to 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, a medical doctor, 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 started and lead his own private 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.

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) have large patient volumes; (2) have long follow up times after starting ART; (3) include both baseline and current CD4 count and VL measurements; (4) have accurate mortality ascertainment via the national death registry; and (5) have significant

relevant insights already published as peer-reviewed research. The authors developed algorithms 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 updating the ASSA SPM were available (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 managed care programme and medical schemes, derive a valid cohort, derive calibration estimates and develop survival models.

Section 2.1 briefly refers to the overall medical population (refer to authors research for more details) from which various results are derived for the purpose of calibrating the 2023 ASSA SPM, section 2.2 describes the HIV-positive cohort and section 2.3 describes the calibration data derived from the cohort data against which the model is calibrated.

2.1 Overview of medical scheme population

The authors research describes in detail that an HIV-positive cohort and HIV-uninfected cohort could be extracted from one of the largest South African medical scheme populations. Therefore, all calibration estimates and comparisons of outcomes in HIV-positive and HIV-uninfected subgroups reflect a common overall sub-population profile (medical scheme, largely employed lives). Section 2.2 describes the HIV-positive cohort in detail. For details on the medical scheme population, refer to the authors' research.

2.2 HIV-positive cohort description

2.2.1 Overview

Section 2.2 provides describes the data from which the 2023 ASSA SPM was developed and calibrated. Aid for AIDS (AfA), a private sector comprehensive managed care HIV program in South Africa, has enrolled nearly 300,000 people living with HIV since 1998 making it the (or one of the) largest private sector HIV managed care programmes globally. With the shifting focus towards differentiated service delivery (DSDs) models to meet the ambitious 95-95-95 by 2020 treatment target, evaluating outcomes within cohorts such as AfA has been crucial. Key strengths within this cohort include differentiated pharmacy dispensing (home-refill versus self-refill), adherence (refill) data, detailed claim data, and starting ART at higher baseline CD4 counts.

2.2.2 Introduction and why was the cohort established?

South Africa remains the country with the largest HIV population globally, estimated at over 8 million in 2022 (Thembisa model). AfA was established in June 1998 as a comprehensive disease management program, responsible for the oversight of HIV care for contracted private medical schemes, companies, and public-private-partnership programs (PPPs) in southern African (South Africa, Malawi, Botswana, Zimbabwe, Namibia, Zambia, Mozambique, Lesotho, and Swaziland) (Regensberg, Cowlin et al. 1998). The surge in HIV-related morbidity and mortality at the time meant that facilities and budgets within the public and private sectors were taking significant

strain (Regensberg, Cowlin et al. 1998, Regensberg and Hislop 2003, 2004). Emerging evidence from high income country (HIC) settings suggested ART, while costly, would be effective in reversing disease progression, reducing morbidity, and improving patient survival (Palella, Delaney et al. 1998). ART, therefore, was desperately needed in low- and middle-income countries (LMICs) (2000). Moreover, a reduction in HIV related morbidity and mortality had potential social and financial benefits that would supersede the absolute costs of ART (2000).

HIV care (including ART) was initially only available through a few pilot public sector programs in South Africa (Medecins Sans Frontieres, University of Cape Town et al. 2003, Bekker, Myer et al. 2006), such as prevention of mother-to-child transmission (PMTCT) from 1999, and ART from 2001 (Coetzee, Hilderbrand et al. 2005). From 2001 to 2006, the eligibility criteria for ongoing ART were conservative: baseline CD4 count < 200 cells/µl or WHO stage IV conditions other than extra-pulmonary tuberculosis. At that time, an estimated 1,600 new infections were occurring daily, with nearly 90% of infected individuals unaware of their status, resulting in late presentation (Palella, Delaney et al. 1998). Given that South Africa was still an emerging democracy with significant hurdles to overcome, especially within the fragmented health care sector, private sector and workplace, private HIV programs soon overtook public sector initiatives (Regensberg and Hislop 2003, Rosen, Feeley et al. 2007). For those with private health insurance, the 1998 implementation of the Medical Schemes Act ensured that several chronic illnesses and emergency care were classified and prescribed minimum benefits (1998). Before 2016, AfA implemented a managed care approach with conservative treatment guidelines, outcome monitoring, patient counseling, and clinical support for providers. Numbers registering with AfA soon swelled (Regensberg and Hislop 2003). In essence, the AfA program was aligned with the public health approach to HIV care therefore also WHO guidelines for resource-limited settings (World Health Organization 2003).

2.2.3 Which cohorts contribute to the managed-care program

The populations accessing care through the AfA program included closed (company or government) and open medical schemes, along with public-private partnerships (PPP) within Southern Africa. Recruitment was continuous and voluntary; while members were able to access HIV-related care without being registered with AfA or using personal funds or medical insurance fund savings, reimbursement of HIV related expenses was subject to registration with AfA and authorization by AfA staff. Some flexibility was allowed when patients presented late and were started in a hospital or after a hospitalization event

2.2.4 What data were collected?

Data were collected prospectively. Patient-level data included gender, date of birth, family structure, and region. Identifiers (names, addresses, family units, and policy numbers), physical address, and Republic of South Africa identification number (RSAID) (for principal members only in the earlier years) were available within patient information systems held by the medical fund and its administrator and shared with AfA to avoid duplication errors. AfA captured additional RSAID numbers from the registration form.

Clinical events, including events before registration with AfA, were captured within the same central system and available to the clinicians and pharmacists. This included WHO stage-defining illnesses, pregnancy, tuberculosis, and other events that would have impacted outcomes or HIV care. ART exposure and HIV-related laboratory monitoring results, including that those occurred before registration with AfA, were captured within the system. Laboratory tests included CD4 count, VL, full blood count, cholesterol, genotypic antiretroviral resistance testing, liver and renal function tests. Increasing digitization has helped improve ascertainment of laboratory results, and, over time, nearly all laboratories were allowing monthly digital laboratory result transfers. Moreover, AfA established a system allowing patients to access the laboratory monitoring tests themselves (e.g., 6-month CD4 count and VL tests) to improve monitoring.

Detailed information on HIV-related medication was collected and included prior antiretroviral exposure, authorization details (date, drug) and context (PMTCT, PrEP, PEP, transfer-in, new patient on ongoing), and dispensed medication with date, quantity, dose and dispenser (from which collect- or courier-pharmacy could be determined). Before 2002, combination ART was not available to all members across all schemes due to the high costs of ART and VL tests. Some patients elected to privately purchase a third drug, and therefore the members' exact regimens were uncertain. Beginning 2002, combination ART regimens were available universally without co-payment across all schemes. ART-related toxicities or adverse events which may have impacted either the choice of ARVs or required authorization for additional medication were also captured.

2.2.5 Who enrolled and what protocols were applied?

The first patients enrolled with AfA in 1998. Membership swelled rapidly in the first few years and again with the establishment of the Government Employment Medical Scheme (GEMS) for public servants in 2005. By 2009, GEMS was the second largest private medical scheme in South Africa, providing for over 1 million public servants in South Africa, many of whom were previously ineligible for private medical insurance (McLeod 2011). By 31 August 2015, more than 180,000 people living with HIV had been authorized for ongoing ART and more than 40,000 had enrolled with AfA, though they had not yet initiated ongoing ART.

Table 1. Characteristics of patients initiating ART through Aid for AIDS, 1998 - 2015

		Calender period					
	Total	1998-2000	2001-2003	2004-2006	2007-2009	2010-2012	2012-2015
N	**233 114**	**8 437**	**22 429**	**23 183**	**61 205**	**95 273**	**22 564**
Adult (19+ years on registration)	95%						
N	221 407	7 814	20 936	21 943	58 118	90 761	21 835
Median age (IQR) in years	36.6 (30.7-43.3)	33.8 (28.5-39.5)	34.7 (29.4-40.7)	36.2 (30.6-42.7)	36.3 (30.6-42.9)	37.4 (31.2-44.1)	37.7 (31.7-45.2)
Male (%)	35%	38%	38%	39%	34%	32%	46%
Median baseline CD4 (ICQ) in cells/mm3	195 (94-302)	172 (75-252)	147 (60-226)	140 (59-218)	187 (92-289)	221 (113-324)	267 (138-405)
Child (<19 years on registration)	5%						
N	11 707	623	1 493	1 240	3 087	4 512	729
0-4 years	4 286	351	850	584	1 189	1 152	160
(5-9 years)	3 081	83	283	341	940	1 280	154
(10-15 years)	2 118	37	84	128	517	1 135	217
(15-18 years)	2 199	152	276	187	441	945	198
Median age (IQR) in years	7.4 (2.9-13)	3.8 (1.4-14.9)	3.9 (1.3-9.6)	5.4 (1.8-10.1)	6.7 (2.9-11.3)	9.4 (4.9-14.1)	11.1 (5.4-15.4)
Male (%)	44%	40%	42%	44%	46%	43%	42%

2.2.6 Clinical and other support

All members received ongoing HIV education via their respective medical schemes. Additionally, any member who tested positive for HIV was encouraged to register with AfA. Medical doctors registered with AfA, and support staff received ongoing communication through newsletters, updated clinical guidelines (more recently through a mobile app as well), access to continuous medical education via online learning modules and regular clinical meetings. The clinical guidelines were developed by the AfA Clinical Advisory Committee in conjunction with academic and private sector collaborators.

An important intention of the AfA program was to identify and capture clinical events relevant to the care of an HIV-positive person. These events would "unlock" benefits (e.g., cotrimoxazole prophylaxis for CD4 count < 200 cells/µL). The effectiveness was subsequently dependent on the cooperation from private doctors and patients to inform AfA staff, and therefore enable authorization for event-related expenses related to benefits. Clinical and claims data were used to support patient-level decisions on program outcome monitoring.

In summary, AfA did not manage clinics but instead covered patients' HIV-related expenses either directly or through reimbursement. If members had depleted their general medical scheme funds, AfA would authorize up to two additional visits per year with an AFA-registered doctor to provide HIV-related care and ensure continuity of care. Most patients accessed private practice and hospital services within their regions, although there were some specialist HIV practices.

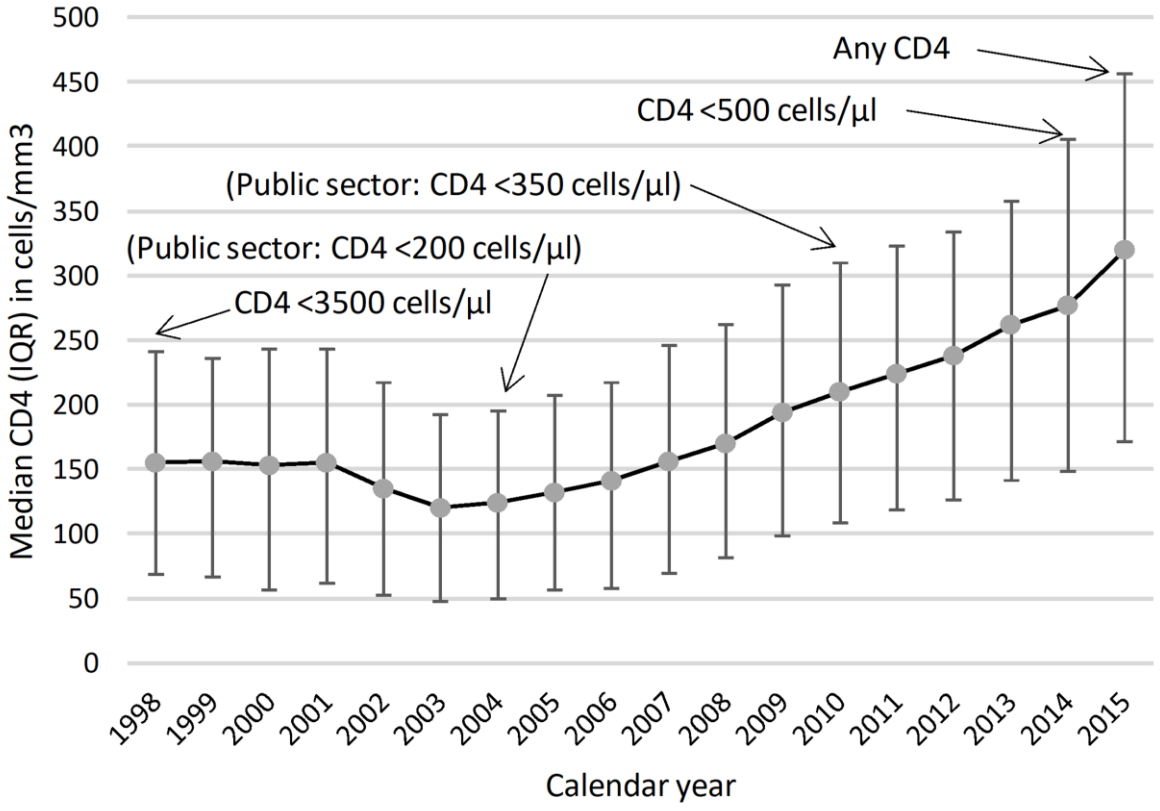
2.2.7 Eligibility for ART

When the AfA program was formed, the internationally accepted guidelines were already recommending that ART be started when the CD4 count dropped below 500 cells/µl with the "hit early, hit hard" approach (Prevention 1998, Richardson, Grant et al. 2014). Financial constraints within an LMIC setting meant that ART was unaffordable

if started too soon (Regensberg, Cowlin et al. 1998), and it was unclear within the literature whether there were benefits for an asymptomatic patient starting ART that early (Regensberg and Hislop 2003). Therefore, the CD4 count threshold for initiating ART was set at ≤ 350 cells/µl (two occasions, 6 to 12 weeks apart); also included in the eligibility criteria for ART were an AIDS defining illness or WHO stage III/IV illness.

The AfA threshold was less conservative than the subsequent 2003 WHO guidelines for resource-limited settings broadly adopted in LMICs (World Health Organization 2003) and the 2004 South African National Department of Health (NDoH) guidelines (National Department of Health South Africa 2004): CD4 count ≤ 200 cells/µl or a WHO stage IV or AIDS-defining illness. Moreover, eligibility for ART in discordant couples was allowed even before it became WHO or NDoH policy to promote supportive environments. Soon afterward, the evidence for treating at higher CD4 counts was established (Strategies for Management of Antiretroviral Therapy Study, Emery et al. 2008, Severe, Pape et al. 2009), and the threshold in the WHO guidelines (World Health Organization 2009, World Health Organization 2010) and NDOH guidelines (National Department of Health South Africa 2010) changed. In 2014, the CD4 count threshold for ART in AfA was formally changed to < 500 cells/µl (or any staging illness (2015)), and in 2016, the threshold was formally abandoned completely (2015). A similar incremental approach of increasing CD4 count and decreasing stage was echoed within WHO and NDoH guidelines. The impacts of changing CD4 count threshold and earlier initiation of ART over time is shown in Figure 1.

Figure 1. Median baseline CD4+ cell count time by calendar year of people starting antiretroviral therapy (ART) in Aid for Aids, indicating changes in Aid for Aids (and public sector) CD4+ threshold for starting ART over time.



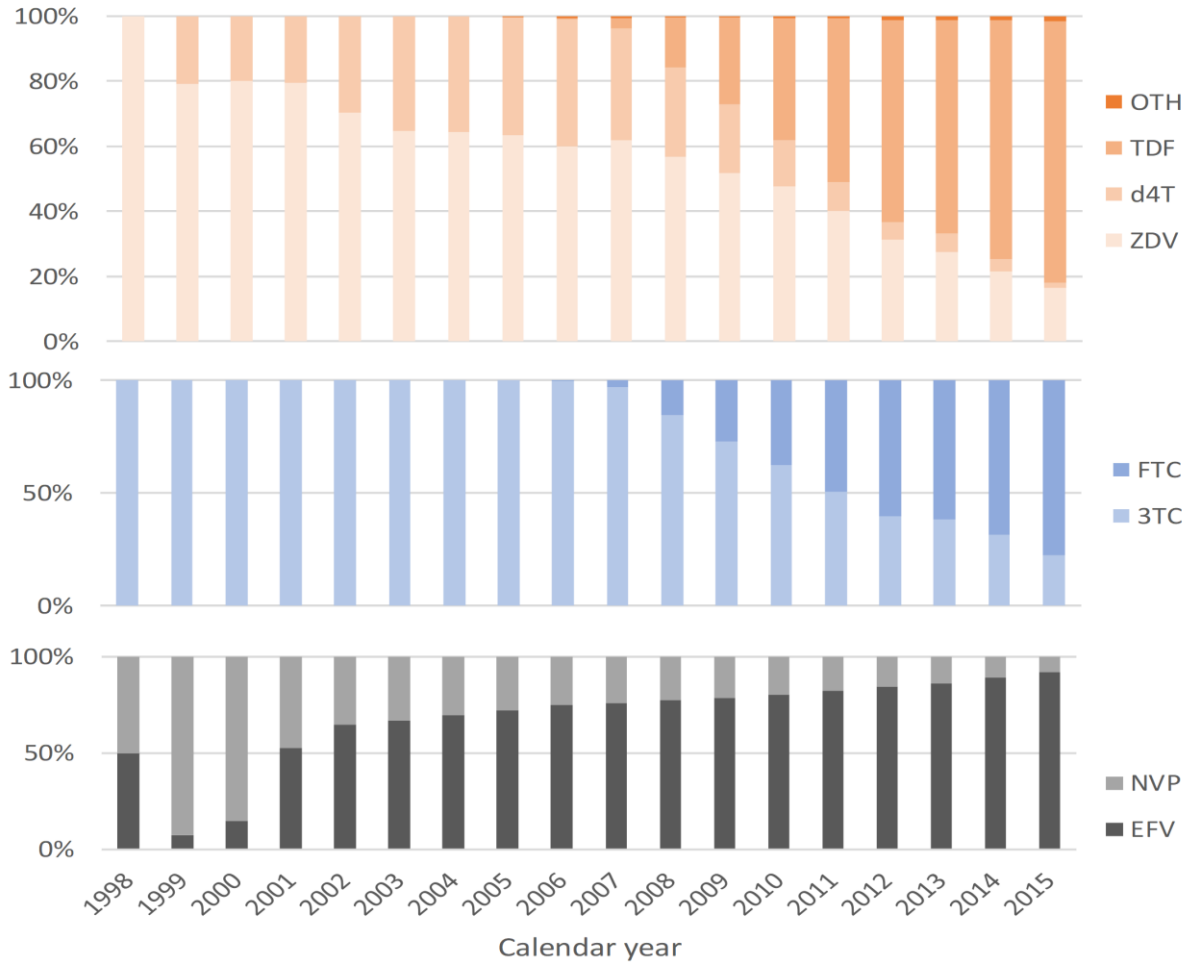
2.2.8 ART regimens

At the launch of the AfA programme in 1998, the internationally accepted guidelines promoted triple therapy or combination ART in any patient with a CD4 count < 500 cells/µl. Initially, the high costs of ART - namely a protease inhibitor (PI) with two non-nucleoside reverse transcriptase inhibitors (NNRTIs) together with CD4, VL and other laboratory monitoring - was not affordable even within the private sector schemes in South Africa (1998, Regensberg, Cowlin et al. 1998). AfA, therefore, recommended "levels of coverage" be established within medical schemes: prevention of mother-to-child transmission or PMTCT with either dual therapy or triple therapy (Regensberg, Cowlin et al. 1998, Regensberg and Hislop 2003). Initially, they focused on rolling out PMTCT and dual therapy without co-payment, and co-payment for triple therapy; by 2002, nearly all schemes were covering triple therapy without co-payment; and NDoH negotiations with pharmacies had resulted in a reduction in dispensing fees. Additionally, international pressure had ensured reduced drug costs through access pricing for LMICs (2000).

As antiretrovirals became widely available in the 2000s, the recommended initial regimen for LMICs including AfA evolved to a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with an NNRTI instead of a PI. AfA guidelines, however, continued to allow for more flexibility in terms of initial regimen, and both NNRTI- and PI-containing regimens were permitted. Up to 10% of patients in the early phase of the programme started treatment with a PI-containing regimen, but this trend gradually abated as confidence in the WHO approach grew. Furthermore, ritonavir-boosted saquinavir, indinavir, or lopinavir were all initially available as PIs. Ritonavir-boosted lopinavir soon replaced other PIs due to its superior effectiveness and tolerability.

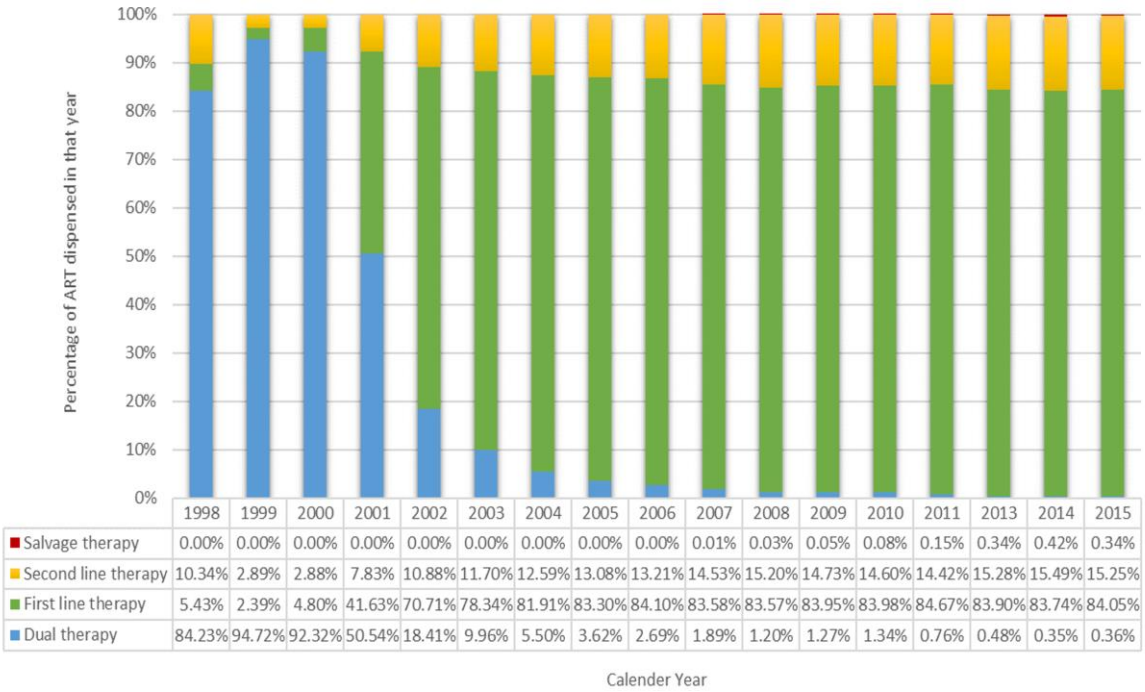
In terms of specific indications, efavirenz-containing regimens were provided for those patients on rifampicin for tuberculosis. Nevirapine (NVP)-containing therapy was recommended for women of childbearing potential who did not commit to using two reliable methods of contraception (e.g., condoms and hormonal contraceptives) due to concerns about the risk of teratogenicity with efavirenz (Chersich, Urban et al. 2006). In keeping with other pilot ART programs in South Africa (Bekker, Myer et al. 2006, Stinson, Goemaere et al. 2016), AfA recommended AZT+3TC as the preferred initial NRTI backbone; many of the public pilot studies later switched to d4T+3TC to align with the first NDOH guidelines in 2004. The preferred NRTI backbone was soon changed to TDF+FTC/3TC, and the use of NVP in women was later eliminated as studies from observation cohorts did not provide evidence that EFV caused harm during pregnancy (2015). The changes to the dispensed first-line regimens by calendar year are shown in Figure 2.

Figure 2. Changing composition of first-line therapy by calendar year for people starting ART in Aid for Aids.



TDF is tenofovir, d4T is stavudine, ZDD is zidovudine, FTC is emtricitabine, 3TC is lamivudine, NVP is nevirapine, EFV is efavirenz, and OTH is other nucleoside/nucleotide reverse transcriptase inhibitor. Third line or salvage regimens have been available since 2007 to patients failing second line therapy and consist of either darunavir/ritonavir, tipranavir/ritonavir, raltegravir, or etravirine containing regimens. After intensive adherence counselling, those with a repeat 3-month VL > 1,000 copies/ml and a history of a possible infection with a resistant strain (e.g. from partner) were offered genotype antiretroviral resistance test (GART); at least one major PI mutation was required to authorized a third line regimen, with the specific regimen being selected from GART results. Patients were then contacted by AFA clinical staff before being switched to assess commitment to adherence to the new regimen. After that, monthly adherence support through telephonic counseling was implemented until the VL was suppressed. The outcomes were encouraging as shown in a publication with 2014 data: 82.9 % had a VL ≤400 copies/ml, and the Kaplan-Meir estimate for survival at 2000 days was 87 % (Meintjes, Dunn et al. 2015). The relative proportion exposure per regimen line over time is shown in Figure 3.

Figure 3. ART regimen exposure per calendar year in adults, 1998-2015



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2013	2014	2015
Salvage therapy	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.01%	0.03%	0.05%	0.08%	0.15%	0.34%	0.42%	0.34%
Second line therapy	10.34%	2.89%	2.88%	7.83%	10.88%	11.70%	12.59%	13.08%	13.21%	14.53%	15.20%	14.73%	14.60%	14.42%	15.28%	15.49%	15.25%
First line therapy	5.43%	2.39%	4.80%	41.63%	70.71%	78.34%	81.91%	83.30%	84.10%	83.58%	83.57%	83.95%	83.98%	84.67%	83.90%	83.74%	84.05%
Dual therapy	84.23%	94.72%	92.32%	50.54%	18.41%	9.96%	5.50%	3.62%	2.69%	1.89%	1.20%	1.27%	1.34%	0.76%	0.48%	0.35%	0.36%

Initially, drugs were collected monthly from private pharmacies (collect-pharmacy). As courier-pharmacy became available, patients increasingly switched to courier-pharmacy. Some medical schemes appointed a courier-pharmacy as the preferred supplier as the increased purchasing power lowered the medical costs for the scheme; patients could still collect medication from their local pharmacy but would have to make a copayment. Others offered both as alternatives.

In summary, the AfA guidelines facilitated more individual choices regarding the regimens and monitoring frequency and intensity than is typically found in LMIC settings. However, a public-sector approach was strongly influential given the resource-constrained context of South Africa. In general, the recommended regimens have, over time, more closely resembled WHO guidelines for LMIC settings (2002) and South African guidelines (National Department of Health South Africa 2015) than HIC guidelines (European AIDS Clinical Society 2015, Association 2016, Gunthard, Saag et al. 2016, Services 2017).

2.2.9 Prophylactic antibiotics, laboratory, and other monitoring

The AfA clinical guidelines defined which aspects of care related to HIV treatment would be covered over time; certain laboratory tests were subject to review and approval by AfA clinical staff to ensure that costs were reimbursed. Important baseline investigations apart from CD4 count and VL (quantitative PCR) included: full blood count and differential count, Pap smear, alanine transferase (ALT), Mantoux Tuberculin skin test, syphilis serology, serum creatinine, estimated glomerular filtration rate, hepatitis B surface antigen, hepatitis C surface antigen (if ALT is elevated), pregnancy test, urine dipstick (proteinuria), serum cryptococcal antigen test, and chest x-ray.

Nutritional support was not routine (2000), but later AfA recommended a multivitamin and Vitamin B complex multivitamin (2002). Prophylaxis included pneumococcal vaccine repeated every five years initially (1998), though this was found later to be controversial and after that reserved for individuals who had had a splenectomy or a chronic lung disease (2000). Annual influenza was recommended as well as Hepatitis B immunization for antibody negative members. Cotrimoxazole/dapsone prophylaxis was recommended for those with a CD4 < 200 cells/µl, which was only stopped once the CD4 count was consistently > 250 cells/µl for at least six months, thereafter > 200 cells/µl. Given that tuberculosis was endemic in South Africa, isoniazid (INH) prophylaxis was initially recommended for six months in patients who had a positive Mantoux test (1998), then later for those who had had recent contact with overt tuberculosis (2000) and those at risk (e.g. miners) (2002).

CD4 count and VL monitoring was recommended to be done 2-3 months after starting ART and after that every 4-6 months (1998). This was aligned with the adopted 2003 WHO (World Health Organization 2003) and 2004 NDOH recommendations (National Department of Health South Africa 2004). The recent shift towards more targeted CD4 count monitoring (only while CD4 count < 200 cells/µl or while failing virologically [VL > 1,000 copies/ml]) is in keeping with HIC guidelines (Services 2017), and is broadly reflected in both the 2016 WHO (World Health Organization 2016) and 2015 NDoH (National Department of Health South Africa 2015) guidelines. Both NDoH and WHO guidelines however also advocated for more targeted VL monitoring, which is not reflected in the AfA guidelines.

2.2.10Adherence and medical support

Given concerns around confidentiality and the complexity of HIV care, a dedicated unit was established to provide patients, doctors, pharmacists, and hospitals with a centralized management and communication portal (Regensberg, Cowlin et al. 1998). For patients, telephonic counseling, pharmacist as well as specialist services were provided by AfA on demand. This was particularly relevant when salvage therapy was introduced as all patients received intensive counseling before commencing treatment (Meintjes, Dunn et al. 2015).

For medical staff, the reimbursement was subject to authorization by the AfA clinical consultant; decisions to start/alter regimens of HIV-related medications (e.g., antibiotics) were therefore communicated with AfA clinical consultants and authorization established before prescribing. More complex decisions (e.g., salvage therapy regimens) were referred to weekly clinical expert meetings, where additional input from academic staff and professional organizations/associations were available.

2.2.11Transfer in

Some patients transferred from other schemes or public sector ART programs (especially in later years). Excluding these patients from analyses proved difficult as the baseline VL data and baseline questionnaire data, which asked for details on previous ART exposure, proved only partially informative (Karamchand, Leisegang et al. 2016).

2.2.12What has been measured: clinical, virologic and immunological outcomes

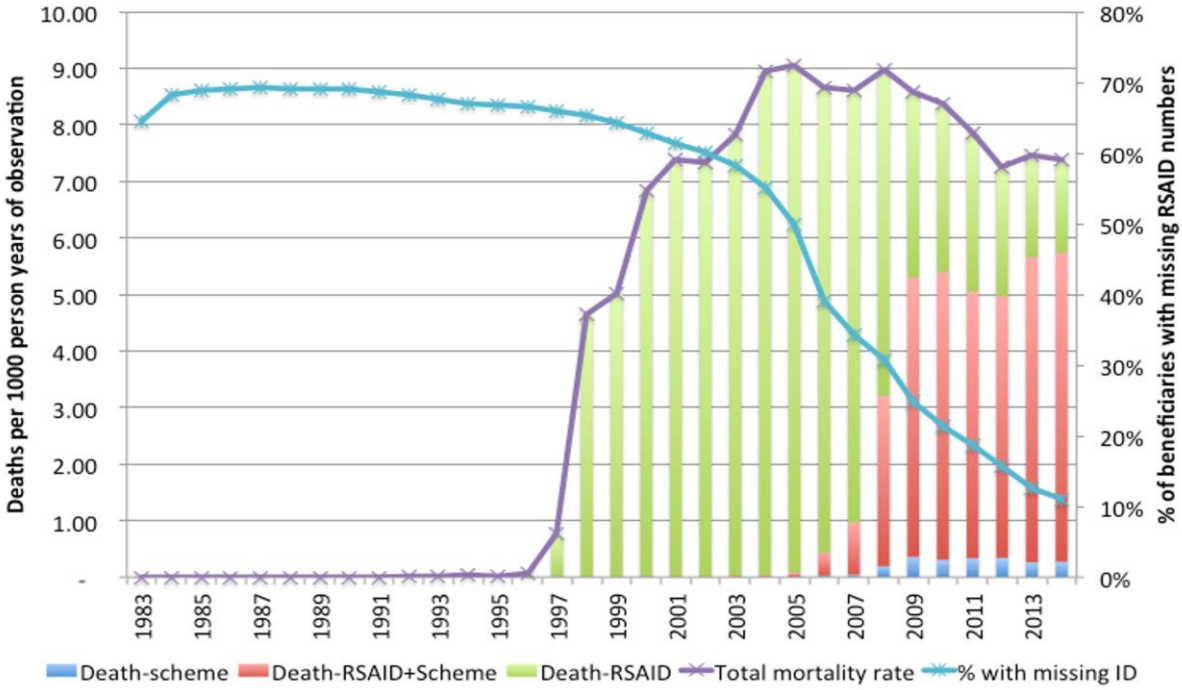
Extensive data is available for patients enrolled in the AfA programme. The patient completes the registration form (usually with their doctor) at enrolment. This information, which includes demographics, prior medication and illness, and HIV-related information (ART exposure, AIDS-defining or WHO stage illness, CD4 count and VL monitoring results), is captured digitally and presented to the medical team for review for authorization. The medical scheme provides information on hospitalization and other outpatient events, including medication dispensed. Initially, pathology results were captured manually, but over time links have been established with private pathology laboratories to facilitate electronic medical record transfers instead. Specific events that may impact HIV care are tracked over time and include pregnancies, infections (meningitis, tuberculosis), and adverse drug reactions.

As an example, data from the AfA cohort were the first from low- and middle-income countries to demonstrate that increased adherence to NNRTI-based ART is strongly associated with improved virologic outcomes in a linear dose-response relationship. In addition, AfA data showed that moderate levels of ART adherence (70% to 90%) to NNRTI-based ART regimens often lead to viral suppression and are not associated with maximum rates of resistance, as in the case for PI-based ART (Nachega, Hislop et al. 2007). Furthermore, compared with adults, data from AfA showed that adolescents in southern Africa were less adherent to ART and had lower rates of virologic suppression and immunologic recovery and a higher rate of virologic rebound after initial suppression (Nachega, Hislop et al. 2009). AfA data also demonstrated that pharmacy refill adherence assessments were as accurate as CD4 counts for detecting current virologic failure in this cohort of patients on ART and have the potential to predict virologic failure before it occurs. Approaches to combination ART scale-up in resource-limited settings should include an adherence-based monitoring approach (Bisson, Gross et al. 2008).

2.2.13What has been measured: mortality ascertainment

During follow-up, deaths were communicated to AfA by the attending medical practitioner, hospital case manager (for in-hospital deaths), medical fund administrator, medical scheme, and registered “responsible” medical provider for HIV care. Other studies from the South African public sector have reported that administrator-reported deaths substantially underestimated true deaths when compared with deaths ascertained through linkage with the vital registry (Boulle, Schomaker et al. 2014), and between 90% to 95% of known deaths have been subsequently verified against the registry (Boulle, Van Cutsem et al. 2010). AfA collected significantly more RSAID numbers (as part of the registration process) than either the scheme administrator or scheme itself, particularly for non-principal members; as a result reported mortality ascertainment improved over time (Figure 4). Most missed deaths were misclassified as censored – i.e., as left the medical scheme. Furthermore, determining mortality from RSAID allowed for an improvement in LTFU status ascertainment as well (Boulle, Van Cutsem et al. 2010, Cornell, Schomaker et al. 2012, Johnson, Mossong et al. 2013, Boulle, Schomaker et al. 2014).

Figure 4. Trends in missing national identity number, mortality rates (and percentage determined from scheme information, national identity, and program information) with in a large medical scheme subset (all lives), illustrating the death known to the scheme versus deaths ascertained via the RSAID linkage to the South Africa National Death Register; the blue line (right axis) represents missing national identity



As many patients had been part of their medical schemes for several years, and therefore had multiple records covering their changes membership details over time, to address the limitations which arose from the missing ID numbers, we established a registry where we mapped validated ID numbers across a members within scheme and between scheme membership history using a variety of approaches including internal scheme number, internal AfA number, ID-name-surname-sex-DOB, and combinations of these and achieved >90 mapping of HIV-1 positive individuals. For the control population, while history from a significantly larger population was available (~ 3 million lives), the proportion of missing ID numbers was higher (~50%), and therefore the mapped validated ID numbers was important in reducing this number (~>70%). The earliest records remained impacted where mortality was not well captured by the scheme, and therefore the data from these individuals was exclude as it would not impact more recent and important estimates.

2.2.14What has been measured: loss to follow-up (LTFU)

Most studies have treated LTFU as an alternative state to alive or dead for patients who have started ART (Schomaker, Gsponer et al. 2014), without considering whether the patient is adherent to ART or not. With the increasing availability of digital dispensing systems, particularly within the private sector as dispensing events generated claims, we defined LTFU in our setting as not having received ART medication for six months without being dead. Given the incentive of suppliers to report dispensing events to get paid, and the low barrier for members with no co-payment for HIV related care and convenience of using a local private sector doctor, we anticipated this to be a more accurate representation of LTFU than in most settings.

The manner in which LTFU is incorporated into HIV cohort analyses can substantially impact findings on program effectiveness (Grimsrud, Cornell et al. 2013, Shepherd, Blevins et al. 2013). Many studies define LTFU (in a similar manner to death), as a terminal state (Boulle, Van Cutsem et al. 2010), yet many patients were subsequently found to return to care. Furthermore, while several studies classify members as being LTFU once they have left the program, many of these may have been seeking treatment elsewhere (Court, Leisegang et al. 2014).Courier pharmacy, in which medicine is delivered on a regular basis to the member's designated location (usually their home), has been implemented broadly within the private sector, and more recently other differentiated service delivery models in the public sector including community adherence clubs for stable patients are expanding in South Africa and other settings in sub-Saharan Africa (Wilkinson 2013). A meta-analysis comparing such community- versus facility-based models of ART delivery suggested comparable outcomes (virological suppression and retention in care) for clinically stable HIV-infected patients on treatment in LMICs as well as cost-effectiveness (Nachega, Adetokunboh et al. 2016).

2.2.15What has been measured: costs/utilization

The availability of claims data is unique within the South African context. In previous analyses (Leisegang, Cleary et al. 2009, Leisegang, Maartens et al. 2010), we found 49,517 unique claim categories within the scheme administrators database, of which 4,000 accounted for over 95% of total costs and were grouped as follows: ARVs, other medication, maternity-related care (antenatal services, delivery, caesarean section, and postdelivery paediatric care), general practitioner care, specialist care, hospital accommodation and procedures, CD4 count and VL monitoring, and other investigations (e.g., laboratory tests and radiology). Among other key findings we found that high ART adherence was associated with lower mean monthly direct health care costs, particularly reduced hospitalization costs, in the AFA Cohort (Leisegang, Cleary et al. 2009, Nachega, Leisegang et al. 2010).

2.2.16Progress: 1998-2017

At the end of 2017, there were 85 500 active patients on the programme of whom 81 500. Considering all the lives within the schemes themselves, an estimated 1.6 million lives have the potential to access treatment and care with AfA and nearly 300 000 of those enrolled with AfA since its inception in 1998; scheme administrator changes resulted in many patients being “transferred out” to other disease management programs. The male to female ratio within the program is 1:1.3, consistent with the national average of 1.4. In terms of age of new entrants, the median female age bad was 40 - 44 year (14.5%) and median male age band was 45 - 49 years (10.3%), again consistent with national averages.

AfA has made significant strides towards achieving the UNAIDS 90-90-90 goals by 2020. The percentage of patients with a baseline CD4 >= 200 has increased from 58% in 2009 to 76% at the end of 2017. The

percentage of patients with VL tests has increased from 72.9% in 2009 to 89.8% in 2017; percentage of patients with VL suppression has increased from 77.5% in 2009 to 88.9% in 2017 (AIDS 2018).

2.2.17Strengths and Weaknesses

The AfA database provides a rich description of clinical and cost expenditure patterns in a large South African HIV-infected population. The data are drawn from a reliable database of a managed care organization with more than 25 years of experience in chronic disease management.

2.2.18Ethics approval and permissions

The authors received ethics approval from the University of Cape Town Faculty of Health Sciences regarding publication of research and also obtained explicit permission from the medical scheme for using the data for ASSA's purpose of updating the SPM.

2.3 Derivation of calibration data

This section describes the key calibration derived results used in subsequent model calibration and the methodology for describing how the results were derived from the cohort data. Section 2.2.1 describes the derivation method and section 2.2.2 outlines key calibration derived results.

The following sections describe the following calibration results and the methods for deriving them from source data:

- HIV prevalence
- All-cause mortality in the whole sub-population (includes HIV-positive and HIV-negative lives)
- All-cause mortality in HIV-negative lives
- ART coverage (% of lives on ART at various points in time)
- A recent demographic profile of the scheme

The above calibration estimates are a crucial prerequisite for calibrating the model to ensure that its projections of past years are consistent with observed data and that the model's projections appear reasonable when considered holistically. The model calibration phase is crucial to ensuring that projections into the future are reasonable since, any significant bias arising in the estimates against which the model is calibrated, could distort future projections performed with the model.

Lastly, evidence is provided of the improvement in the quality of the data as a result of implementing the authors' methodology for identifying unique beneficiaries and linking their historic records to establish a valid cohort.

2.3.1 Methodology

Linking unique lives' or scheme beneficiaries' historic records is a crucial prerequisite to deriving the above calibration estimates and for establishing a valid cohort. For example, in order to track beneficiaries' HIV status across time, it was essential that beneficiaries' HIV status could be mapped across historic records. The authors developed an algorithm in order to improve the linkage of historic beneficiary records. The authors also developed a method for estimating HIV status from historic scheme claims. By linking historic records, it was possible to map (carry forward) the HIV status across subsequent records. Without the linkage and carry forward methods, HIV prevalence was not possible to estimate. Sections 2.2.1.1 and 2.2.1.2 outline these methods for improving the data quality and diagnostics that demonstrate the extent of the improvement.

2.3.1.1 Linkage

National South African ID number (RSAID)

South African Identity Number (hereafter RSAID) served as:

- A reliable identifier of unique individual members (beneficiaries) of the scheme;
- A unique identifier (key) for linking various tables such as claim costs, utilizations, pathology, etc.; and
- The key for linking with the national death registry to ascertain vital status and date of death.

RSAID significantly improved mortality ascertainment within the scheme as will be shown when reporting mortality estimates in section 2.2.2.2. Various checks were done on the available RSAID numbers in the beneficiary table (historical records of members) regarding RSAIDs that were empty, incomplete (not 13 digits), valid and invalid (13 digits but checksum or gender or sequence did not align with government standards). The principal member beneficiary category had the highest percentage of RSAID fields that were both populated and valid. The other beneficiary categories contained much more missing RSAID numbers but the extent improved when looking across calendar years. However, the novel unique identifier method described below by the authors significantly improved the proportion of records with populated valid RSAIDs and represents a significant enhancement to the quality of medical scheme mortality ascertainment in South Africa.

Linkage of longitudinal beneficiary records via construction of unique identifier method

Given the limited number of valid RSAID numbers available in earlier calendar years where RSAID was less completely captured within internal scheme data, more especially within the non-principal member records, a novel method was developed for identifying unique beneficiaries and linking their longitudinal records. This allowed calendar years where RSAID number were available to be mapped to other years, significantly increasing the linkage potential with the national death registry. Various identifying variables were considered:

a) Membership and beneficiary numbers – of limited value as they may change in the event of a change in beneficiary category (e.g. spouse to principal member, child to principal member) and were not considered more suitable than the scheme's internal number
b) Scheme internal number – limited value as this may change if a member left and re-joined (even if only 3 months later). This was best demonstrated with records that contained the same valid RSAID number (i.e., most likely a unique individual) but more than one internal number.
c) The combination of name/initial, surname, gender, date of birth (DOB) and ethnicity (where available) were necessary for adequately identifying unique individuals and linking records. This information was only used once linkage of records using internal number and RSAID had been explored.

The novel method effectively identified beneficiaries given the limitations of the data provided and was based on the following principles:

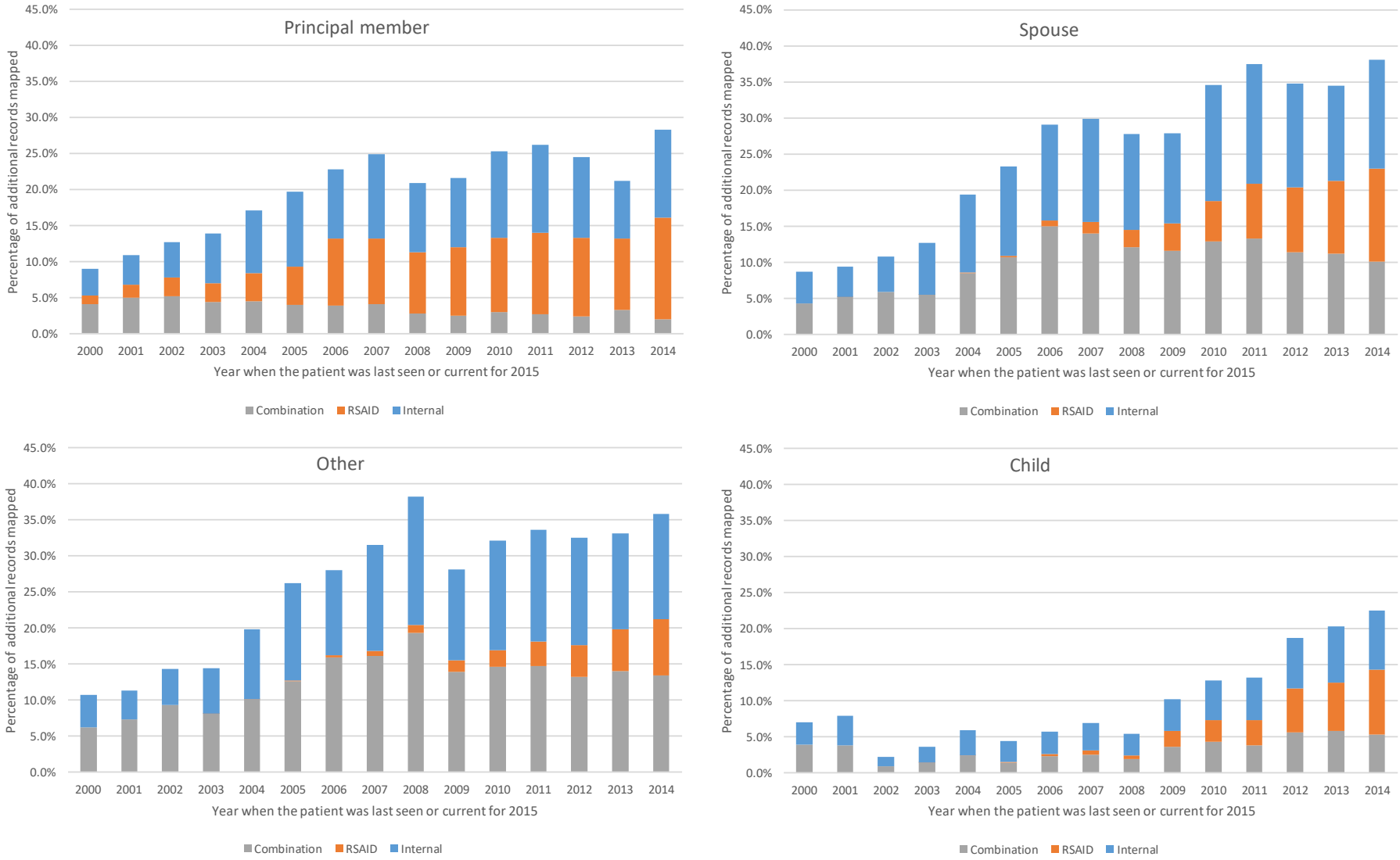
- An interactive approach, whereby a unique set of beneficiaries and their records were identified and assigned to a register, followed by the next set of members and their records.
- Recent data was more relevant and therefore the criteria for selecting the unique set of beneficiaries was current beneficiaries, followed by the beneficiaries who had most recently left, etc.
- Records would be linked to a beneficiary using internal number, followed by RSAID, and finally name/initial, gender, surname, DOB and ethnicity where available). Where RSAID was used to link between records, additional checks against other variables (e.g. surname, name, DOB and gender) were performed to avoid invalid links (e.g. the principal's RSAID is applied to all beneficiaries).

- The value of the above method is shown in Figure 5 as the number of additional rows that could be linked expressed as a percentage of the total number source rows within a given year. Orange and blue bars represent the additional records that could be linked using only RSAID and only scheme internal number respectively. Grey bars indicate records where both scheme internal number or RSAID could be used to link. Key findings include:

- Scheme internal number was not sufficient to link all historical records associated with a unique beneficiary (value of RSAID to address this is illustrated by the orange bars)
- The importance of linking historical records was higher in recent years – the relative percentage of additional records that could be linked with a beneficiary increased over time.
- Scheme internal number and RSAID were adequate for linking records for the principal member beneficiary category. This was expected given the high percentage of valid RSAID numbers within principal member records.
- Spouse and other beneficiary categories had the highest number of additional linked records indicating the greatest benefit from the new linking method given the limited number of populated RSAID fields

- Child beneficiary category had the lowest number of additional linked records and but still benefited from the new method given the limited number of populated RSAID fields

Figure 5: Number of additional rows that were linked via various methods as a percentage of the number source rows within a given year

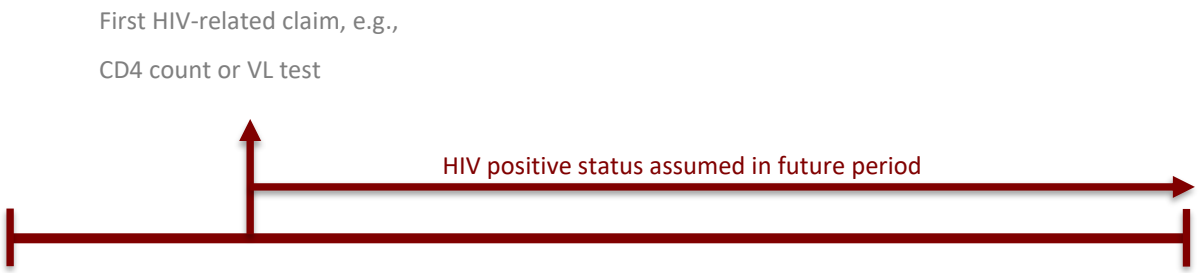


2.3.1.2 HIV Prevalence

HIV prevalence estimation is usually only possible for a sub-population through an HIV prevalence testing / wellness survey and even then, bias arising from lower participation rates is always an inherent feature to consider. All prior ASSA SPMs had relevant prevalence rates to calibrate against. The 2023 ASSA SPM is therefore the first such model to have reasonably robust HIV prevalence estimates available. To derive HIV prevalence estimates for the above medical scheme population, the following methodology was developed using beneficiary claims data as follows:

- For beneficiaries that enrolled on the Aid-for-AIDS (AfA) disease management programme (DMP), an HIV positive status is logical to assume for all beneficiary records arising after registering on AfA.
- For beneficiaries that have never been registered on AfA, a beneficiary's full claims history (2000 – 2014) was used to infer HIV status and, if positive, the earliest suspected date of a positive status. The earliest time point at which an HIV-related claim (e.g. CD4 count test, VL test, ART medication) was made is assumed to be the time point from which an HIV positive status is carried forward (Figure 6) over time or over all subsequent beneficiary records. For further details, refer to the authors' research.

Figure 6: illustration of method for estimating crude HIV prevalence



The newly-developed method for linking historic beneficiary records combined with the HIV status estimation method, enables the estimated HIV status of a unique individual to be tracked longitudinally regardless of scheme option changes, withdrawal and reentry into the scheme, calendar year, etc. This is crucial to establish credible HIV prevalence trends across calendar years.

2.3.1.3 Overall all-cause mortality ascertainment

Through the authors research collaboration with the South African Medical Research Council, the death registry was accessed, allowing the vital status of all scheme beneficiaries with valid RSAID numbers to be ascertained. This is a key value add to the 2023 ASSA SPM since relevant mortality estimates would otherwise not be available for calibration. Mortality would have been significantly underestimated in the absence of linkage with the death registry – the extent is quantified in section 2.4.1.2. For the purpose of calibration the model's projected all-cause

mortality incidence, all-cause mortality incidence rates (deaths per thousand person years of observation (PYO)) were calculated by age, gender, calendar.

2.3.1.4 All-cause mortality in HIV-uninfected lives

All prior ASSA models (and many other epidemiological models) require the user to specify appropriate all-cause mortality in an HIV-uninfected population. Such mortality rates however were seldom possible to estimate from recent and relevant data given the reliability and granularity of available cause-of-death data in sub-population data (insured lives, employed lives, etc.). The authors' research is therefore unique in contributing credible estimates of mortality in HIV-uninfected lives. An HIV-uninfected status was possible to infer across time for beneficiaries of the scheme by developing a method that analyzed the full history of scheme claims data (refer to authors' research for details).

2.3.1.5 Definition of beneficiaries on ART

The number of beneficiaries on ART is defined as the number of active beneficiaries as at 1 July of each calendar year that had been previously authorized by the scheme to initiate ART. These estimates inform the assumption for historic and future ART initiation rates in the model. For further details on which specific ART regimens were authorized for the cohort, please refer to the authors' research.

2.3.2 Calibration derived results

Crude estimates of HIV prevalence, all-cause mortality and the coverage on ART are provided in sections 3.1, 3.2 and 3.3 respectively below.

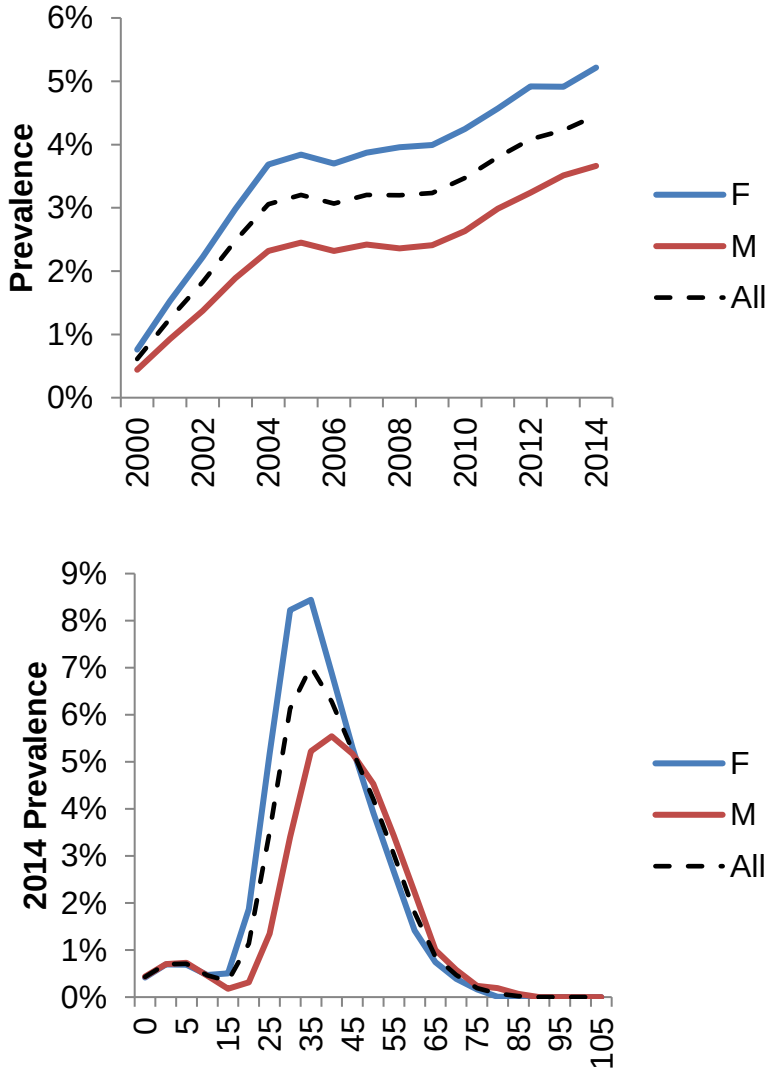
2.3.2.1 HIV prevalence

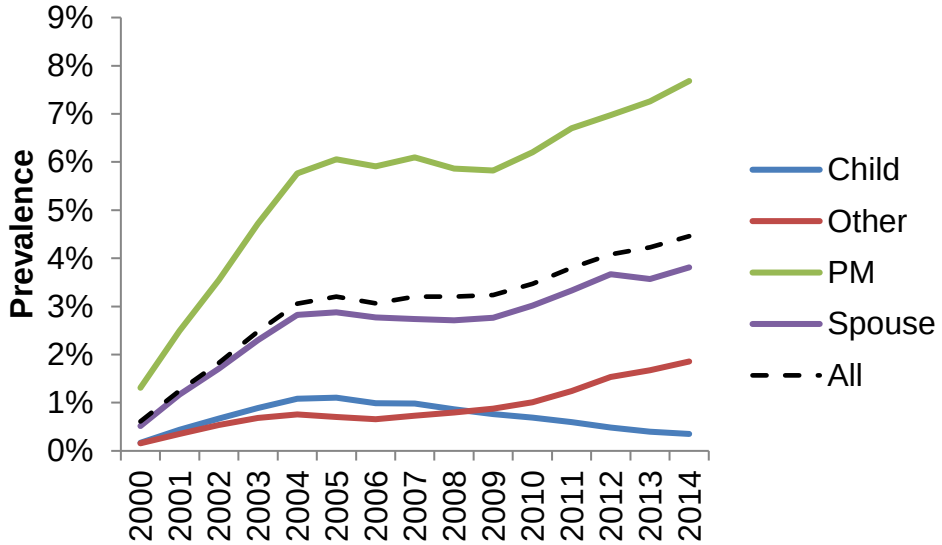
Using the method outlined in section 2.3.3, the first-ever cross-sectional history of the scheme's HIV prevalence is estimated. Key observations:

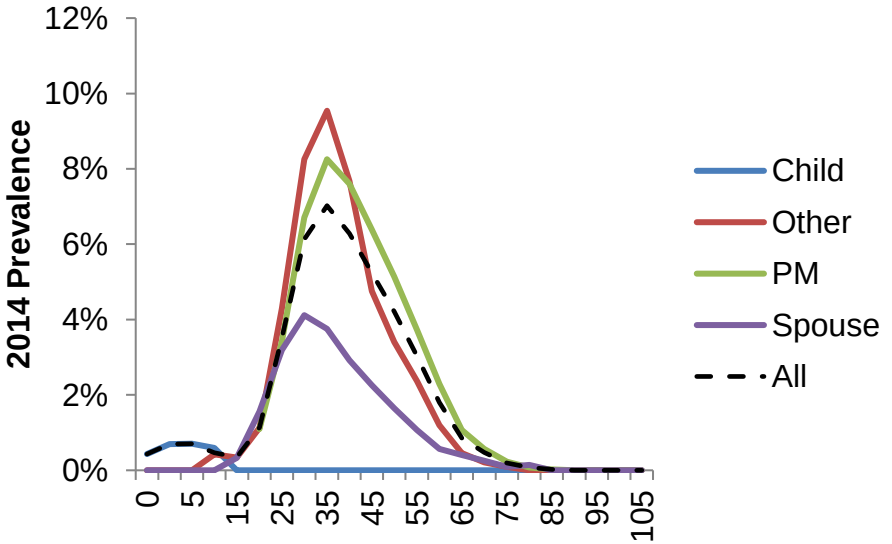
- Females had consistently higher prevalence over time as expected and the progression over age by gender also appears reasonable (Figure 7) compared to
- Principal members have the highest prevalence. Their prevalence exceeds that of spouses owing to the principal members' age profile becoming younger over time and the spouses' age profile becoming older (Appendix 1). Further, the African ethnic group accounts for a higher proportion of principal members in recent years than spouses that contributes towards a higher prevalence in principal members.
- Prevalence in children has decreased since 2005 possibly due to the increasing rollout of prevention-of-mother-to-child transmission (PMTCT).
- Prevalence by age has not only increased dramatically in level over time (Figures 8-10) but also shifted outwards to older ages. A contributing factor towards the latter effect in recent years has been the impact of

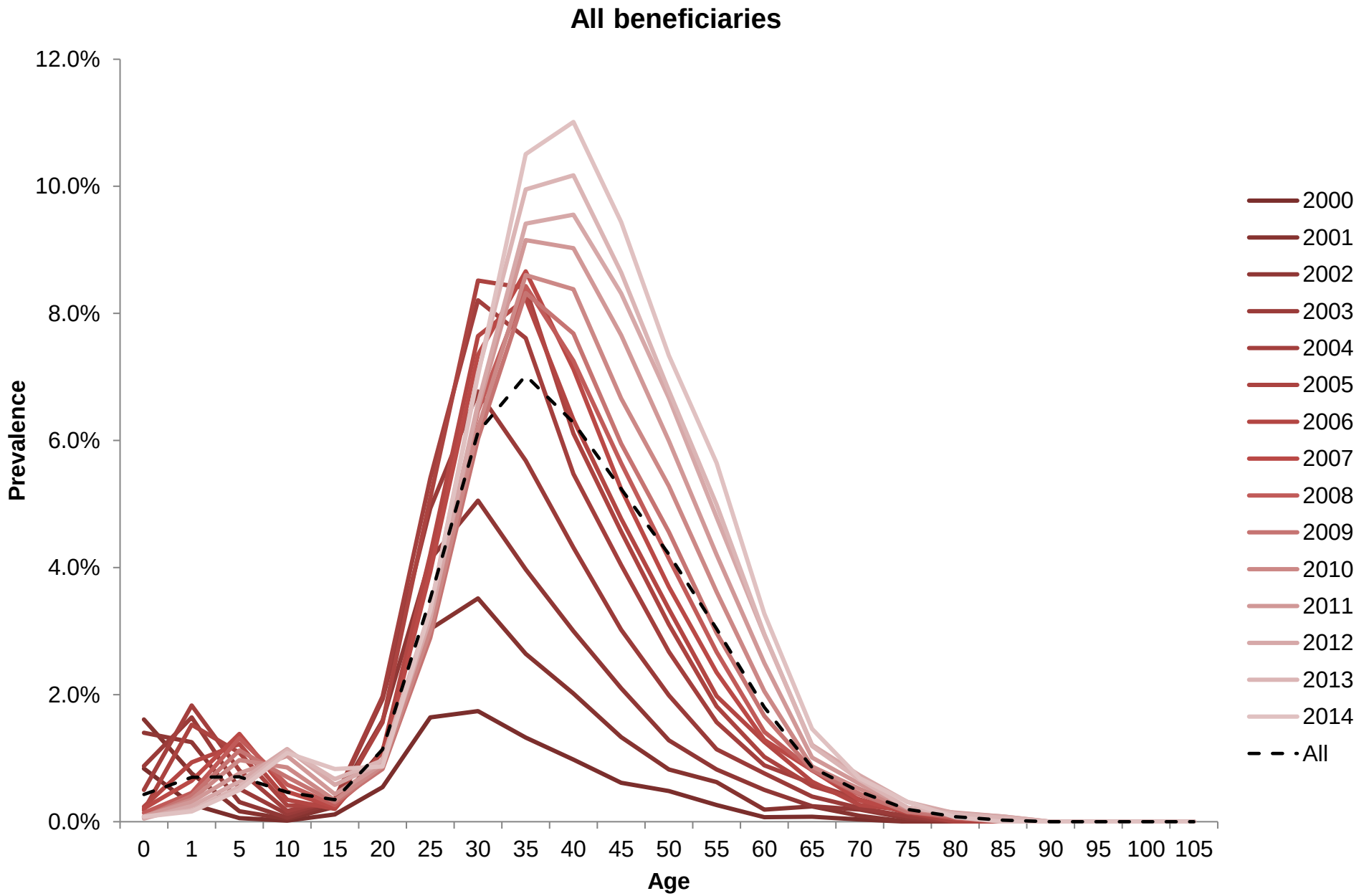
ART whereby survival to older ages is increasingly more likely. The effect is so pronounced that the age band at which prevalence peaks has shifted both for males and females with female prevalence peaking at 14% in the age band 35-39 years. This has implications for an increased burden of non-communicable disease as HIV positive beneficiaries increasingly survive to older ages where diseases like Type 2 Diabetes, Stroke, Cancer become more prevalent. Further, the interaction of ART with an increased incidence of comorbidities such as Type 2 Diabetes become possible with survival to longer durations on ART.

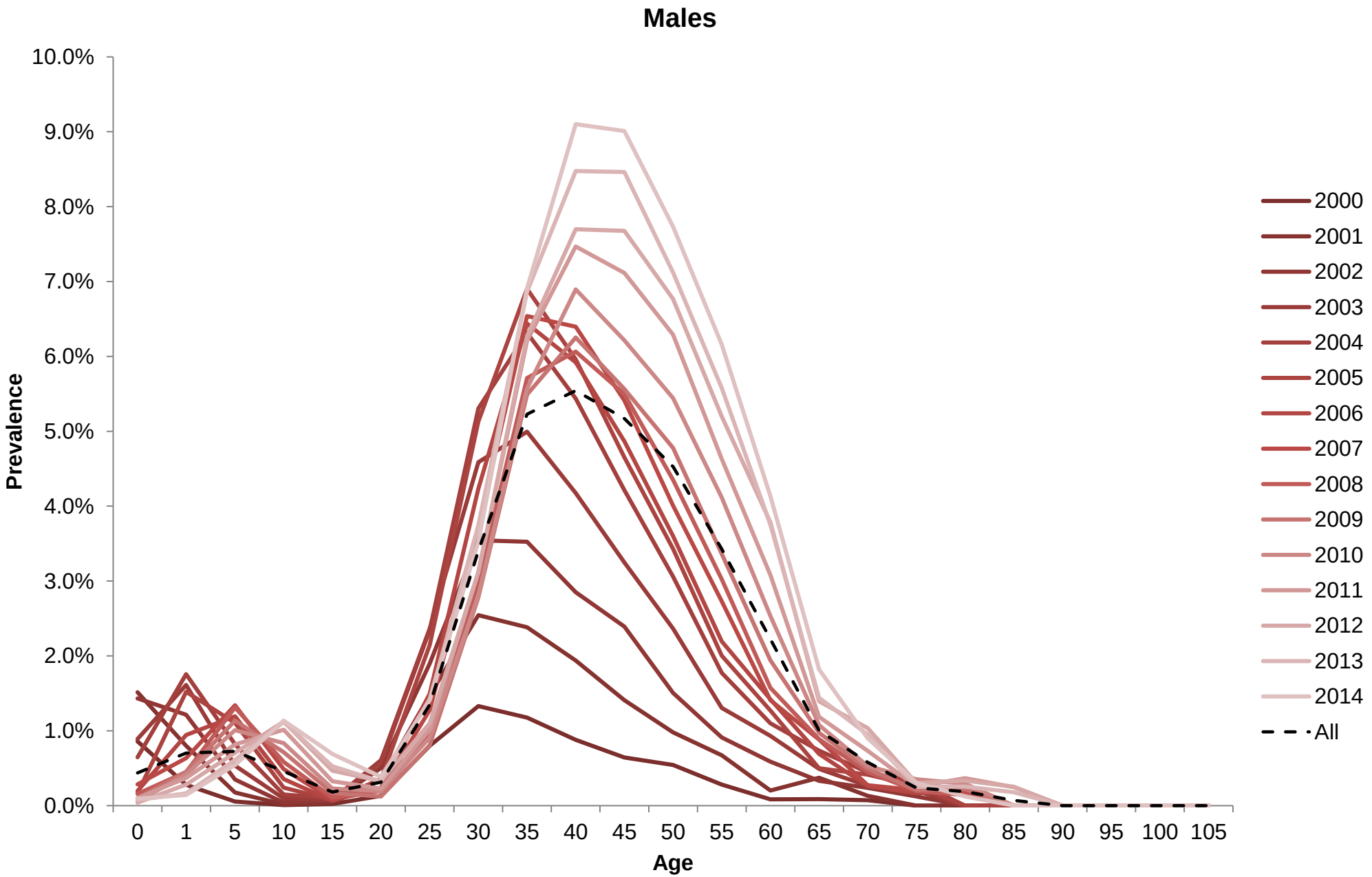
Figure 7: HIV prevalence by calendar year, age, gender, beneficiary category

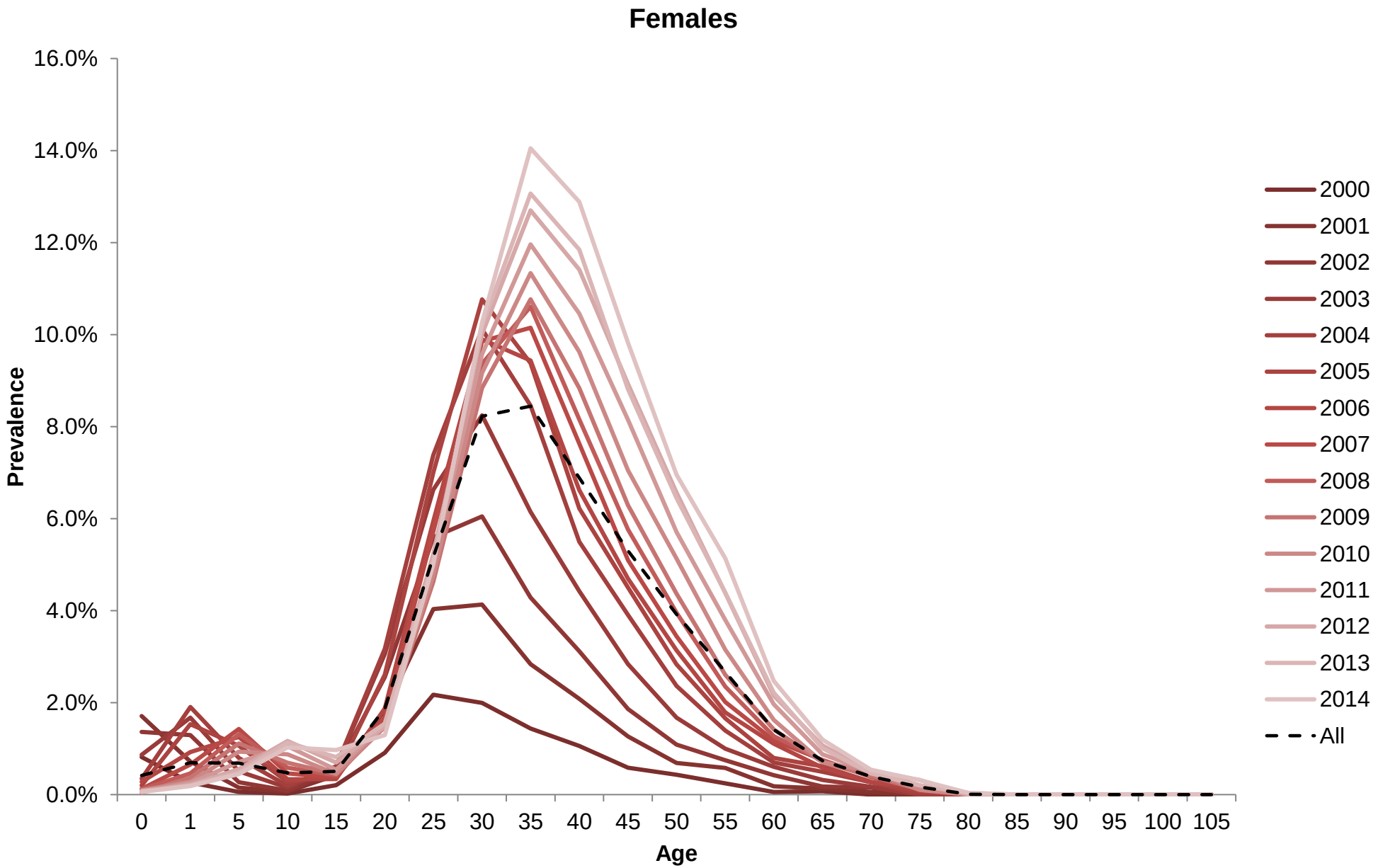







All beneficiaries
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Prevalence
0
1
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
Age
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
All


Males
Prevalence
10.0%
9.0%
8.0%
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0.0%
0 1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105
Age
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
All


Females
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Prevalence
0
1
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
Age
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
All

2.3.2.2 All-cause mortality rates

Figure 11 shows how access to the national death registry has significantly improved the accuracy of mortality incidence rates (deaths per 1000 person years of observation (PYO)). Mortality is estimated only for beneficiaries that had valid RSAID numbers since death could not be accurately verified from other sources. Figure 11 is explained as follows:

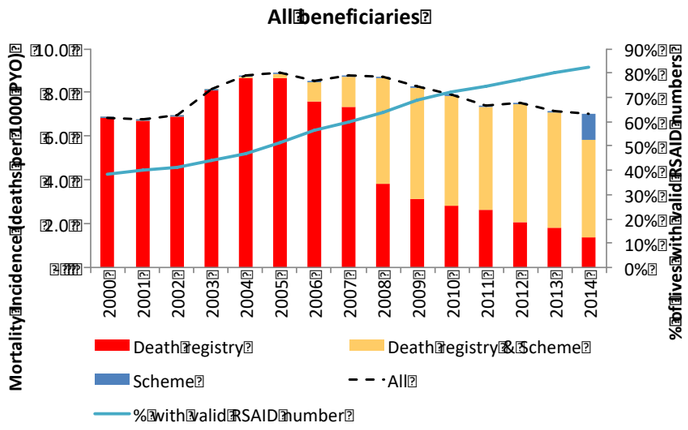
- Mortality incidence rates are shows on the left-hand vertical axis and the % of lives with valid RSAID numbers on the right-hand vertical axis
- Beige bars: death according to both the death registry and scheme information
- Red bars: death according to only the death registry i.e., not available from scheme information
- Blue bars: death according to scheme information only i.e., potential errors since these deaths are not confirmed by the death registry

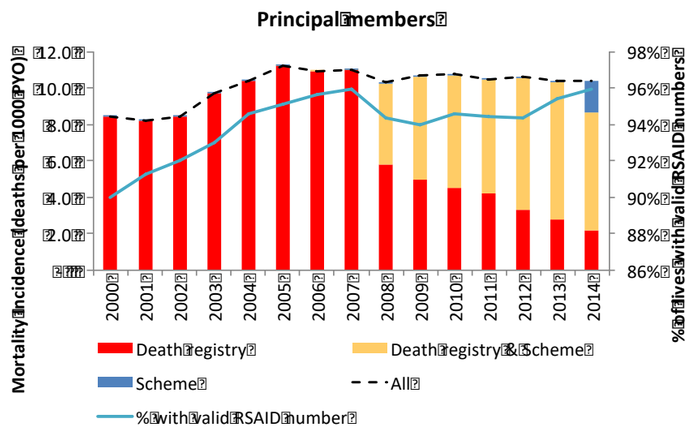
Deaths ascertained via the death registry therefore represent a significant proportion of the overall scheme mortality rate. Without the death registry, mortality rates would have been materially underestimated.

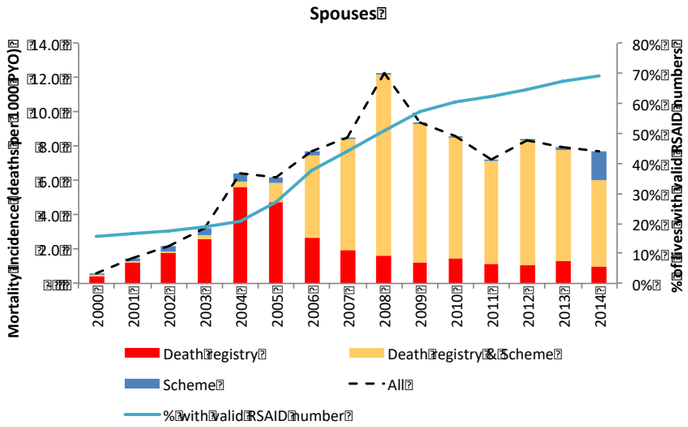
Notably, the significant reduction in mortality observed (Figure 11) is thought to be a result of increasing coverage on ART, earlier initiation of and better outcomes on ART. The authors' research (link) clearly shows that 80-90% of beneficiaries (patients) that commenced ART on the AfA programme achieved suppressed VL (≤400 copies/ml) within 12 months of starting ART and maintained suppressed VL thereafter. The significant reductions in mortality are again confirmed when stratifying by age and gender (Figure 13) with the largest mortality improvements observed in the 30 – 45 age range where HIV contributed the highest excess deaths historically. Mortality over the recent period 2011-2014 has been around 7.3 deaths per 1000 beneficiary years observed which is considered reasonable for this period and for a working population on a medical scheme.

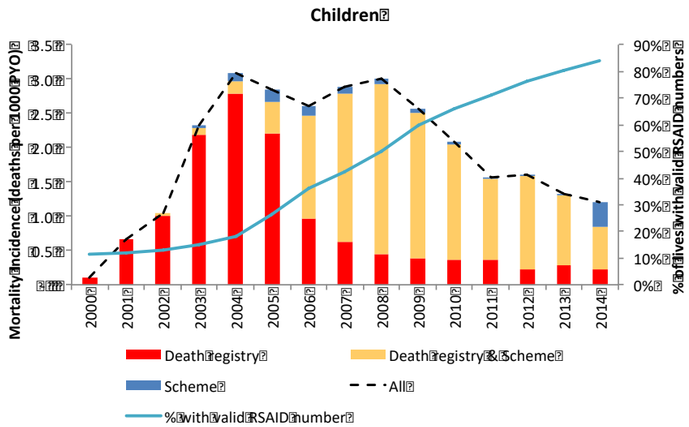
Mortality by age and gender appears reasonable. The "Other" beneficiary category shows higher mortality even at older ages – this may be associated with principal members adding extended family in ill-health with an increased HIV prevalence or poor survival on ART. i.e. "anti-selection" against the scheme.

Figure 11: Impact of linkage with death registry on mortality incidence (by beneficiary category)









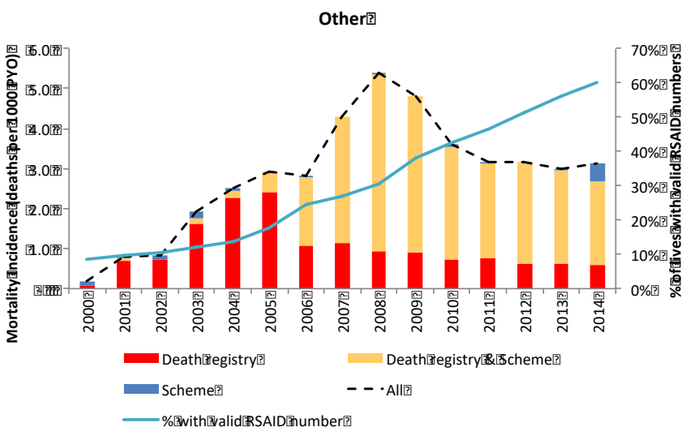


Figure 12: Mortality Incidence (deaths per 1000 PYO) by calendar year, age, gender, scheme option and beneficiary category. Age-specific aggregates across all years

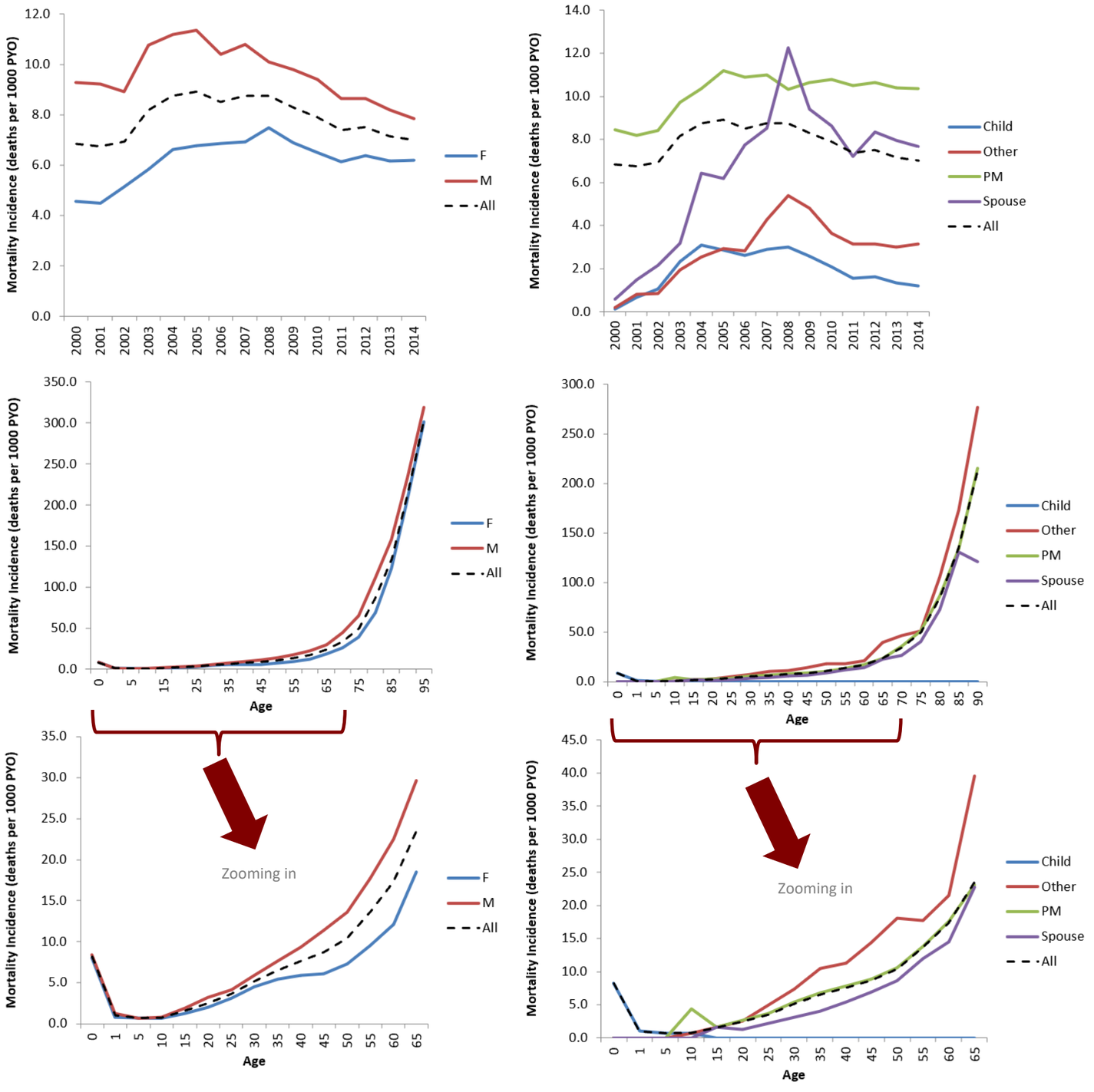
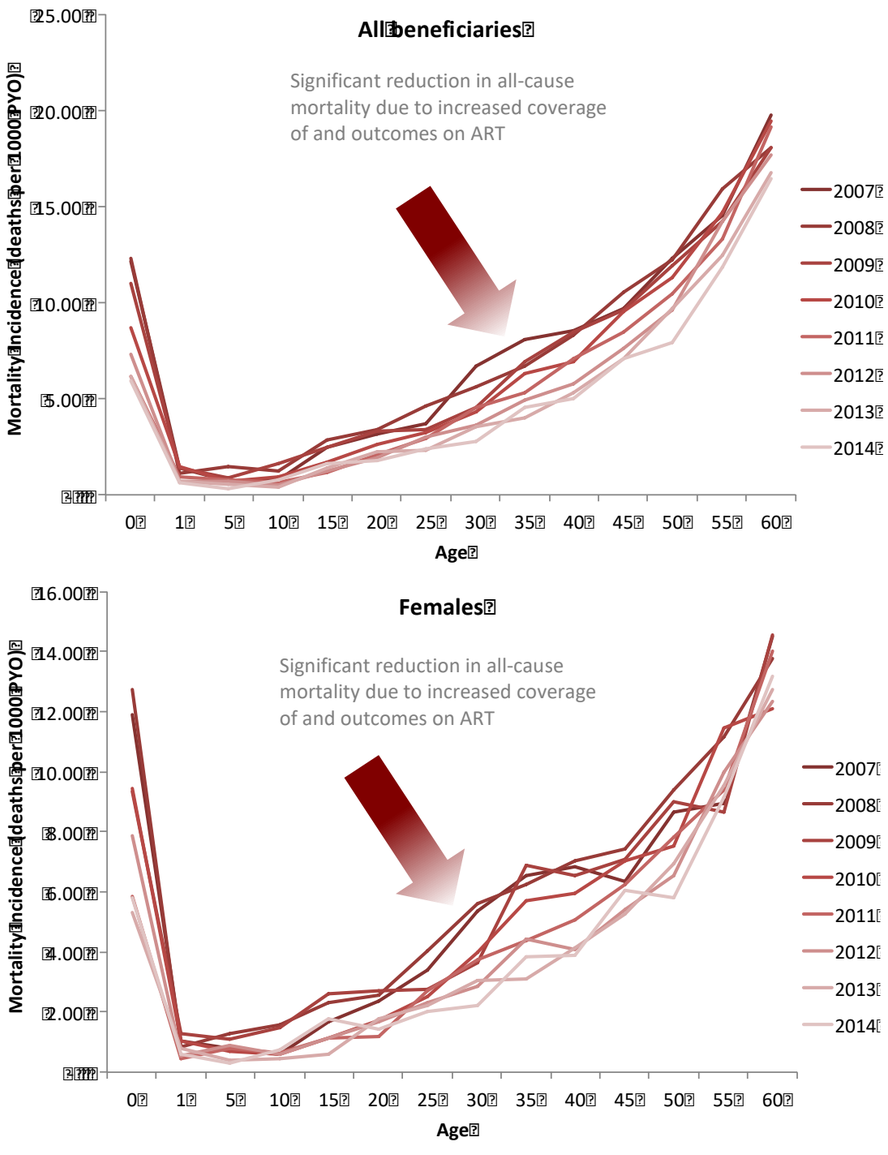
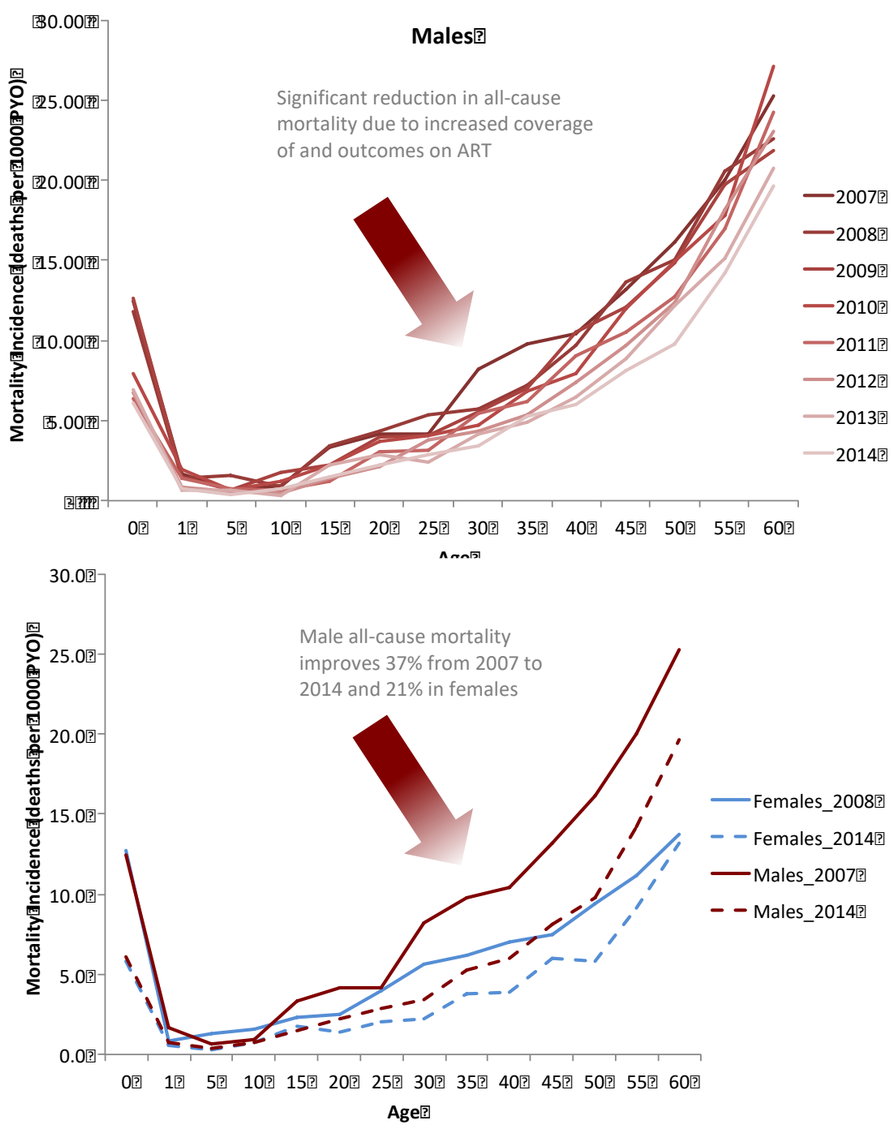


Figure 13: All-cause mortality incidence (deaths per 1000 PYO) by calendar year, age and gender

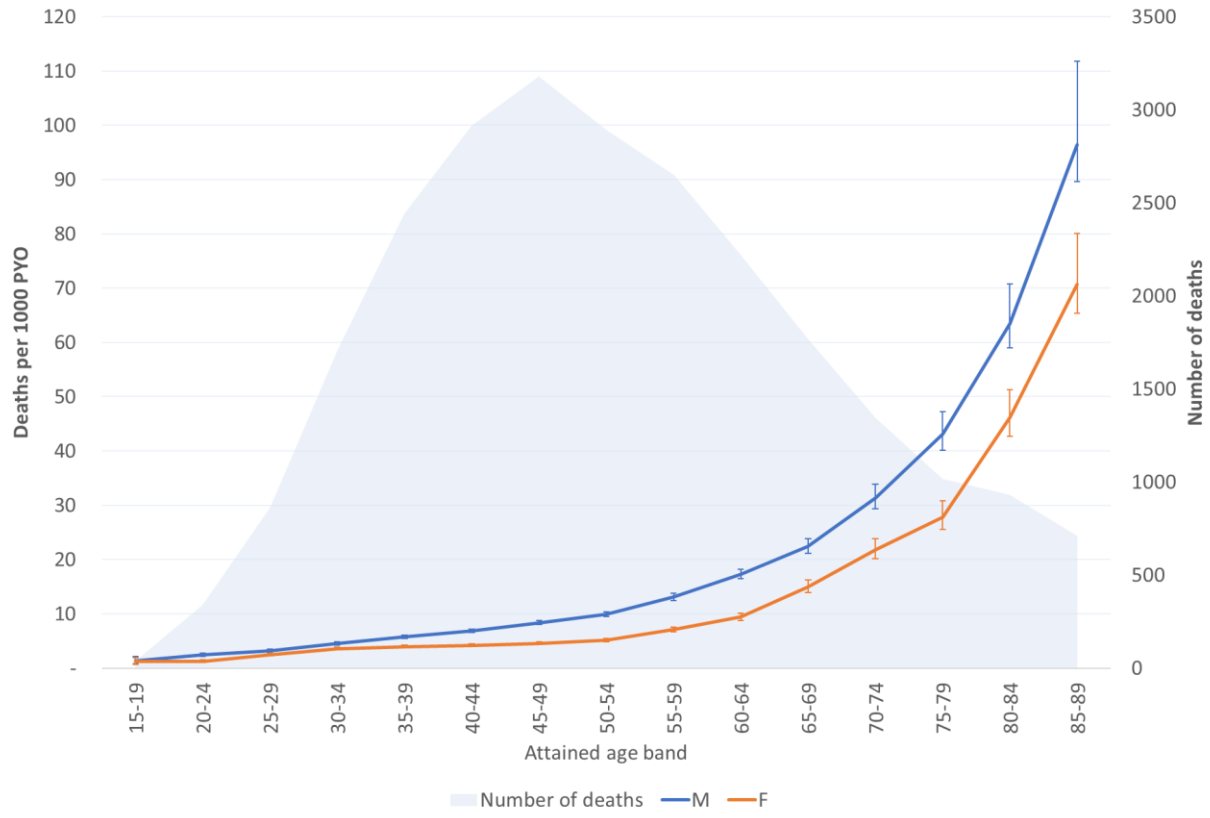




2.3.2.3 All-cause mortality rates in HIV-uninfected lives

A key assumption required in SPMs is the assumed all-cause mortality in HIV-uninfected lives. All-cause mortality incidence rates were derived for lives that are estimated to be consistently HIV uninfected over time (also known as a control group or background mortality in studies of extra-HIV mortality). The authors' research is based on a strong scientific study design in that all subgroups (both HIV positive and HIV uninfected) are derived from the same medical scheme sub-population. This study design increases comparability of subgroups which alleviates a limitation in other published studies that derive HIV-uninfected mortality assumptions from a different population to the study group (usually HIV positive cohort). Mortality in HIV-uninfected lives was seldom possible to estimate in South Africa owing to unreliably classified causes of death, incomplete reporting of deaths and uncertain estimates of HIV status. However, the method described in section 2.3.1.2 was reasonably effective in estimating HIV status and, combined with accurate mortality ascertainment via the death registry, mortality estimates in lives estimated to be HIV uninfected were possible to derive (refer to authors' research (link) for details). Figure 14 below illustrates the derived all-cause mortality incidence in lives estimated to be HIV-uninfected and corresponding numbers of deaths to illustrate the high credibility of observed deaths.

Figure 14: All-cause mortality rates in HIV-negatives (deaths per 1000 PYO) by age and gender



Significant reasonability checks were performed on the above estimates through comparison with multiple other sources described in Table 2 below. Sources of comparison included non-HIV and total mortality in the general population, ASSA CSI assured lives 1999-2000 investigation, ASSA CSI SA85-90 assured lives investigation and published European insured and underwritten lives' mortality.

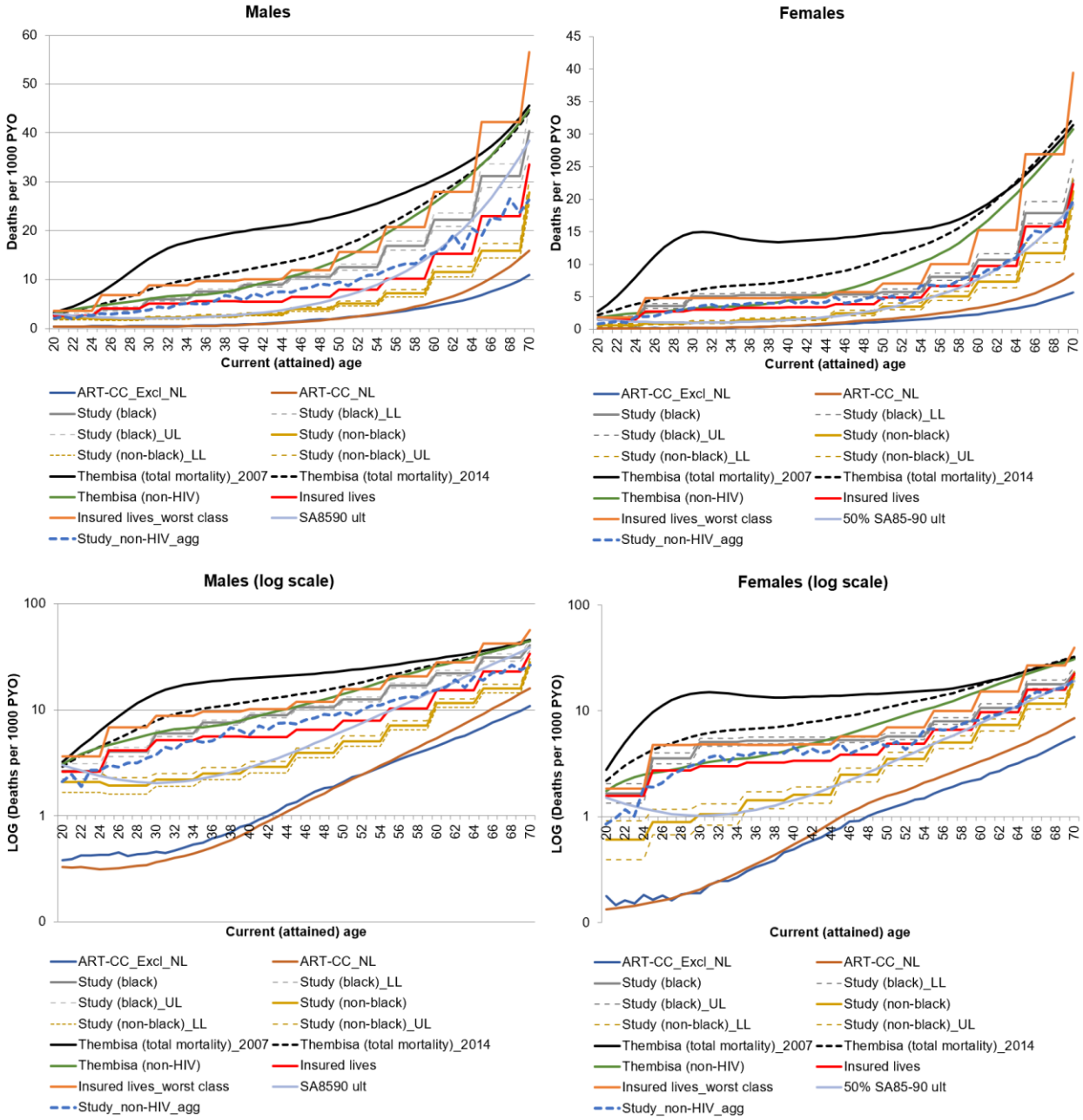
Table 2. Mortality sources compared against authors' estimated HIV-uninfected mortality

Source	Description
Thembisa (total mortality)_2007	South African general population all-cause mortality estimated using the Thembisa model v4.5 (www.thembisa.org) for 2007 (midpoint of study data)
Thembisa (total mortality)_2014	South African general population all-cause mortality estimated using the Thembisa model v4.5 (www.thembisa.org) for 2014
Thembisa (non-HIV)	South African general population non-HIV mortality estimated using the Thembisa model v4.3 (www.thembisa.org) for 2007 (midpoint of study data)
Study (black)	Authors' derived mortality in the HIV-uninfected sub-group selected from the overall medical scheme population for the black population
Study (non-black)	Authors' derived mortality in the HIV-uninfected control group, selected from the overall medical scheme population for the non-black population
Study (black)_LL	Lower uncertainty interval limit for the above
Study (black)_UL	Upper uncertainty interval limit for the above
Study (non-black)_LL	Lower uncertainty interval limit for the above
Study (non-black)_UL	Upper uncertainty interval limit for the above
Study_non-HIV_agg	Authors' derived mortality in the HIV-uninfected control group, selected from the overall medical scheme population (aggregated across race groups)
Insured lives	ASSA CSI assured lives mortality investigation (1999-2002), all durations and all classes of lives combined
Insured lives_worst class	ASSA CSI assured lives mortality investigation (1999-2002), for the worst socio-economic class, all durations
SA8590 ult	ASSA CSI SA85-90 assured lives mortality, ultimate duration (link)
ART-CC_Excl_NL	Insured lives assumed mortality in various European countries used as background mortality in the study "Insurability of HIV-positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies" (link). Excludes Netherlands
ART-CC_NL	Insured lives assumed mortality in the Netherlands used as background mortality in the study "Insurability of HIV-positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies" (link).

Figure 15 compares the sources in Table 1. The authors' derived HIV uninfected mortality compared reasonably given the following observations:

- All estimates of HIV uninfected ("Study_non-HIV_agg", "Study (black)", and "Study (non-black)") were lower than total mortality estimates for the general population (Thembisa model in both 2007 and 2014).
- Overall HIV uninfected mortality ("Study_non-HIV_agg") was lower than HIV uninfected mortality in the general population (Thembisa model for 2007 as the midpoint of the study period) which is reasonable given the authors' study population was a medical scheme, generally employed lives with higher socio-economic status, access to health care, health awareness, etc.,.
- Significant variation in the study population's estimated HIV-uninfected mortality was observed by race, with the black population having much higher levels than the non-black. Insured lives mortality is well known to vary according to socio-economic variables such as education and income which are correlated with race. When comparing the ASSA CSI assured lives 1999-2002 mortality against the study data, the total (includes HIV and non-HIV) mortality of the overall ("Insured lives") claims experience across all policy durations and socio-economic classes always ranged between the black and non-black levels of the study data HIV uninfected mortality. The ASSA CSI 1999-2002 assured lives investigation had comparatively lower HIV-related deaths, being underwritten and HIV prevalence in this population being much lower at the time.
- HIV-uninfected mortality in the study non-black population closely aligned with SA85-90 until around age 40 and thereafter was lower. This is considered reasonable considering that SA85-90 represented a relatively non-black population at the time and was expected to have negligible HIV deaths given the lower HIV prevalence across the time period.
- HIV-uninfected mortality in the study black population closely aligned with the assumed HIV-uninfected mortality in the general population (Thembisa model). The race mix of the general population is more aligned with a higher proportion black and hence from this perspective, the alignment is expected however the study black population is still a medical scheme, employed population and could still be expected to have lower mortality than the general population – this is observed from the mid 40s and older.
- European insured lives total mortality is, as expected, the lowest mortality of all sources.
- HIV uninfected mortality in the overall study population ("Study_non-HIV_agg") and black population (Study (black)) was lower than the ASSA CSI 1999-2002 worst socio-economic class total mortality.

Figure 15: Reasonability check: various mortality sources compared against study HIV-uninfected mortality



2.3.2.4 Antiretroviral Therapy

The number of beneficiaries that have been authorized for ongoing ART is shown in Figure 17 to have been increasing similarly to the general population and dominated by females. ART coverage is defined as the number of beneficiaries that have been authorized for ongoing ART divided by the number of beneficiaries estimated to be HIV positive at a point in time. ART coverage has also increased and appears to increase with age until around 40 and then reducing from around age 60.

2.3.2.5 Recent demographic profile

All ASSA SPMs require the user to specify the assumed demographic profile at the start of the model projection (typically in the early 1980s when the epidemic is assumed to have begun). The model then projects new infections, deaths, new entrants and withdrawals. The demographic profile can either be kept stable over time or change under other scenarios. The starting demographic profile used in the calibration was derived from the most recent period (2016) and shown below in Figure 16. This profile was kept approximately stable over time. As per other medical scheme populations, the characteristic "M-shaped" profile is observed. Appendix 1 shows that significant changes occurred in the age distribution over time. It was not the objective of the calibration to calibrate observed trends in all years since a stable demographic profile was assumed in the model over time.

Figure 16: Study population demographic profile in 2016

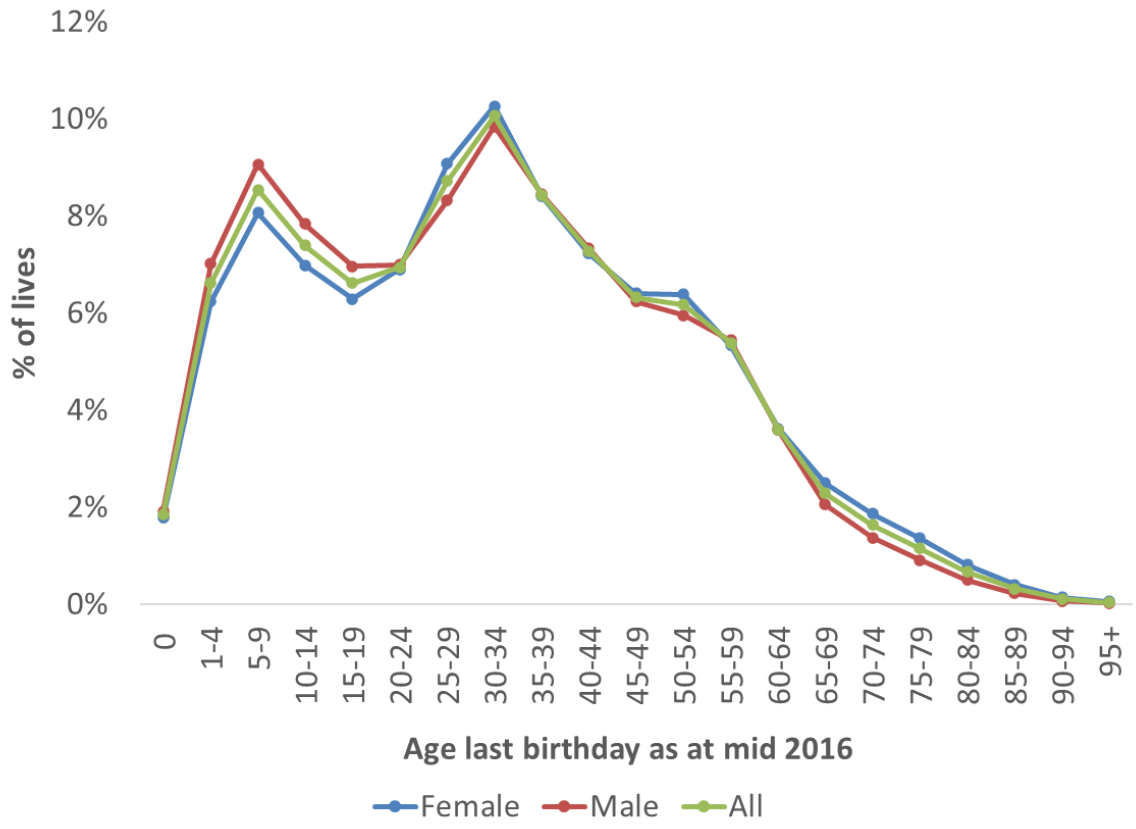
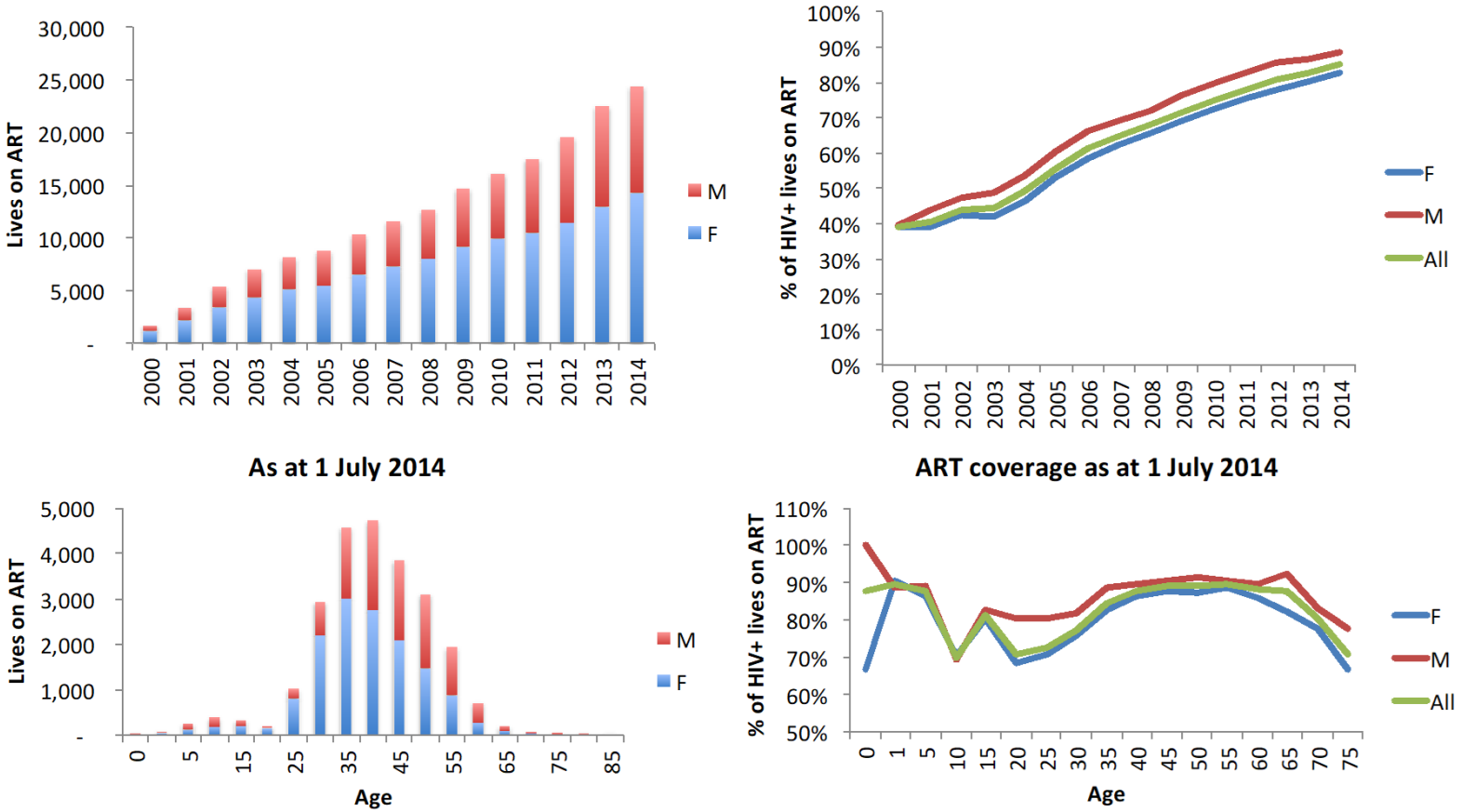


Figure 17: Numbers of beneficiaries authorized for ongoing ART and ART coverage (%)

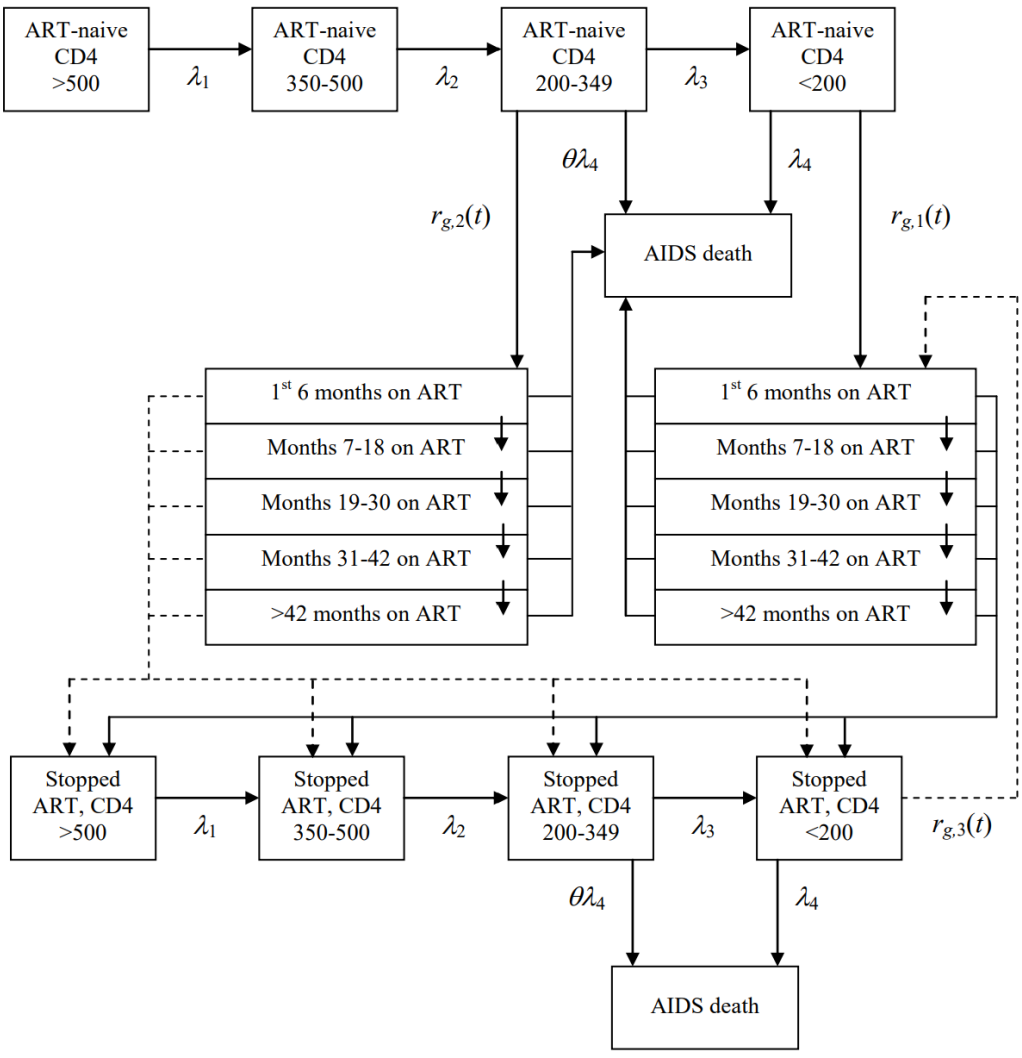


3. Model methodology

3.1 Baseline model considered

Leigh F. Johnson, Katharina Kranzer, Keren Middelkoop, Robin Wood published a sub-population model (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). For further details on the Masiphumelele model please contact Leigh Johnson. Given the absence of CD4 count from the multi-state model of HIV survival in prior ASSA SPMs, the Masiphumelele model was of relevance for the 2023 ASSA SPM update given its CD4-based multi-state model of survival (Figure 18). 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.

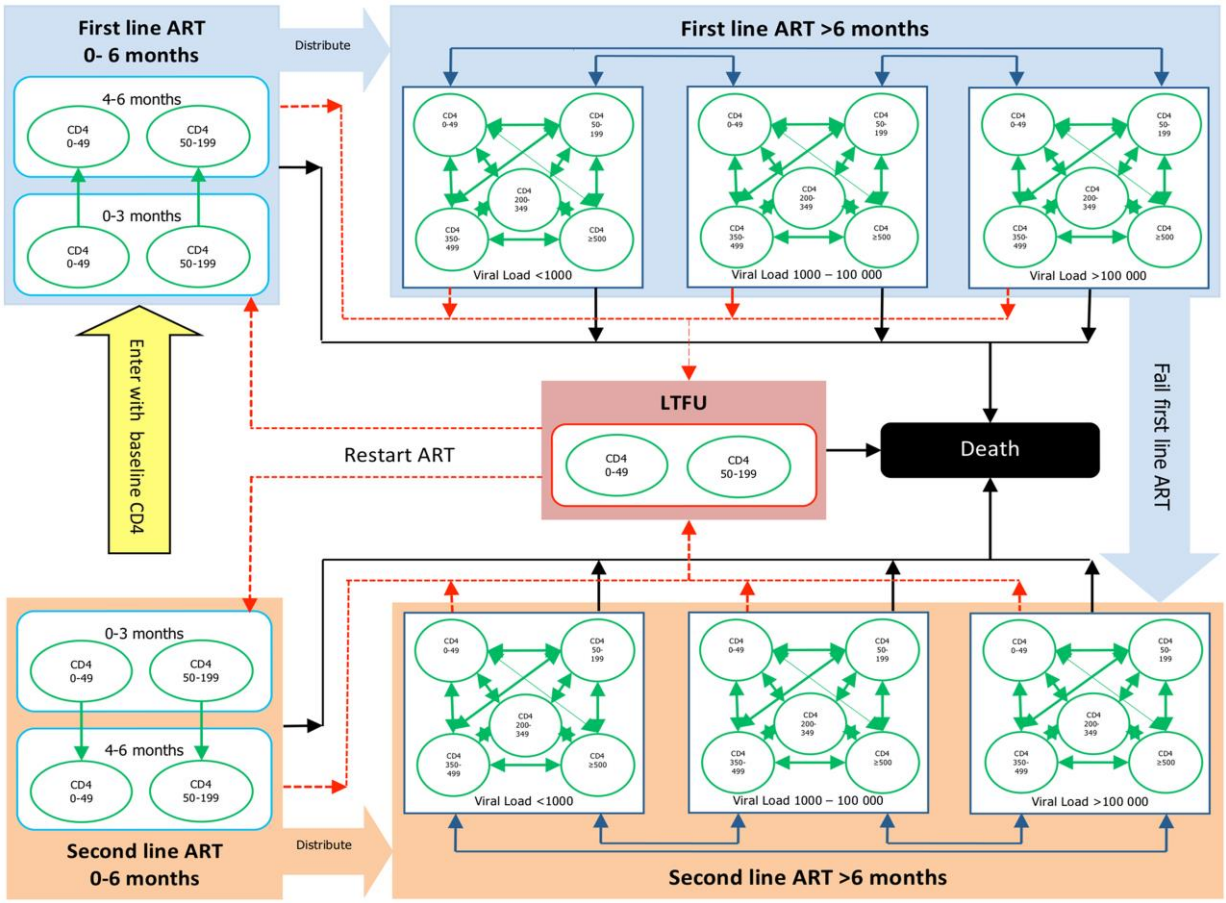
Figure 18: Multi-state model of survival after ART initiation (Johnson et al, 2011). For simplicity, transitions due to non-HIV mortality and migration are not shown.



3.2 Recent models including current CD4 count and viral load (Leisegang)

A new sub-population model, which accounts for dynamic changes in CD4 and VL status in addition to program LTFU and reentry, offers significant benefits when understanding the impact of the net impact of differences over time as demonstrated by Leisegang et al. (2013). For example, GP-based case 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 an profound impact on outcomes and costs as demonstrated by Leisegang et al. (2013).

Figure 19: Model proposed by Leisegang et al. (2013) including loss to follow-up and return-to-care



3.3 Implementation of new model features

The new model is derived from the structure of the Liesegang et al. (2013) model, with some changes in order to allow for the intended use case and the toolset available to perform the projections. The Excel spreadsheet itself 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 retained.

3.3.1 High-level description

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.

Assumptions for transition probabilities between states are largely expressed as continuous forces of transition, although for the projection these are ultimately converted to monthly transition probabilities.
Apart from the core transition rates assumptions need to be provided for starting populations and prevalence among new entrants.

The explicit form of the force of transition to LTFU and AIDS death during the 6+ months on ART states is not given in the Liesegang et al and hence is stated here: the continuous hazard rate for transition to AIDS death from VL v and CD4 count c having been on ART for t months is:

$$\lambda_m = e^{K^m_{v,c}+\alpha_m e^{-\beta_m t}}$$

where $K^m_{v,c}$ is a constant given for combination of VL and CD4 states, and α_m and β_m are constants controlling the decay of the mortality over time on ART.

The corresponding expression for LTFU is:

$$\lambda_l = e^{K^l_{v,c}+\alpha_l\left(1-e^{-\beta_l t}\right)}$$

These time-varying expressions were chosen by Liesegang et al. in order to fit time-varying behaviour evident in the empirical data.

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

A number of simplifications have been made in order to make implementation of the model as an Excel spreadsheet more practical:

- No distinction is made between first line and second line treatment 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 treatment – death due to AIDS or otherwise, LTFU (ending treatment) or exit from the population.

- Individual cohorts within each treatment state are not tracked. In the Liesegang model these are used because duration on treatment impacts the transition rates. In order to approximate this detail the average duration on treatment within each state is tracked instead.

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

- Within the first 6 months of treatment and LTFU the CD4 states used are 0-199, 200-349, 350-500 and ≥ 500 as compared to the 0-49 and 0-199 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. For the purposes of allocating lives to appropriate states after the first 6 months, it is assumed that 30% of the lives in the 0-199 state are within the 0-49 band.
- 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. Overview of excel model

This section describes the intended usage of the model and a high-level description of the functionality of each sheet.

4.1 Descriptions of main worksheets

Table 3. Description of excel model workbook sheets

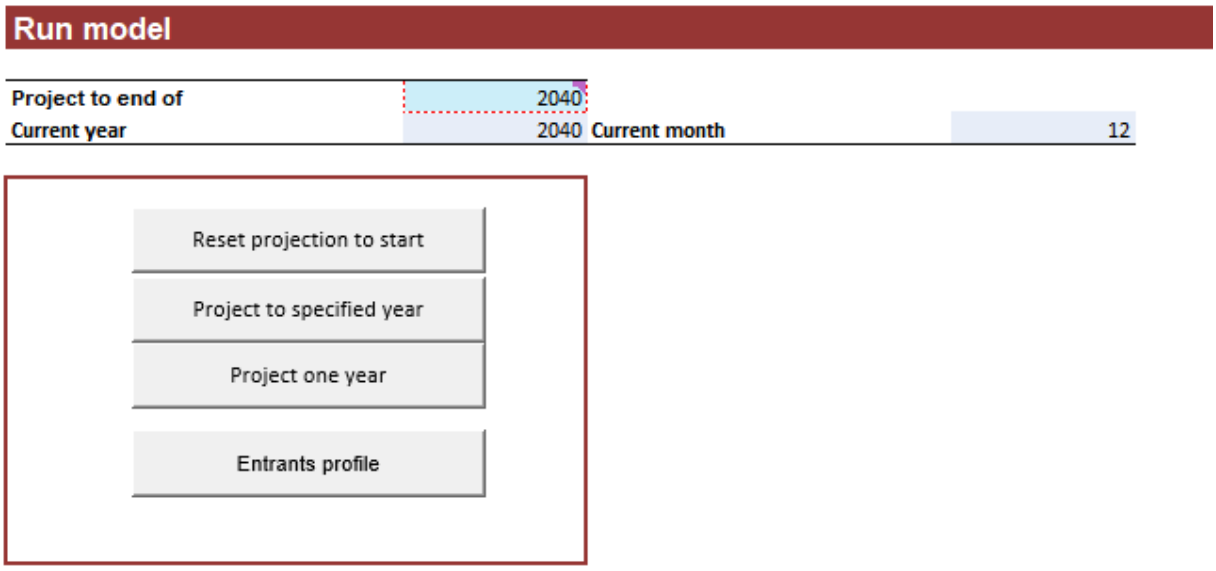
Sheet Name(s)	Description
Assumptions	This sheet provides the key controls and assumptions for the model. See section 4.2.
StartPop	Provides the baseline population to be used for projections. It is set as at a given calendar year. The distribution is to be provided in the form of the number of lives at each given age, by gender. For the purposes of the monthly projection, each age's figure will be smoothly spread out over the months between each age increment.
Base Tables	Source of baseline non-AIDS mortality and withdrawal rates to be used by the projection, by age.
Results	This sheet is used to record outputs of the model. At the end of each calendar the formulae in column C are calculated, and the results pasted to the right of prior years' corresponding outputs. It is possible for the user to add arbitrary additional figures by adding new formulae above the dotted line at the bottom of the sheet.
Results Monthly	As above, except the results are calculated for every month of the projection. Outputs in this sheet may be referenced by the annual outputs.
Calibration tpx Calibration Males Calibration Females	Provides a number of diagnostics that may be used by the calibration process.
YearSpecific	Provides a convenient summary of the output mortality rates from the model for a given year.
NonAIDSMortality	Provides a projection of non-AIDS mortality forwards and backwards from the reference year, using the non-AIDS mortality improvement assumption provided.
Incidence	HIV incidence rates by age, gender, and calendar year may be set in this sheet. The current assumptions are derived from the Thembisa model.
Withdrawals	This allows withdrawal rates to be set by age and calendar year
Population	Generates the assumed total population by age and calendar year, based on the starting population and population growth assumptions
EntrantsCalculations Entrants	This is a simple projection used to estimate the CD4 count distribution of new lives entering the group, ignoring treatment.

Mean Time on ART M Mean Time on ART F	Gives the expected duration for which lives in a specific CD4/VL state will have been on ART at a given point in the projection. Needed because transition rates on ART are a function of treatment duration.
Males Females	The core of the projection. These sheets take the current distribution of lives within the states of the model, and project the new distribution after the current time step.
Age-specific rates M Age-specific rates F	Calculates the transition rates to apply, given that some of these are time-dependent.
ART initiation M ART initiation F	ART initiation rates by CD4 count, age and calendar year

4.2 Assumptions

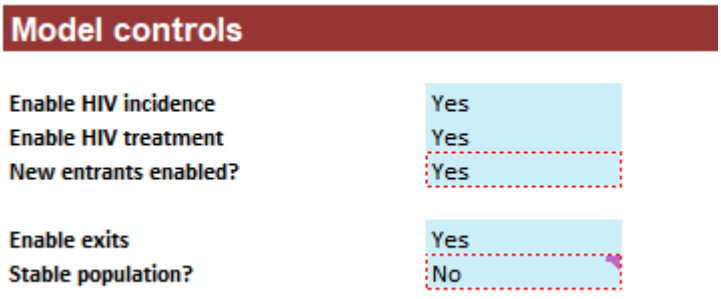
The assumptions sheet contains the core assumptions used for the model, and the controls for running the projection. It is broken into a number of different sections which are discussed here, as well as the sources of the assumptions

4.4.1 Run model



This section is used to the run the macros that perform the projection. End year may be specified, and the model can be run from the current point in time to the end of the selected end year. It is also possible to run the model for a single calendar year. If any inputs are changed it is also necessary to re-run the calculations for new entrants, the button for which is also here.

4.4.2 Model Controls



There are a number of features of the model may be turned on and off, useful mostly for diagnostic purposes or, for example, to model the runoff of a closed block of business.

4.4.3 Decrement Assumptions

This section contains a number of assumptions adjusting the base rates of transition between states in the model.

4.4.3.1 Multiplicative Adjustments to obtain age- and gender-specific incidence rates

Multiplicative adjustments to obtain age- and gender-specific incidence rates

Age band		Male	Female
14-19	14	0.05	0.05
20-24	20	0.10	0.20
25-29	25	0.20	0.30
30-34	30	0.45	0.30
35-39	35	0.45	0.30
40-44	40	0.45	0.25
45-49	45	0.34	0.25
50-54	50	0.30	0.25
55-59	55	0.30	0.25

The incidence rates on the *Incidence* sheet are population incidence rates. These factors adjust those rates to convert to incidence rates appropriate to the population being modelled. These values have been set as part of the calibration process and are applied to incidence rates in the *Incidences* sheet that have been extracted from the Thembisa model.

4.4.3.2 Transition rate adjustments

Transition rates adjustments

	Factor Males	Factor Females	Base age
Increase in rate of CD4 transition per year of age, untreated	1.01265452	1.001259043	30
Increase in rate of mortality per year of age, treated	1.011397329	1.008655009	30
Increase in rate of ART discontinuation per year of age	1	1	30

	Males	Females
Increase in mortality, treated	1.00	1.00
Increase in rate of ART discontinuation	1.15	0.92

	Factor by which base entrant prevalence is multiplied	
in order to obtain HIV prevalence in new entrants	1.00	1.35

Mortality and CD4 transition rates before treatment are assumed to deteriorate by age. The first section here provides the deterioration factors for each year of increase in age and are extracted from the Thembisa model. The next two sections contain high level flat adjustments to mortality and ART discontinuation, and to the prevalence rates for new entrants respectively. These have been set through the calibration process.

4.4.3.3 Mortality rate adjustments

Mortality rate adjustments

	Males	Females
Overall adjustment	100%	100%
Annual non-AIDS mortality improvement	0.0%	0.0%
Reference Year	1985	

An overall adjustment and mortality improvement assumption may be applied here. Note that it is the responsibility of the user to ensure that the base non-AIDS mortality rates in use on the Base Tables sheet are appropriate for the group being modelled.

4.4.3.4 Withdrawal rates

Withdrawal rate adjustments

	Males	Females
Overall adjustment	100%	100%

High level adjustments to the withdrawal rates in the Base Tables sheet.

4.4.3.5 ART statistics

ART statistics

Percent of HIV positive lives on ART	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Males	0.0%	0.0%	0.0%	0.0%	2.9%	5.7%	8.6%	11.4%	14.3%	17.1%	20.0%	26.0%
Females	0.0%	0.0%	0.0%	0.0%	3.5%	7.1%	10.6%	14.1%	17.7%	21.2%	24.7%	32.3%

Base ART initiation rates (age 35)		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Males	500+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	350-499	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	200-349	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	25.0%	50.0%
	<200	0.0%	0.0%	0.0%	0.0%	32.5%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%	65.0%
Females	500+	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	350-499	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	200-349	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	17.5%	35.0%
	<200	0.0%	0.0%	0.0%	0.0%	30.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%

		Relative Initiation Rates by Age Band, Gender and CD4							
		Male				Female			
Age band		500+	350-499	200-349	<200	500+	350-499	200-349	<200
14-19	14	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
20-24	20	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
25-29	25	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
30-34	30	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
35-39	35	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
40-44	40	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
45-49	45	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
50-54	50	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
55-59	55	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10

	Males	Females
Number of years of rollout before national population	2	2

Rate of transfer out	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
During year in which ART is started	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150

Rate of default	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
During year in which ART is started	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012	0.012

	Males	Females
Adjustment to ART initiation rate for ART experienced lives	150%	150%

This section is quite complex and contains a significant number of parameters controlling the rates of ART initiation, and the ART coverage of new entrants. The percent of HIV positive lives on ART is based on UNAIDS AIDSInfo statistics. Base ART initiation rates are derived from expected rates for the calibration population. These figures were kept constant across all years, except that the dates at which rollout begins for each CD4 category

has been aligned with South African treatment guidelines. The relative initiation rates by age band, gender and CD4 are adjustments to the above set by calibration, as is the adjustment for early rollout. Rate of transfer out and rate of default refer to the rates of exit from the population and rate of ART discontinuance in the first 6 months. Discontinuance rates are derived from Liesegang et al. Adjustment to ART initiation rate for ART experienced lives allows for lives who have defaulted on ART to reinitiate treatment at a higher rate than ART-naïve lives.

4.4.3.6 1-month rate of default by current CD4 and Viral Load

1-month rate of default, by current CD4 and viral load, for patients treated 6 months or more

Gompertz Alpha			0.500	
Gompertz Beta			0.087	
Hazard Coefficient				Viral Load
		< 1000	1000 - 100 000	> 100000
CD4 Count	<50	-5.130	-4.160	-4.370
	50-199	-5.440	-4.470	-4.680
	200-349	-4.520	-3.560	-3.760
	350-499	-4.520	-3.560	-3.760
	>500	-4.520	-3.560	-3.760

After the first 6 months of treatment the lives transition to the full treatment model whereby transition rates depend on both VL and CD4. The transition rates for default follow a Gompertz-Makeham form (dependent on time on ART) with common α and β parameters, and hazard coefficients which vary by VL and CD4 count, as given in section 3.3.1.

These assumptions are from Leisegang et al. (2013).

4.4.4 Population Assumptions

Population assumptions

New entrants assumptions

	Probability of entry for an individual in the given HIV stage, as a % of the probability for an uninfected individual			
	CD4 stage			
	>500	350-500	200-349	<200
Relative prob of entry	100%	100%	50%	5%

At present this section only contains an assumption for the distribution of CD4 counts in new entrants. This is retained from the Masiphumelele model.

4.4.5 CD4/Viral Load Model Parameters

This section controls the state transitions of lives after infection with HIV. This includes transition between disease states, as well as mortality and treatment adherence.

4.4.5.1 Transition Rates and Adjustments

Transition rates and adjustments

	CD4 stage			
	>500	350-500	200-349	<200
Rate of transition to lower CD4 state, untreated	0.308985292	0.459	0.338250742	0.2486
RR death in patients with CD4 200-349 (cf <200)	0.130			

This section sets the hazard rate for transitions to a worse CD4 state in untreated lives. Assumptions are derived from the Thembisa model.

4.4.5.2 1-month rate of mortality, by baseline CD4, in treated patients for the first 6 months

1-month rate of mortality, by baseline CD4, in treated patients for first 6 months

		CD4 stage			
		>500	350-500	200-349	<200
Month 1	0 mth	0.000	0.000	0.002	0.017
Month 2	1 mth	0.000	0.000	0.002	0.017
Month 3	2 mth	0.000	0.000	0.002	0.017
Month 4	3 mth	0.000	0.000	0.001	0.011
Month 5	4 mth	0.000	0.000	0.001	0.011
Month 6	5 mth	0.000	0.000	0.001	0.011

	Males	Females
Overall adjustment	130%	130%

The model has separate hazard rates for mortality in each of the first 6 months of treatment, split by CD4 count at the start of treatment. There is a factor to allow for a high-level adjustment. These are sourced from the Liesegang et al. model. An overall calibration adjustment is available. This is used because the model does not split out lives with a CD4 count below 50, unlike the Liesegang et al. model.

4.4.5.3 1-month rate of mortality, by current CD4 and viral load, for patients treated 6-months or more.

1-month rate of mortality, by current CD4 and viral load, for patients treated 6 months or more

Gompertz Alpha	1.730
Gompertz Beta	0.035

Hazard Coefficient		Viral Load		
		< 1000	1000 - 100 000	> 100000
CD4 Count	<50	-5.030	-4.690	-4.130
	50-199	-6.500	-6.160	-5.600
	200-349	-7.480	-7.140	-6.580
	350-499	-8.530	-8.190	-7.630
	>500	-8.160	-7.820	-7.260

This section controls the force of transition due to mortality during treatment. As per the rate of default under Decrement Assumptions, this follows as Gompertz-Makeham form (section 3.3.1), and comes from Liesegang et al.

4.4.5.4 Viral Load and CD4 distribution 6 months after ART initiation

Viral Load and CD4 distribution 6 months after ART initiation

		Viral Load < 1000					Viral Load 1000 - 100000					Viral Load > 100000				
		<50	50-199	200-349	350-499	>500	<50	50-199	200-349	350-499	>500	<50	50-199	200-349	350-499	>500
<50	30%	0.020	0.040	0.020	0.010	0.000	0.020	0.020	0.000	0.000	0.000	0.620	0.200	0.030	0.020	0.000
50-199	70%	0.010	0.280	0.410	0.130	0.040	0.000	0.060	0.040	0.010	0.000	0.000	0.020	0.000	0.000	0.000
200-350		0.000	0.020	0.040	0.020	0.790	0.000	0.000	0.060	0.040	0.010	0.000	0.000	0.020	0.000	0.000
350-500		0.000	0.000	0.020	0.040	0.810	0.000	0.000	0.000	0.060	0.050	0.000	0.000	0.000	0.020	0.000
>500		0.000	0.000	0.000	0.020	0.850	0.000	0.000	0.000	0.000	0.110	0.000	0.000	0.000	0.000	0.020

After the first 6 months of treatment, lives are distributed between the different VL states based on the figures in this section, given the CD4 at the time of treatment commencing. These probabilities are from Liesegang et al.

4.4.5.5 1-month VL/CD4 transition probabilities after 6 months on ART

1-month VL/CD4 transition probabilities after 6 months on ART

			Viral Load < 1000					Viral Load 1000 - 100000					Viral Load > 100000					Ch
			<50	50-199	200-349	350-499	>500	<50	50-199	200-349	350-499	>500	<50	50-199	200-349	350-499	>500	
0		<50	0.651	0.334	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
1	Viral Load < 1000	50-199	0.002	0.907	0.076	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
2		200-349	0.000	0.015	0.908	0.061	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	0.000	0.000	
3		350-499	0.000	0.000	0.030	0.905	0.049	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	0.000	
4		>500	0.000	0.000	0.000	0.034	0.952	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.000	0.000	
5		<50	0.061	0.000	0.000	0.000	0.000	0.754	0.172	0.000	0.000	0.000	0.013	0.000	0.000	0.000	0.000	
6	Viral Load 1000 - 100000	50-199	0.000	0.061	0.000	0.000	0.000	0.013	0.834	0.079	0.000	0.000	0.000	0.013	0.000	0.000	0.000	
7		200-349	0.000	0.000	0.061	0.000	0.000	0.000	0.042	0.850	0.034	0.000	0.000	0.000	0.013	0.000	0.000	
8		350-499	0.000	0.000	0.000	0.061	0.000	0.000	0.000	0.049	0.852	0.025	0.000	0.000	0.000	0.013	0.000	
9		>500	0.000	0.000	0.000	0.000	0.061	0.000	0.000	0.000	0.054	0.872	0.000	0.000	0.000	0.000	0.013	
10		<50	0.000	0.000	0.000	0.000	0.000	0.167	0.000	0.000	0.000	0.000	0.601	0.232	0.000	0.000	0.000	
11	Viral Load > 100000	50-199	0.000	0.000	0.000	0.000	0.000	0.000	0.167	0.000	0.000	0.000	0.007	0.690	0.136	0.000	0.000	
12		200-349	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.167	0.000	0.000	0.000	0.042	0.757	0.034	0.000	
13		350-499	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.167	0.000	0.000	0.000	0.056	0.699	0.078	
14		>500	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.167	0.000	0.000	0.000	0.047	0.786	

This grid here provides the 1-month transition probabilities between different VL and CD4 count states during treatment. It is assumed that at the 1-month timestep it is not possible to jump states, that is it is only possible to move to the adjacent states, and only one of VL and CD4 count may change in a single timestep. In the section to the right these transition probabilities are converted to continuous-time hazard rates as are used within the model itself. These probabilities are derived from Leisegang et al.

4.5 Guide to running and calibrating the model

4.6.1 Model controls

The model has been pre-calibrated using the medical scheme population described in earlier sections of this document.

The controls at the start of the *Assumptions* sheet are used to run the projection.

- The *Reset projection to start* button erases all results and resets the projection date to the end of the year 1985.
- *Project to specified* year runs the projection to the end of the year specified in the *Project to end of* cell. The *current year* and *current month* cells track the date of the most recent output. Note that although the projection is monthly, the macros always run for a full calendar year.
- *Project one year* can be used to manually run the projection a single additional year from the current projection state.

- *Entrants profile* needs to be run if there has been a change to assumptions that would affect the HIV prevalence of new entrants to the population.

4.6.2 Calibration process

There are a large number of assumptions that feed into the model. Many of them are unlikely to need to be changed by the end user without good reason.

As a starting point some standard assumptions expected to be set by the user are:

- Population size – population size by age band can be set for a particular reference year on the *StartPop* sheet. The *Population* sheet is used to split these figures into monthly bands and to project back and forth from the reference year using assumed population growth rates. The user could potentially populate the *Population* sheet directly if they have detailed annual data available.
- Non-AIDS mortality and withdrawal rates – these are set on the *Base Tables* sheet. There is provision to set both a base mortality table and adjustments as deemed appropriate by the user. For convenience the SA85-90 tables are also provided. Withdrawal/exit rates can be set in the lower section – base rates can be provided in column C with high level adjustments applied on the *Assumptions* sheet, or rates can be directly supplied in columns I and J.

A list of values on the *Assumptions* sheet that it may be reasonable to adjust in order to calibrate the model is:

- Multiplicative adjustments to obtain age- and gender-specific incidence rates
- Entrant prevalence adjustment (in Transition rate adjustments section)
- Mortality rate adjustments
- Withdrawal rate adjustments
- Relative ART initiation rates by Age Band, Gender and baseline CD4 count (ART Statistics section)
- Number of years rollout before national population
- Overall adjustment to mortality in treated patients in first 6 months

The data that the user may have available for calibration will vary, but at the very least it would be expected to have detail of prevalence figures and total mortality. The *Calibration Males/Females* sheets provide a few default diagnostics that might be used. The charts pull in results directly from the *Results* sheet and compare to the corresponding statistics supplied by the user in in the blue cells.

4.7 Model outputs

The *Results* sheet contains many different outputs. At the end of each year of projection, the values from column C are copied to the next empty column to the right. Outputs that are projected by default in the model include:

- Prevalence by age
- ART initiation figures
- CD4 distributions

- AIDS mortality
- Non-AIDS mortality

The user can add arbitrary additional outputs by creating new rows at the bottom of the worksheet, above the marked line. These will automatically be copied each year.

4.8 Calibration results

The 2023 ASSA SPM model was calibrated to the data described in section 3 to demonstrate that the model's projections and results are reasonable overall from a domain-expert perspective but also with other published research. Critically, ASSA does not seek to publish a model that will, by default, contain appropriate assumptions for users' given sub-populations' risk profiles. It therefore always remains the professional responsibility of the user to calibrate the model to their relevant sub-population and purpose. As mentioned in section 2, the objective of the calibration was not to reproduce observed trends across all calendar years that would be impacted by changes in the size of the population and demographic mix. When projecting the model, an approximately stable demographic profile is assumed projections should not be expected to align closely in earlier calendar years and instead emphasis is placed on alignment in recent years and further, within a recent year across age and gender.

Figures 20-22 compare projected and calibration data (actual observed in the authors' study population data) on HIV prevalence and total (all-cause) mortality across calendar year but also in a most recent year (2015 for HIV prevalence and 2014 for mortality to reflect any incompleteness of deaths in the most recent year).

The calibration of the level of HIV prevalence (Figure 20) in the most recent years was achieved (demographic profile changes in males in earlier calendar years are one reason for less alignment of the level in earlier years) while also achieving a reasonable shape and level across age and gender and similarly for total mortality (Figure 21). The breakdown of projected total mortality into HIV-related and HIV-unrelated causes of deaths is given to illustrate a sensible split of total mortality vs. the shape of total (all-cause) mortality. Total mortality is compared in both 2007 and 2014 since the latter period had much higher HIV-related mortality than in 2014 due in part to changes in ART coverage, ART guidelines and outcomes on ART as shown in Figure 13. This is reflected in the much lower HIV-related mortality in 2014 compared with that in 2007.

Finally, since a major limitation of historic (existing) ASSA models was the significantly prudent assumptions for survival on ART (and hence the resulting overestimation of extra-HIV mortality), Figure 22 compares projected life expectancies from the 2023 ASSA SPM in various HIV-positive sub-groups against that in HIV-uninfected lives. Life expectancies were calculated using a cohort assumed to become infected in the year 2000 to allow a period of sufficient future duration to cover mortality rates at much older ages. Life expectancies are calculated in various sub-groups: HIV-positives lives starting ART at a CD4 count >500 cells/µl (orange bars) as well as <200 cells/µl (yellow bars) and those that do not initiate ART (grey bars) and finally HIV-uninfected lives (blue bars). For

illustration, three ages (20, 30 and 40) are shown, and age represents either age at HIV diagnosis or at ART initiation or attained age for HIV-uninfected lives. No HIV-unrelated mortality improvements were applied in calculating life expectancies (life expectancy estimates would be expected to increase if applying such assumptions). Life expectancy in HIV-positive lives that don't start ART (natural disease progression) is projected as 9-12 years (depending on the age) which compares reasonably to historic models of ASSA.

Figure 22 includes an important reasonability check of the model of survival on ART, namely comparing life expectancies in HIV-positive and HIV-uninfected lives. Life expectancies of the above HIV-positive subgroups are expressed as a proportion of life expectancies in HIV-uninfected lives (bottom row of graphs, Figure 22). The ratio for HIV-positive lives starting ART at CD4 counts <200 cells/µl is 67-79% which compares reasonably to research from Johnson et. al (2013) shown in Figure 23 (note when comparing against the latter, Johnson et. al segments the CD4 band <200 into smaller groups). Figure 22 shows that the ratio for HIV-positives lives starting ART at CD4 counts >500 cells/µl is 80-86%. Importantly, projections using the 2023 ASSA SPM in recent calendar years reflect the current ART clinical guidelines which recommend ART initiation from diagnosis unlike the prevailing ART clinical guidelines underlying the time period of focus for Johnson et.al which was based on ART initiation from lower CD4 counts (< 200 or <350 cells/µl) and ART initiation from above 350 or 500 cells/µl was only recommended in early years if advanced clinical stage symptoms were present, a subgroup known to have higher mortality than a modern cohort asymptomatically initiating above 500 cells/ µl today. Further, the 2023 ASSA SPM approach modelling survival on ART includes current CD4 count and VL which was not possible for Johnson et. al at that stage due to limited public sector data. Lives starting ART at CD4 counts >500 cells/µl in recent years are assumed to be asymptomatic and be following modern ART clinical guidelines unlike historically where ART initiation above 200, 300 or 500 was triggered by advanced clinical stages (higher mortality). Given that the authors' research covered a time period where patients were eligible for ART at CD4 counts below 350 or above 350 cells/µl with advanced clinical stages, insufficient asymptomatic patients could be followed up that had initiated ART above 350 or 500 cells/µl (per modern ART clinical guidelines) and therefore the authors have made best-estimate assumptions. Finally, the authors' research which estimated extra-HIV mortality loadings to HIV-uninfected lives' mortality did estimate that HIV subgroups with the lowest mortality (starting ART at CD4 counts 200-350 cells/µl and reaching current CD4 counts >200 cells/µl and suppressed VL (<400 copies/ml)) had comparable mortality to HIV-uninfected lives using a 10–15-year period of observation overall. Given the above caveats about the historic available data having limited coverage of patients initiating > CD4 500 cells/µl, the 80-86% ratio of life expectancies shown in Figure 22 for lives starting ART at CD4 counts >500 cells/µl must be considered to be subject to uncertainty. The authors' research on relative mortality risk, research from Johnson et. al and several others on life expectancies does increasingly suggest a convergence of mortality for optimally treated HIV-positive lives with that of HIV-uninfected lives. One factor creating uncertainty is the limited follow up at on ART at durations >15 years where some publications have suggested ART side effects result in increased risk of non-communicable diseases. Hence long-term extrapolation of mortality beyond available cohort observation is always a key consideration to life expectancy calculations. The authors have not made such sensitivity tests and note this as a potential area for further enhancement of the 2023 ASSA SPM.

Figure 20: projected vs. actual (calibration) HIV prevalence

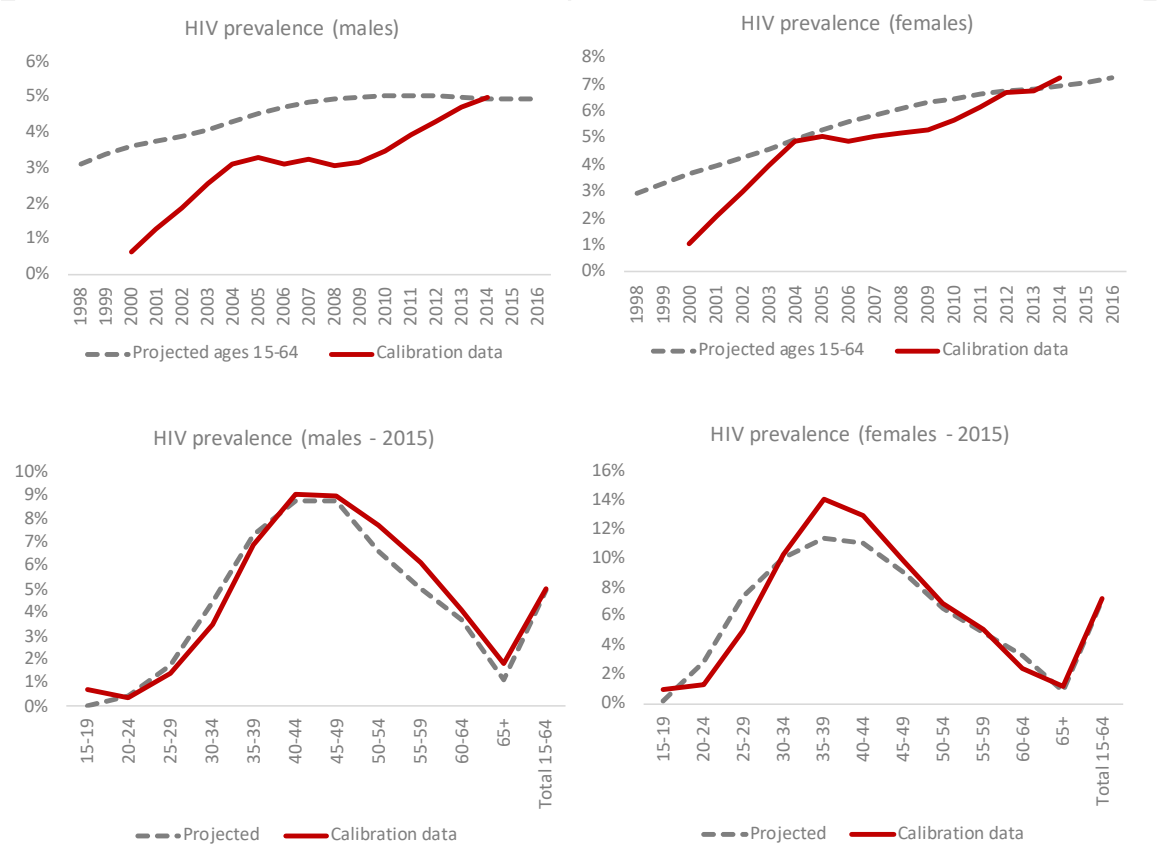


Figure 21: projected vs. actual (calibration) total mortality

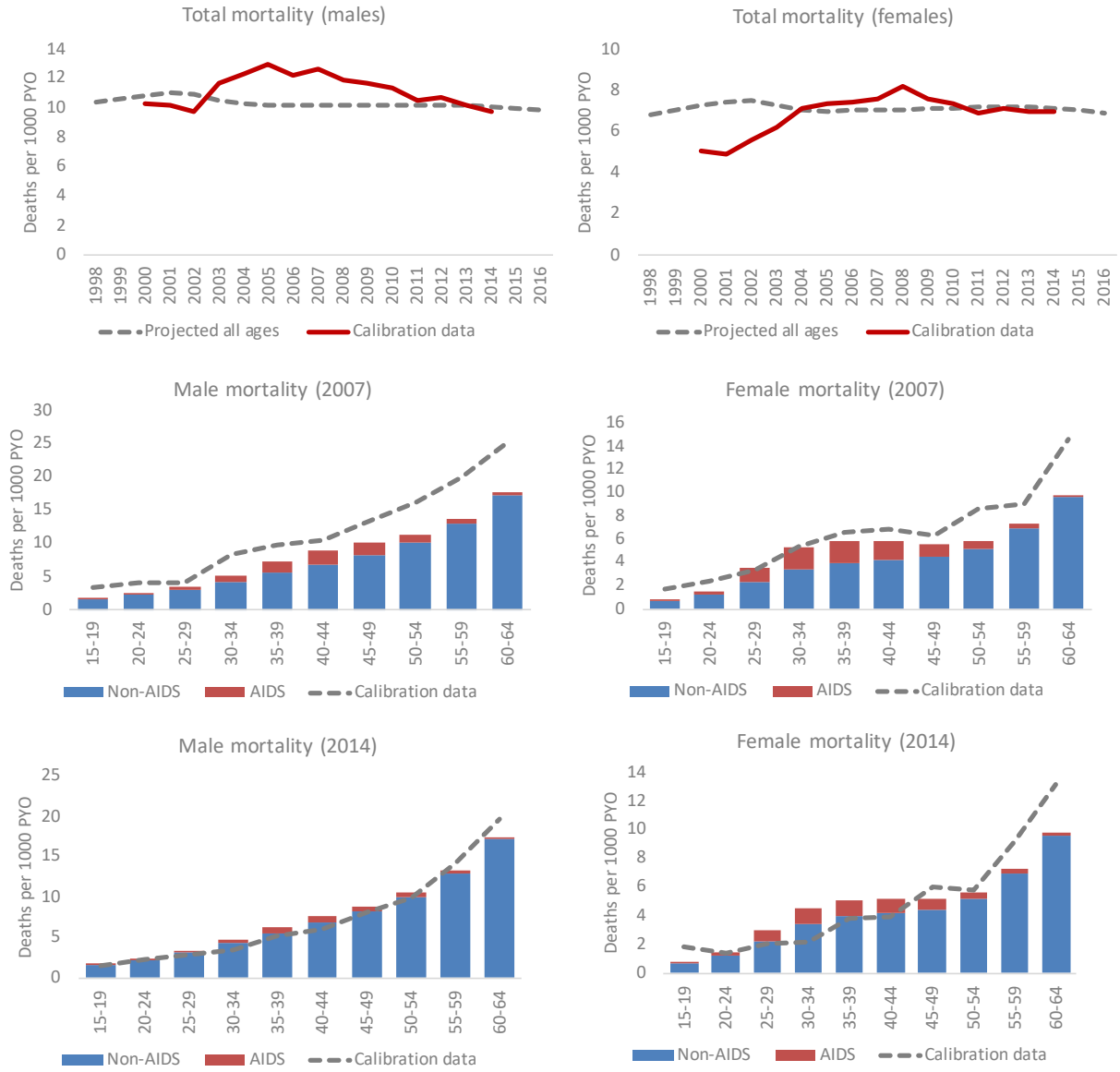


Figure 22: comparison of life expectancies in HIV-positive and HIV-uninfected lives

Note: excludes allowance for future improvements in HIV-unrelated mortality hence overall life expectancy estimates would be higher when allowing for this

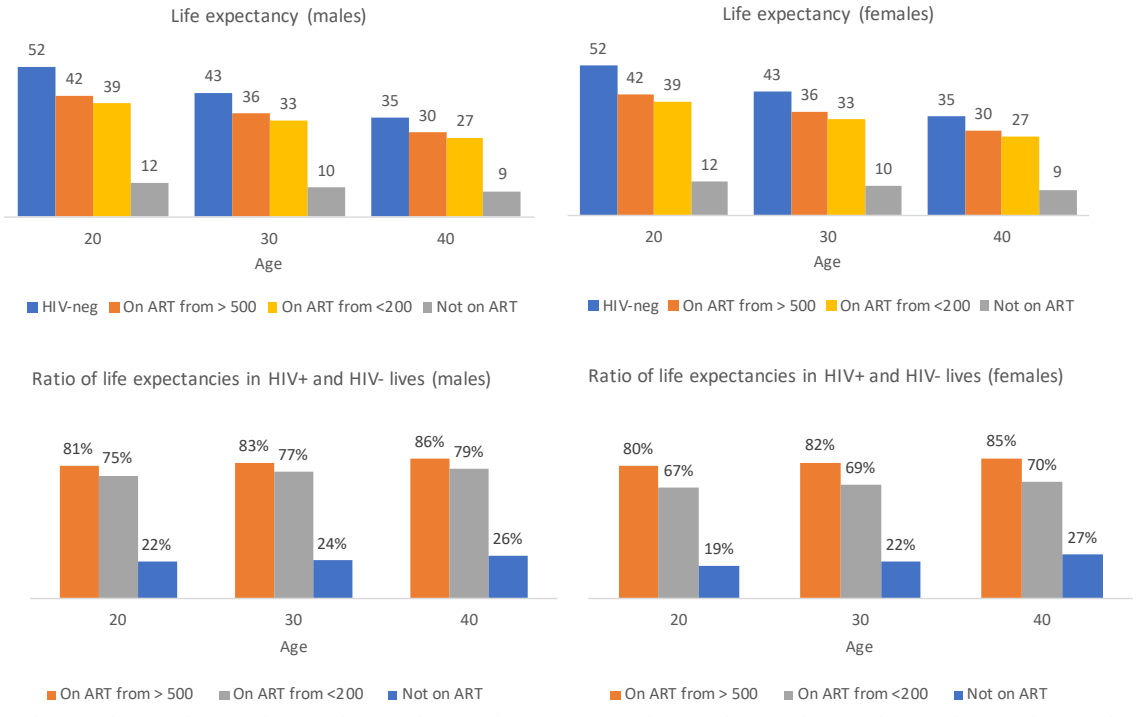
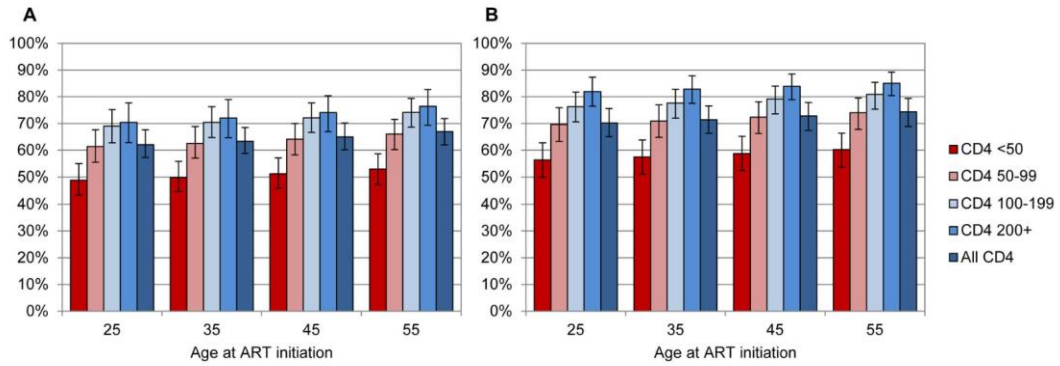


Figure 23: research by Johnson et. al (2013) on the ratio in life expectancies in HIV-positive and HIV-uninfected lives by gender (A (males), B (females)) and baseline CD4 count



5. Reliances, limitations and proposed future enhancements

While the authors have taken all professional measures to ensure reliability and accuracy of research, the authors are not responsible for inaccuracies arising as a result of erroneous or incomplete data from the disease management programme and medical schemes describes in section 2.

As per all previous ASSA SPMs, it is not the intention to release a model to users and the actuarial profession that will by default be appropriate for all risk profiles of populations and contexts. The professional responsibility always applies to the user or actuary to appropriately calibrate the model for their given purposes (refer to ASSA professional guidance Advisory Practice Note (APN) 105 (link) on deriving extra HIV-related mortality assumptions).

Several known limitations require future enhancements to the 2023 ASSA SPM as follows:

- Refined approaches to the demographic projection methodology for achieving stable population
- As more observational cohort data emerges on patients starting ART at CD4 counts above 350 or 500 cells/µl, refine the ART survival assumptions for this subgroup
- Further consider how lives are allocated to CD4 groups upon loss to follow up, and the associated reinitiation rates.
- As more observational cohort data emerges of survival of patients on ART at longer durations of ART (>10, 15 or even 20 years), review the appropriateness of the corresponding 2023 ASSA SPM assumptions. This includes building in appropriate parameters for increased risk of factors that could increase mortality on ART at longer durations such as ART side effects which have suggested increased risk of non-communicable diseases.
- Consider the impact of other definitions of virological suppression (e.g., <400, <50 or <25 copies/ml)
- Adding life expectancy calculations and related reasonability check calculations as default outputs on the Results sheet of the model

6. References

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Appendix 1: Historic scheme age profiles

All beneficiaries: