Supplementary Report S1 - Description of the PopART individual-based model

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Contents

Chapter 1

Overview

1.1 Summary

The PopART individual-based model (**PopART IBM**) is an individual-based mathematical model of HIV transmission in a heterosexual population. The overall aim of the model is to be granular enough to capture details that can be supported by data and that are reasonably thought to affect epidemic dynamics. The model is coded in a modular structure, with components that each affect the predicted dynamics in trial communities. (Unless otherwise stated, all statements about individuals such as 'individuals reside in one of two patches' refer to the simulated individuals rather than reality. We will make it clear when we are referring to data from real individuals rather than properties of the simulation.)

- **Geographic structure and partnerships involving people outside the community**: Individuals reside in one of two *patches*: a patch representing a trial community, and one representing the 'outside'. In the absence of data suggesting otherwise, both patches are assumed identical in demographics and HIV prevalence until the start of the trial. Individuals may have sexual partners either in their own patch (community) or outside (i.e. with individuals in the other patch). We do not model migration between patches.

- **Population demographics:** Each patch contains a growing population of individuals aged 14 and over (referred to as adults here), with a population of approximately 50,000 individuals aged 14 and over at around the start of the PopART trial in 2014, comparable to a trial community. Each individual has a given gender, date of birth, and level of sexual activity. Individuals get older over time and, if they do not die from AIDS-related illness, they die from natural causes at age-specific rates matched to UN Population Division (UNPD) estimates. Children are not modelled; rather, new adults enter the population aged 14 years old at a rate depending on the UNPD fertility rate and female population 14 years previously (at the time they were born), further discounted by taking into account estimates of childhood mortality. Mother to child transmission is not modelled.

- **Sexual partnerships:** Individuals form sexual partnerships with other individuals. The model is parameterised in terms of rates of partnership formation, rates of partnership dissolution, and a maximum number of concurrent partners (which may be one). These rates are dependent on age as well as a level of inherent sexual activity, which is determined at birth and constant for life. There are currently three levels of inherent riskiness: low, medium or high. Partners are chosen according to an age-mixing matrix parameterised using the detailed partnership data from the PC0 survey. The extent to which individuals prefer other individuals with the same level of inherent riskiness is determined by an assortativity parameter. Females report lower partnership formation rates than men; the extent to which actual partnership formation rates reflect these two reported rates is determined by a compromise parameter.

- **HIV natural history:** Every individual has an HIV status, which can be one of: HIV-negative; acute and early HIV infection (AEHI); HIV-positive and CD4 in one of > 500, 350-500, 200-350 or ≤ 200 cells/mm^3. They also have a set-point viral load (SPVL) which affects their infectiousness and their rate of CD4 progression in the absence of treatment. Rates of untreated disease progression are matched to estimates from long-term patient cohorts, mostly from Europe. In our opinion, there is little solid evidence of substantial variation in natural history by geographic area.

- **HIV transmission:** HIV transmission only occurs in serodiscordant couples, with a transmission rate governed by the HIV stage of the infected partner (including AEHI), their SPVL, whether they are on antiretroviral therapy (ART), the gender of the susceptible partner, and their circumcision status if the negative partner is male. HIV transmission rates are lower for partnerships across patches than within patches, to reflect analysis of PC data that suggests that condom use is higher for such partnerships.

- **HIV testing:** HIV testing occurs through both the trial team's CHiPs visits in Arm A and Arm B communities, and through background testing such as for example visits to clinics. These two testing processes occur independently in Arm A and Arm B communities, whereas in Arm C communities and in outside communities, only background testing takes place. Background rates of HIV testing are calibrated to give the proportion of adults who report an HIV test in surveys (DHS/HSRC), and as observed by the CHiPs upon first meeting participants in trail communities. The rate at which CHiPs testing new individuals is directly parameterised from the CHiPs intervention data, and is stratified by gender and age, and varies over calendar time.

- **HIV care and antiretroviral treatment:** Individuals who test HIV-positive can subsequently enter HIV care. If eligible for ART, either because their CD4 is within guidelines at the time, or because they are in an Arm A community, they may initiate ART after a short delay. If not eligible for ART, then they may

continue to undergo CD4 testing until they do become eligible. Those who start ART may, after an initial period, become long-term virally suppressed, or long-term virally unsuppressed. At any point individuals may drop out of care or, off treatment.

- **Male circumcision** Men can be uncircumcised, traditionally circumcised prior to age 14, or medically circumcised following a negative HIV test. Circumcision status affects susceptibility to HIV, with traditional circumcision having a different effectiveness compared to medical circumcision. Analysis of Population Cohort data suggests that voluntary male circumcision has not been effective at preventing transmission, and so the effectiveness of voluntary male circumcision is assumed to be zero. The effectiveness of medical male circumcision is matched to estimates from the literature.

- **Stochasticity:** In the PopART IBM, events are drawn randomly. There is thus a degree of stochasticity in the model outputs. However the large modelled population size reduces this effect, and it is thus much less than the differences arising from uncertainty in parameters.

- **Calibration:** Despite many parameters being drawn from the literature, from statistics collected from UNDP, DHS and HSRC, and many parameters being estimated directly from PopART data, there remains several parameters for which we have considerable uncertainty. In total the model has over 300 parameters, of which a subset are allowed to vary during calibration. The varied parameters were chosen because they were either unknown but thought to be potentially influential (e.g. sexual mixing assortativity by risk group), or were important for the calibration itself (for example time to initiate ART is a parameter which can be informed during calibration by CHiPs data). The model is calibrated by varying parameters systematically, and choosing runs that match historical and baseline PopART data on HIV prevalence by gender and age, and on proportion of HIV +ve who know their status by gender and age, and proportion on ART by gender and age.

- **Predicted trial impact:** The predicted impact is computed for each arm A community as the relative reduction in population HIV incidence between 2014.5 (mid-point of PC0) and 2018.0 (expected midpoint of PC36). The comparison is made between a simulation where the CHiPs intervention takes place, and a simulation in the same community where the intervention does not take place. The impact is computed overall, and by gender. We also account for gender imbalance in PC by computing the weighted mean of the impact in men and women, with weights given by the observed proportion of men and women in PC0. The predict impact is computed for 100 simulations, including ten runs for stochastic variation for each of the ten best fitting parameter sets obtained during calibration.

1.2 Model structure overview

In this document we describe the different components of the model in detail. While the PopART IBM has been specifically built for the HPTN-071 PopART trial, it is envisaged to have many potential applications. Thus the description of the model in this document is generally made non-specific to the trial, although 'patches' can be taken to be equivalent to 'trial communities' in the context of the trial. It should be noted that the description of the 'intervention' is specific to HPTN-071, although in practice it can be applied (with modified details) to other interventions.

1.2.1 Patches, mixing and migration

In the trial we consider two patches: patch 0 consists of a trial community, and patch 1 consists of the immediate neighbourhood where individuals will have similar behaviour, and may form sexual partnerships with individuals in the trial community patch 0, but where HIV testing and treatment occur at background (non-PopART) rates. The input parameters are the same in both patches for most parameters, but with the crucial difference that CHiPs household visits take place in patch 0 (which is the trial community patch), which therefore also has improved ART initiation and circumcision compared to the patch outside the trial. The interaction between patches is through sexual partnerships: individuals in two different patches may form sexual partnerships together, reflecting the reality that people often have sexual partners outside a given community. Migration is not currently modelled in the version of the model used in this report.

1.2.2 Time evolution of the simulation

In the model calendar time t is treated discretely; one timestep is equal to $1/48$ of a year (so that 1 month is equal to 4 time-steps). Throughout this document, time (and the variable t) refer to calendar time unless explicitly stated otherwise. The model is initially run for an extended period without HIV, to allow the demographics (in particular the age distribution) and sexual partner network to stabilize. At a given time (`start_time_hiv`) HIV is introduced for the first time. The model then runs to completion (`end_time_simul`=2030)

At each timestep each process is carried out sequentially for the adult population, before the next process. For instance the first process is deaths from natural causes, followed by entry of new individuals ageing into the adult population just before they turn 14 years old, then new births (of children age 0). Certain processes - those related to HIV testing and ART initiation, voluntary male medical circumcision, and PopART-related activities such as those carried out by community HIV care providers teams (CHiPs) - only occur after a certain time t in the simulation corresponding to when they began in real life.

1.2.3 Events and processes

We now establish the terminology which will be used to describe the PopART IBM. In each patch the model has *individuals* with *characteristics*, and *processes* occur to some of these individuals at each timestep. Characteristics and processes are intertwined. The processes that happen to individuals depending on their own characteristics and those of other individuals (such as sexual partners), as well as other factors such as time t. Characteristics are changed by processes, for example the process of HIV infection changes an individual's HIV status.

Each individual experiences different events over the course of their life, such as forming new sexual partnerships, getting older, testing for HIV, and dying. The events that occur to someone may depend on their characteristics, the characteristics of the population as a whole, and time t. For example HIV infection can occur to an individual if they are HIV- and they have a partner who is HIV+. A person may initiate ART if they are HIV+ and aware of their serostatus, and meet the eligibility criteria for ART at the given time t. We group these events into different processes. Two processes can happen in the same timestep (for example someone can acquire an extra sexual partner and become HIV infected at the same timestep - either by the new partner or an existing one). For each timestep, the processes always occur in the same set order. The list of processes, ordered as they occur in a timestep, in this model version 1.3 are:

- Demographic processes (births, ageing, death apart from AIDS-related death);
- Sexual partnership breakup;
- Sexual partnership formation;
- HIV acquisition;
- HIV-related events when not on ART (disease progression, initiation of ART once CD4 count drops below 200 cells/mm^3, AIDS-related death);
- Background (i.e. non-PopART) HIV testing and the ART cascade: includes the processes of HIV and CD4 testing, entering care or initiating ART, dropping out of care and re-entering the cascade;
- HPTN-071 annual CHiPs visits (HIV testing);
- Voluntary male medical circumcision (VMMC).

At a given timestep each process occurs to the whole population (or relevant sub-population: for example only uncircumcised men may receive VMMC), before the next process in the list occurs.

1.2.4 Scheduling processes and events: the scheduling array

For the majority of processes, the next event for each individual is scheduled, so that the model runs as quickly as possible. Scheduling arrays are large 2D matrices which store the schedule of a given process. Each scheduling array acts as a diary containing the next event for each individual for a given process, and there is one scheduling array for each process that is scheduled. If an individual is not in a scheduling array for a given process, nothing will happen to them in that process until some external change is made: for example an HIV-negative individual will not undergo any HIV-related events when not on ART, so will not appear in that scheduling array, until they become HIV infected, at which point a future HIV-related event (progression from acute to chronic HIV infection) will be assigned to them. Another way that individuals may be put into a scheduling array is when some event occurs only after some given time t, such as the HPTN-071 annual CHiPs visits.

1.3 Individuals and characteristics

1.3.1 Adults and children

The modelled population is divided into children and adults. The adult population is the primary population in the model: this is the population which has characteristics and to which processes occur. In other words, detailed individual information is kept for each adult in the simulation, and this is updated over time as processes change individual characteristics. This assumes that children as defined in the model are not sexually active, or at risk of HIV infection except perinatally. For children the model therefore just keeps track of the number born at each timestep who will survive to adulthood and their perinatal HIV status. Once an age cohort of children reaches adulthood, an equivalent number of adults are added to the IBM, representing these children reaching adulthood. A full description of births and the transition to adulthood in the model is given in chapter 2.

1.3.2 Characteristics of individuals

Each individual has a large number of characteristics stored at any given time. One class of characteristics - referred to as scheduling characteristics - are only relevant to the way that processes are scheduled, keeping track of where an individual is in each scheduling array. A second class - validation characteristics - are used to validate the model by checking for self-consistency within the model and for comparison with data such as national-level DHS surveys.

The remaining characteristics are referred to as epidemiological characteristics, and are those relevant to HIV transmission in some way. The epidemiological characteristics of the adult population are listed in Table 1.1. Some epidemiological characteristics of an individual are immutable once the individual enters the adult population (ID number, gender, date of birth, risk group, maximum number of simultaneous sexual partners),

some are set by a process during the simulation (having previously been assigned a placeholder value of -1) but then remain fixed thereafter (time of HIV seroconversion, set-point viral load), and the remaining characteristics change over time in response to specific processes.

Other quantities in the model are derived using the stored characteristics, for example the age of the individual is calculated as necessary based on the date of birth and current time. The choice of whether a characteristic is stored or derived is largely driven by memory considerations, the frequency with which the given data is needed, and whether the quantity requires updating. For example age would require annual updating, while a date of birth is fixed.

1.4 Coding and debugging

Extensive work has gone into debugging and validating the PopART IBM, through: use of cross-checks within the code to ensure that only allowed events occur to individuals (for example a dead person is not able to start ART); code walk-throughs; and use of debugging software, such as valgrind to identify memory issues. The model has also been run switching off and adding components one at a time to ensure it behaves as expected.

Characteristic	**Relevance**
ID number	Unique identifier for each person.
Gender	Whether the person is male or female.
Date of birth	Used to derive age and age group. Determines natural mortality rate, and partnership mixing has an age-related component.
Risk group	Low, medium or high risk (determines their preferred number of partners).
HIV status	Divided into uninfected, acute infection and chronic infection. Chronic infection includes individuals on ART.
Time of HIV seroconversion	Used to determine if individual lies outside testing window of HIV test kit used.
Current CD4 category	Categories are: CD4>500, 350-500, 200-350, and CD4<200. Determines eligibility for ART, infectivity and AIDS-related death rate.
Set-point viral load category	Categories are <4, 4-4.5, 4.5-5 and $\geq$ 5 log10 copies/μl. Determines HIV progression rate and infectivity.
ART status	Divided into never tested positive, positive but not yet on ART (or dropped out), on ART for <12 months, on ART for $\geq$12 months and virally suppressed, on ART for $\geq$12 months and not virally suppressed. ART status determines HIV progression rate, infectivity and AIDS-related death rate.
Circumcision status	For men stores whether they are currently uncircumcised, circumcised by voluntary male medical circumcision (VMMC), VMMC but during healing period, traditional circumcision.
Number and IDs of current partners who live in the community	This is a list of the current sexual partners of the individual.
Current partners outside the community	Contamination from outside cluster.
Number and IDs of HIV+ partners	To look at just serodiscordant partnerships for transmission.
Maximum number of partners	Maximum number of concurrent partnerships the individual can have at any time.

Table 1.1: List of epidemiological characteristics of each adult individual stored by the PopART IBM.

Chapter 2

Demographics

2.1 Overview of the demographic model component

Within the PopART IBM demographics consists of the the following processes:

- New births
- Entry into the adult population
- Deaths due to natural causes (not HIV-related)
- Ageing

In the PopART IBM, each patch contains an open population where individuals are born, age, and die. The size of the population in each patch changes over time, driven by differences in fertility and mortality rates. These rates are based on the country-specific United Nations Population Division (UNPD) 2015 World Population Prospects estimates [21]. The initial adult population size in the model is calibrated by hand to produce a population size similar to that of a HPTN-071/PopART community of around 50,000 individuals aged 14 and above by 2015. The model is initialised in 1900, well before the introduction of HIV, to allow the model time to burn in demographics and sexual partnerships.

The model treats adults and children separately. Adults form the primary population: they have full characteristics (HIV status, riskiness, etc), and processes occur to them, including forming sexual partnerships, getting infected with HIV, initiating treatment and death. The model only keeps track of the number of children in each patch born at each timestep, and nothing further happens to them until they reach adulthood. As described in section 2.1.2, rather than model explicitly death during childhood, perinatal and childhood mortality is taken into account by discounting the fertility rate so that only children who will survive to adulthood are included.

Within the model "adult" means anyone aged 14 years old or above. Individuals aged 14 and over are included to capture the majority of time of exposure to HIV risk. For technical reasons, because there is continuous introduction of new adults throughout the

year, but ageing happens in yearly cohorts at the very beginning of a new year, the actual adult threshold in the model is one timestep before age 14. The cohorts are defined by having the same age at the start of the year (e.g. be age 14.0-14.99 where '14.99' is really (15 minus one timestep)), or equivalently by the year in which they reached adulthood. As an illustration, individuals who enter the adult population aged 13.99 at either 1990.0 or 1990.99 are all aged 14.0-14.99 in 1991.0.

2.1.1 Initialization of demographics

At the start of each simulation the adult population is set up. This is done by first choosing the number of individuals of a given gender g, sexual risk group r and age group a at that time $N^g_{a,r}(t_0)$, and then generating that many individuals with those characteristics (i.e. gender and risk group, with age in the given age group) in the model. This is prior to the introduction of HIV, so all the initialised individuals are HIV-negative. The total number of individuals in a patch at the start of the simulation is specified via the input parameter $initial\_adult\_population\_size$. It thus satisfies the constraint that it is equal to the sum of the number of men and women in every age and risk group:

$$initial\_adult\_population\_size = \sum_{gender} \sum_{a=0}^{N_{age}} \sum_{r=0}^{N_{risk}} N^g_{a,r}(t_0)$$

We calculate the $N^g_{a,r}$ at time t_0 from $initial\_adult\_population\_size$ as follows: we assume that the initial proportion in each of the age groups 13-17, 18-22, 23-29, 30-39, 40-49, 50-59, 60+ is equal to $initial\_prop[a]$, which is based on UNPD estimates from 1950, the earliest time available. Within each age group the fraction who are male is set by the parameter sex_ratio, assuming age and gender are independent, and the fraction in each risk group, which depends on the gender, is $initial\_prop\_gender\_risk[g]$.

Once we know $N^g_{a,r}$, we generate that corresponding number of individuals in the model of gender g and sexual risk group r, who are in age group a. Their exact age is calculated afterward, along with other characteristics. This process is similar to that of individuals reaching adulthood later in the simulation as described in section 2.1.3, apart from their age. Each individual is assigned a patch-specific ID, and is set up to be uninfected with HIV, as the simulation starts before the introduction of HIV, and without any sexual partners. They are assigned a date of birth based on their exact age and the current time as follows: their exact age is drawn uniformly between the minimum and maximum of that age group a using the GNU scientific library routine gsl_rng_uniform_pos() so that the value can never take the boundary values - e.g. if $a = 1$ their age is drawn from the open interval (18,23)[1] - to avoid potential issues with boundaries. In the youngest age group $a = 0$ the age is drawn from the open interval (14,18). For the oldest age group the age is drawn from (60,80) so that no individual is aged > 80 at the start of the simulation.

[1] They can thus be aged 18.01 or 22.99 years but not 18.0 or 23.0 years.

At initialisation a proportion p_{circ} of men are taken to be circumcised traditionally. If the number of men in a given age group a and sexual risk group r is $N^m_{a,r}(t_0)$ then the first $floor(N^m_{a,r}(t_0) * p_{circ})$ of the men in that age group are taken to be circumcised traditionally, where $floor()$ is a function that rounds down to the nearest integer. As described later, traditional circumcision may have a different effectiveness to voluntary male medical circumcision for reducing HIV susceptibility within the PopART IBM. Other characteristics related to the technical running of the model - scheduling and validation characteristics - are given appropriate default values, the same as is described in detail in section 2.1.3.

The list of children is populated at the start of the simulation by assuming that the fertility rate and population size was constant prior to the start of the simulation. The number of children who had been born in each timestep prior to the start of the simulation is therefore drawn from a binomial distribution using the fertility rate and adult female population size at the start of the simulation (the exact details are described in more detail in 2.1.2). While the simulation has a long burn-in time so that the exact choice of initial conditions should not affect the demographics by the time the HIV epidemic begins, the age distribution by gender is checked against UNPD estimates at several time-points to ensure that there are no issues.

2.1.2 New births and children

At each timestep the model calculates the number of new children born in that timestep who will survive to reach adulthood. This is drawn as a binomial random variable $Binomial(N^a_f(t), p^a_{child}(t))$, where $N^a_f(t)$ is the female population size aged a years at time t and $p^a_{child}(t)$ is the estimated probability that a woman aged a years has a child in that timestep that will survive to adulthood, using the GNU Scientific Library function gsl_ran_binomial(). The probability $p^a_{child}(t)$ is derived from UNPD WPP 2015 age-specific fertility rates for the given country, which gives estimates of the number of births to women in a particular age group, divided by the number of women in that age group, during the periods 1950-55, 1955-60,... 2095-2100, using the UNPD medium fertility variant for future projections as described in [22]. UNPD uses age groups 15-19, 20-24, ..., 45-49. In the PopART IBM the fertility rate is assumed for simplicity to be constant within each age group, but interpolating between different calendar time periods. Fertility rates are assumed to have been constant before 1950 and post-2100. Following UNPD fertility is assumed to be negligible in women aged 50 years and older [21].

To calculate $p^a_{child}(t)$ this fertility rate is then discounted by the probability of the child dying before it reaches adulthood $p_{childmortality}(t)$, which is calculated as follows:

$$p_{childmortality}(t) = 1-(1-\text{mortality\_rate}_{under5}(t))^5 * (1-\text{mortality\_rate}_{age5-10}(t+7.5))^5$$

where $\text{mortality\_rate}_{under5}(t)$ and $\text{mortality\_rate}_{age5-10}(t + 7.5)$ are the UNPD WPP 2015 estimates of annual mortality rates aged 0-5 and 5-9 at time t and t+7.5 respectively. The different times t and $t + 7.5$ are to account for changes in mortality rates between the time of birth and when the child reaches the given age range: for the former it is

assumed that the majority of mortality aged 0-4 occurs around the time of birth (i.e. at time t) while mortality in children 5-9 is assumed to occur uniformly during that age, so on average 7.5 years after the time of birth t. Mortality in children aged 11-13.99 is assumed negligible in comparison and is ignored.

$$p^a_{child}(t) = \mathrm{dt} * (1 - p_{childmortality}(t)) * \mathrm{Age\_specific\_fertility}(a, t)$$

Within the model, children become adults one timestep before they turn 14. When a child reaches this age they are removed from the list of children, and a corresponding adult individual is created, who is assigned detailed individual information at that point. This is described in detail in section 2.1.3.

2.1.3 Entry into the adult population

For each individual reaching adulthood in a given patch, a number of characteristics are assigned, mirroring the assignment that occurs when the population is initialised at the start of the simulation. Firstly they are assigned an ID number and a date of birth, with the latter calculated as the time at which they would have been born given that they are now 13.99 years old. They have a gender and sex risk drawn randomly. The probability that the individual is male is given by the parameter sex_ratio, while the probability that an individual is in sexual risk group r is $initial\_prop\_gender\_risk[g]$, and depends on gender. At present all individuals are assumed to be HIV-negative when entering the adult population.

On entry to the adult population individuals are able to form sexual partnerships: they are not assigned any sexual partners at entry, but they are added to the pool of potential sexual partners, so that they may acquire sexual partners thereafter (see next section on partnerships).

Amongst male individuals reaching adulthood a proportion p_{circ} undergo traditional male circumcision. In the HPTN-071 trial p_{circ} comes from data from the baseline Population Cohort survey on the proportion of men in each community who self-report being circumcised by a traditional practitioner.

Scheduling characteristics are set to null values (-1) to represent the fact that nothing is happening to them yet - they have no partners (so cannot break up partnerships), and are HIV-negative (so will not undergo either CD4 progression or any steps in the ART cascade). They are also assumed to not have scheduled any HIV testing at that point, although they may be tested in future.

Similarly other characteristics relevant to the technical details of the model such as validation characteristics and cumulative counters are initialised to appropriate values (generally 0 for cumulative counters such as the number of sexual partners the individual has had, or null values). An example of a validation characteristic is how CD4 is used in HIV-negative individuals: as the individual is HIV-negative their CD4 is set to -1, and then this is used as a validation to test for example that someone initiating ART is HIV-positive.

2.1.4 Deaths due to natural causes (not HIV-related)

Death is carried out at each timestep through the following process. For each gender and yearly age group we have a natural (non-HIV) mortality rate at that time, derived from UNPD estimates as described below, and the number of individuals in that group. We draw the number of people in that group who will die in that timestep $n^a_{death}(t)$ as a binomial random variable, using the GNU Scientific Library function gsl_ran_binomial(). If there are any deaths ($n^a_{death}(t) > 0$) we choose the individuals who will die randomly from that yearly age group using the function gsl_ran_choose(). For each individual chosen to die we first check that they are in the correct age group and are currently alive, as part of the model error-checking. These individuals are then systematically removed from every relevant scheduling list - for example a HIV-positive individual is removed from the list HIV-related events when not on ART - as no future events can now happen to them. Similarly any scheduled background HIV testing/ART cascade, or scheduled VMMC events are removed for the dead individual.

The sexual partners of the dead individual are also updated. The dead individual is removed from the list of potential partners, and the list of susceptibles in serodiscordant partnerships, if they were on those lists. Any ex-partners of that individual have their partnership information updated: we decrease the number of current partners they have by one, update the list of their partners, and add an extra potential partnership from that ex-partner to the list of available partnerships. If the dead individual was HIV-positive and the ex-partner was HIV-negative we update the list of the ex-partner's serodiscordant partners and check if the ex-partner has any other current HIV-positive partners; if they do not then we remove the ex-partner from the list of individuals who are in a serodiscordant partnership.

The natural (non-HIV) mortality rate used in the model is derived from UNPD WPP 2015 estimates in the given country [21]. UNPD provides estimates of the number of deaths that occur in a given 5 year age group (0-4, 5-9,...) during the five year time periods 1950-55, 1955-60, 1960-65,...2010-2015 for each gender. UNPD also publishes the estimated size of each 5 year age group during that period. Projections of future number of deaths and population sizes are also published, and we use the 'medium fertility' variant as described in [22].

2.1.5 Ageing

Each individual has a date of birth, stored as part of their characteristics, from which their age can be derived at any given time t. However, for practical coding/algorithmic reasons there are several lists which contain individuals in one year age cohorts (age 13, 14, 15,...79, 80+), or in the 'partnership'age groups': 13-17, 18-22, 23-29, 30-39, 40-49, 50-59, 60-79, 80+. The cohorts are defined by the age at the start of a calendar year. Note that individuals only enter the adult population aged 13.99 years, and therefore the one year age group for 13 year olds only contains individuals who have entered the adult population at this time; the remaining 13 year olds are stored in the list of children. The 13-17 year old age group similarly only includes those 13 years and above who are 13.99

years or older at present.

For computational efficiency ageing in the one year cohorts is accomplished at the start of the year by relabelling the cohorts 14...78 to be 15...79. Individuals in the age 79 cohort are moved into the 80+ cohort, while the array previously containing the age 79 cohort is now the age 14 cohort and is initially empty until new individuals enter the adult population. The same relabelling technique is used for other objects storing data in one year age groups such as population size.

In the partnership age groups we use the one year age cohort to list all the individuals who are about to transition from one partnership age group to the next age group. These individuals are moved in a multi-step process. Firstly they are added to the end of the next age group list. Then the previous age group list is updated: the last individual on the previous list is moved into the position of the individual who is moving age groups, overwriting their details. Finally the number of individuals in each age group is updated, reducing the number in the previous age group by one and increasing the number in the new age group by one.

2.1.6 Sex ratio

The sex ratio in the population is primarily governed by the parameter sex_ratio which determines the proportion of new adults who are male. The sex ratio in the population is also affected by mortality, both non-HIV related and HIV related, as these vary by gender. The sex ratio used is the country-level sex ratio from UNPD.

Chapter 3

Partnership acquisition and dissolution

3.1 Theoretical framework

3.1.1 Summary

In the PopART IBM, we explicitly model partnerships between individuals, with the partnerships lasting a certain duration before breaking up (dissolving). We only model heterosexual partnerships. Individuals are classified into age and activity categories (where higher activity reflects higher propensity to form partnerships). Individuals in different age / activity groups have different rates of forming new partnerships, based on country-level analysis of PC0 data. Once formed, a partnership is assigned a future time of dissolution (assuming neither partner dies in the interim), based on a gamma distribution parameterised by PC0 data.

We assume independence between the effects of age and activity on the rate of partnership formation. A proportion of partnerships (fixed across gender, activity and age) are assumed to be formed within the same community, and the remaining partners outside the community. When modelling more than 2 communities or patches (which we don't for the purpose of PopART as we run the model separately for each community and their 'outside' patch) we assume that the partners outside the community are as likely to be chosen in any of the other communities (note this does not depend on community size at the moment). Partners in and out of the community are chosen according to activity and age preferences, assumed independent of one another. Once formed, partnerships between individuals who are both high-activity are on average shorter, and partnerships between individuals who are both low-activity are on average longer, informed by PC0 data. Partnerships between individuals not in the same patch are also shorter on average. Finally, the risk of HIV transmission within a partnership depends on a number of characteristics of the two individuals, described in detail in the next section on HIV transmission; but it also depends on whether individuals are in the same patch or in different patch; the risk of HIV transmission is lower when partners are not in the same

patch, to reflect lower frequency of unprotected sex, as reported in PC0.

3.1.2 Partnership formation according to age

In this paragraph, we present the partnership formation process according to gender and age. For simplicity, we ignore activity-classes for now, and introduce this additional level of complexity in the next paragraph only.

Let c^f (respectively c^m) be a vector so that c^f_a (respectively c^m_a) is the average number of new partners per year for a female (respectively a male) aged a.

Let p^f_{age} be a matrix so that $p^f_{age}[a,.]$ is the distribution over age of "desired" male sexual partners of a female aged a. Similarly, let Let p^m_{age} be a matrix so that $p^m_{age}[a,.]$ is the distribution over age of "desired" female sexual partners of a male aged a.

Let $N^f(t)$ and $N^m(t)$ be two vectors containing the population size of each age group within females and males respectively, which may vary over time.

At each time step, we compute the number of new partnerships that the group of females of age a desire to form in this time step with males of age a^* as $S^f_{a,a^*}(t) = N^f_a(t)\, c^f_a p^f_{age}[a,a^*]dt$, where dt is the duration of a time step. Similarly, we compute the number of partnerships that the group of males of age a^* desire to form in this time step with females of age a as $S^m_{a^*,a}(t) = N^m_{a^*}(t)\, c^m_{a^*} p^m_{age}[a^*,a]dt$.

In order for contacts to be balanced, we need $\forall(a,a^*), S^f_{a,a^*}(t) = S^m_{a^*,a}(t)$ (number of partnerships formed between females aged a and males aged a^* between t and $t+dt$).

Garnett and Anderson [15] propose that to balance contacts, one should take the geometric mean between number of contacts as reported by females and as reported by males, weighted by a parameter θ so that $\theta = 0$ if only women make compromises (so men decide entirely) and $\theta = 1$ if only men make compromises (and women decide entirely). In this approach, the balanced number of new partnerships formed between a female aged a and a male aged a^* is $T_{a,a^*}(t) = S^f_{a,a^*}(t)^{1-\theta} S^m_{a^*,a}(t)^{\theta}$. Garnett and Anderson argue that $\theta = 0.5$ corresponds to the case where the two sexes compromise equally [15].

Here we argue that an equal compromise would be that half of the unmatched partnerships (wanted by one gender but not by the other) are satisfied. This corresponds to taking the arithmetic instead of the geometric mean, weighted by a parameter θ, with again, $\theta = 0$ if only women make compromises, $\theta = 1$ if only men make compromises, and $\theta = 0.5$ if men and women make equal compromises.

Therefore, at each time step, the actual number of partnerships formed between females aged a and males aged a^* is $T_{a,a^*}(t) = (1-\theta) S^f_{a,a^*}(t) + \theta S^m_{a^*,a}(t)$.

The geometric mean approach tends to favour the group that report fewer partners compared to the arithmetic mean approach.

Note that in this approach we assume that the desired number and ages of new partners is constant over time (p^f_{age}, p^m_{age}, c^f and c^m assumed constant over time) but limited by the availability of individuals in each age group (time varying N^f and N^m). We vary θ between 0 and 0.5.

We use the following age groups: 13-17, 18-22, 23-29, 30-39, 40-49, 50-59, 60-79, 80+, and we use values of c^f, c^m, p^f_{age} and p^m_{age} which are country specific, and based

on analyses of the PopART baseline population cohort (PC0) data (see further in this document).

3.1.3 Partnership formation according to sexual activity

We further assume that individuals are classified into activity classes corresponding to different levels of sexual activity. Each individual remains in the same activity class for their whole life. We assume that the age and risk preferences in forming partnerships are independent for parsimony (see [24] for details on non independent cases).

We use three activity classes (low, medium, high).

We assume that individuals in each activity class forms partnerships according to the process described in the previous section, albeit with individuals in higher activity classes forming overall more partnerships.

Expanding on the notations of the previous paragraph, we call $c^{f,r}$ (respectively $c^{m,r}$) the rate of partnership formation of females (respectively males) in activity class r. We further assume that the relative rate of partnership formation according to activity class is the same in males and females so that:

$$c^{f,high} = \delta^{high} c^{f,low}; c^{f,med} = \delta^{med} c^{f,low}$$
$$c^{m,high} = \delta^{high} c^{m,low}; c^{m,med} = \delta^{med} c^{m,low}$$

In the following we fix $\delta^{low} = 1$ by convention, so that all the rates of partnership formations are written relative to the low activity class.

Let p^f_{risk} be a matrix so that $p^f_{risk}[r, .]$ is the distribution over activity class of desired male sexual partners of a female of risk r. Similarly, let p^m_{risk} be a matrix so that $p^m_{risk}[r, .]$ is the distribution over risk groups of desired female sexual partners of a male of risk r. We assume the elements of these matrices are of the form (given here for females but completely symmetric for males:

$p^f_{risk}[r, r] = \chi + (1 - \chi) P^m_r$ and $p^f_{risk}[r, r^*] = (1 - \chi) P^m_{r^*}$ if $r \neq r^*$ for females, where $P^m_r = \sum_{a=1}^{n_{age}} N^m_{a,r} / \sum_{s=1}^{n_{risk}} \sum_{a=1}^{n_{age}} N^m_{a,s}$ is the proportion of the male population in activity class r (with $N^m_{a,r}$ and $N^f_{a,r}$ the number of males and females in age group a and activity class r).

In this formulation, χ is the assortativity, i.e. the proportion of contacts made preferentially within the same activity class (as opposed to random contacts made within any activity class).

Note that as the proportion of females/males in each activity class may vary over times, p^f_{risk} and p^m_{risk} are also time varying.

The number of partnerships that women aged a in activity class r "want" to make, between t and $t + dt$, with men aged a^* in activity class r^* is:

$$S^f_{(a,r),(a^*,r^*)}(t) = N^f_{a,r}(t) c^f_a \delta^r p^f_{age}[a, a^*] p^f_{risk}[r, r^*](t) dt$$

And the number of partnerships that men aged a^* in activity class r^* "want" to make, each year, with women aged a in activity class r is:

$$S^m_{(a^*,r^*),(a,r)}(t) = N^m_{a^*,r^*}(t)\, c^m_{a^*} \delta_{r^*} p^m_{age}[a^*, a] p^m_{risk}[r^*, r](t)\, dt$$

If "desired" number of partnerships are not the same for both sexes, we compute an adjusted number of partnerships, calculated as the weighted arithmetic mean between the two:

$$T^f_{(a,r),(a^*,r^*)}(t) = (1-\theta)\, S^f_{(a,r),(a^*,r^*)}(t) + \theta S^m_{(a^*,r^*),(a,r)}(t)$$

3.1.4 Choosing partners inside and outside one's community

We assume that individuals form a proportion of their new partnerships with partners in their own community, and the rest in other communities. Risk and age mixing is assumed to be exactly the same with partners inside and outside the community. In practice, we assume that the within community partnership formation rates are $c^{f,in}_a$ for females and $c^{m,in}_a$ for males aged a. We then assume that the between community partnership formation rates are $c^{f,out}_a = \xi c^{f,in}_a$ for females and $c^{m,out}_a = \xi c^{m,in}_a$ for males aged a. This is equivalent to assume that a proportion $\frac{\xi}{1+\xi}$ of partnerships formed by both males and females (of all ages) are formed with partners outside their community.

3.1.5 Maximum number of partners

We assume that individuals cannot have more than a certain number of partners at any point in time. This maximum number of partners is assumed to depend on the activity class and to be higher in the higher activity classes. For each individual, formation of new partnerships is independent of the current number of partners, albeit with this constraint of maximum number of partners.

3.1.6 Relative riskiness of partnerships

In order to reflect differences in frequency of unprotected sex acts between different types of partnerships, we assume that the risk of HIV acquisition within a serodiscordant partnership depends, beyond ART/circumcision status and HIV stage, on the location of the two partners (same or different patches). We use the risk of HIV acquisition within serodiscordant partnerships between partners in the same patch as the baseline. We assume that the risk in serodiscordant partnerships between two individuals in different patches is reduced compared to the baseline.

3.1.7 Partnership duration

We assume partnership durations to be exponentially distributed, with mean duration depending on the activity classes of the two partners. We assume a mean duration μ_{low}, μ_{med} or μ_{high} (with $\mu_{high} < \mu_{med} < \mu_{low}$), determined by the "higher" of the two activity

classes the partners belong to. For instance a partnership between a high and a low risk individuals will have a duration exponentially distributed with mean μ_{high}.

The above parameters are used to model the duration of partnerships between partners in the same patch. We further allow partnerships between different patches to be shorter on average, with a multiplying factor ν.

These parameters are used to draw an expected date of end of partnerships for each newly formed partnership. However partnerships can be dissolved prior to this expected end if one of the two individuals dies.

3.2 Parameter estimation using the PC0 data

In this section we explain how we used data from the baseline population cohort (PC0) of the HPTN 071/PopART trial to derive the parameters related to partnership formation and dissolution used in the PoPART IBM. The results presented below are based on an early version of the PC0 dataset (survey data from 30 April 2015 and HIV test data based on 23 June 2015).

3.2.1 Defining activity classes

These are defined based on threshold number of lifetime partners by age groups, as shown in table 3.1 and figure 3.1. These thresholds were designed to maximise differences in prevalence between different activity classes. The proportion of individuals in each activity class is given in Table 3.2. Prevalence for men and women is indeed higher in the higher risk categories according to this definition, even when accounting for age (see Figure 3.2).

	13-17	18-22	23-30	31-40	41+
Low activity class	0	0	0-1	0-1	0-1
Middle activity class	1-2	1-3	2-4	2-5	2-5
High activity class	3+	4+	5+	6+	6+

Table 3.1: Number of lifetime partners by age and activity class

	% low risk	% middle risk	% high risk
Females, Zambia	35.60	59.00	5.37
Males, Zambia	28.60	46.50	24.90
Females, South Africa	29.60	56.10	14.30
Males, South Africa	27.80	40.90	31.30

Table 3.2: Proportion of population in each activity class by country and gender

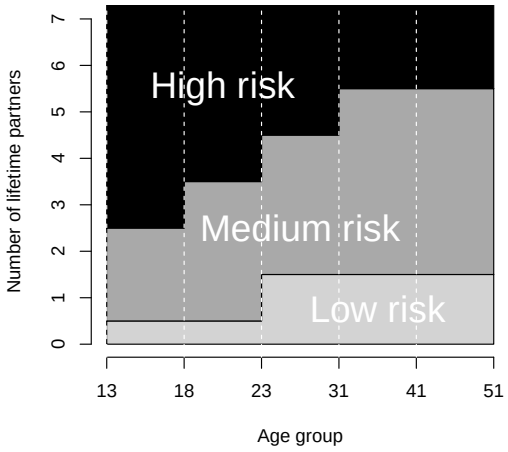

Figure 3.1: Definition of activity classes according to age and lifetime number of partners

3.2.2 Maximum number of partners at a given time

We fix this maximum number of partner to 1 in the low activity class, 3 in the medium activity class and 10 in the high activity class.

3.2.3 Estimating the rate of partnership formation by country, gender, age and risk

To estimate the rate of partnership formation, we considered the reported date of first sex with the up to last three partners of all individuals who were administered the extended PC0 questionnaire, and evaluated whether it was more or less than a year before the PC0 interview. For each individual, we thereby classified their up to last 3 partners as "new" (first sex in the last year) or "not new". For individuals who reported more than 3 partners, the proportion of the additional partners who were "new" was imputed based on the proportion of new partners among the last 3, assuming that these 3 were representative of all partners. For the last up to 3 partners, individuals also reported whether these partners lived inside or outside the community. We assumed the new partners among these last 3 were representative of potential additional new partners, so inferred (deterministically) the location of these extra new partners, when needed, based on the reported location of the new partners among the last 3 partners. This allowed us to estimate the number of "new" partnership initiated by each individual in the last year both inside and outside the community.

We then used this data to estimate, using a Poisson likelihood, the parameters of our partnership formation model for each country. These parameters are $c_a^{f,in}$ and $c_a^{m,in}$ (the rates at which low-activity females and males aged a form partnerships with part-

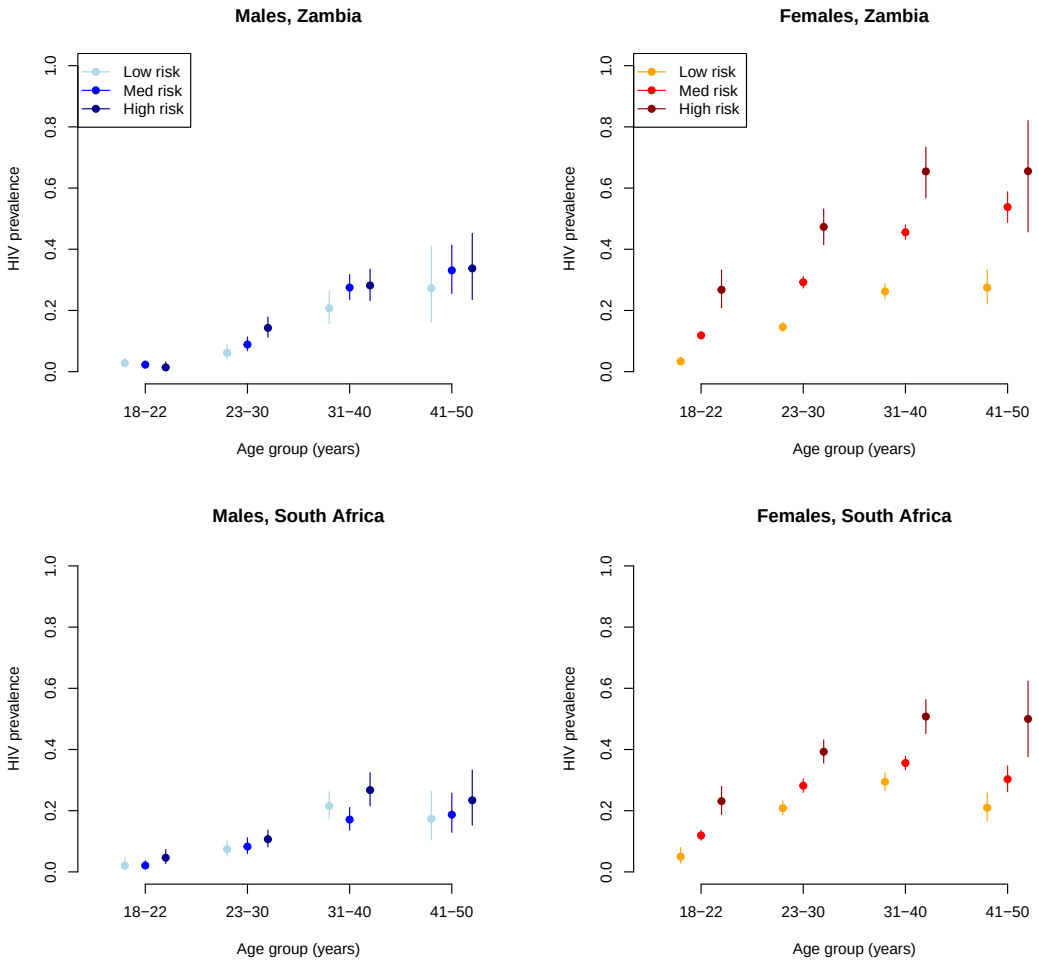

Figure 3.2: HIV prevalence by gender, risk and age group

ners inside their community respectively), ξ (the relative rate of partnership formation with partners outside versus inside the community) and δ^{med} and δ^{high} (the relative rate of partnership formation for medium and high activity individuals). We compared our model to an 'unconstrained' model where rates of partnership formation inside / outside the community and in each gender / age / activity class are estimated completely independently, without assuming multiplying effects as we have done in our 'constrained' model.

Results are shown in Figures 3.3 for Zambia and 3.4 for South Africa.

3.2.4 Age Assortativity

Tables 3.3, 3.4, 3.5 and 3.6 present the age mixing matrices p_{age} by gender and country, obtained by considering the age of the last reported partner (within the last year) of each

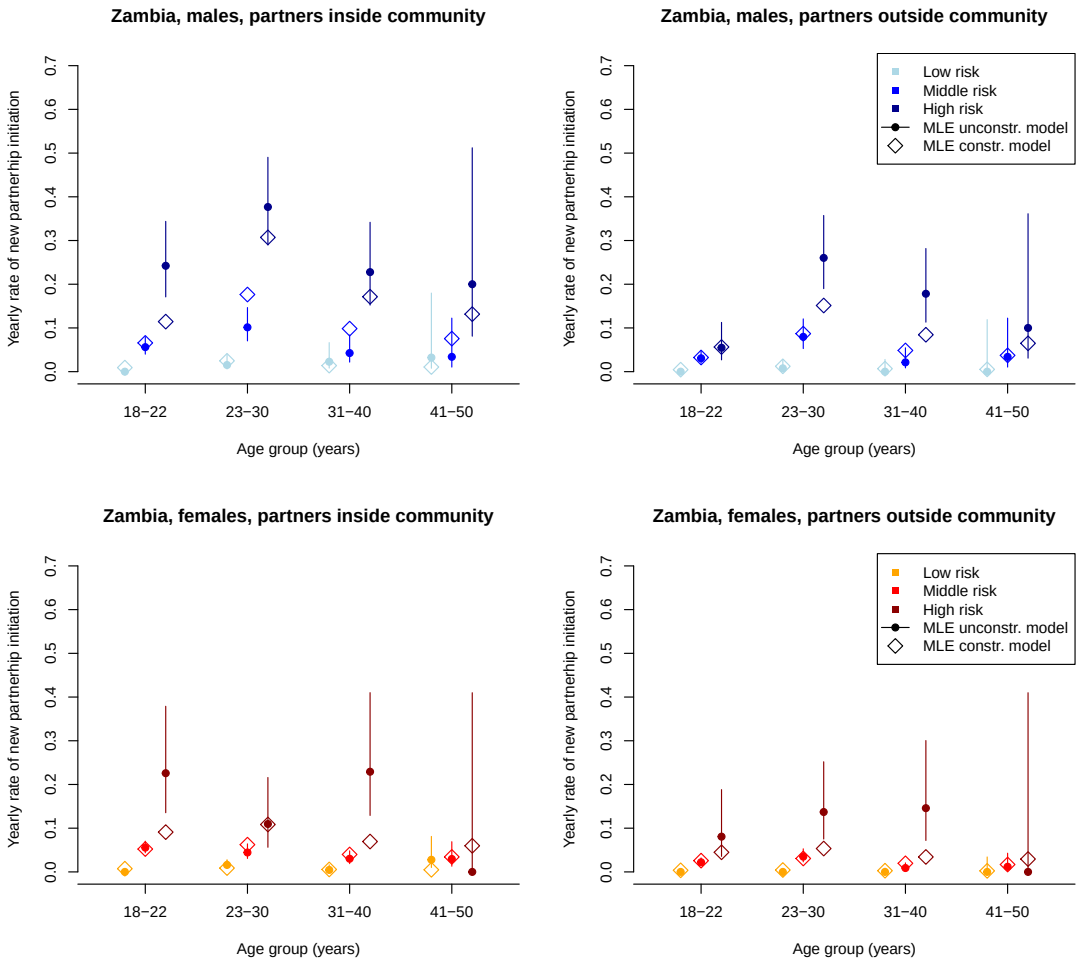

Figure 3.3: Rate of partnership formation inside (left) and outside (right) the community, by age, activity class and gender for Zambia. Age groups not shown had too few observations to provide a reliable estimate. The diamonds correspond to the maximum likelihood estimates of the rates in our model, where the effects of age, activity class and location (inside/outside) are modelled using multiplying effects on the partnership formation rate (see text for details). The dots and confidence intervals correspond to the likelihood for the unconstrained model where rates of partnership formation inside / outside the community and in each gender / age / activity class are estimated completely independently.

individual surveyed in PC0.

3.2.5 Risk Assortativity

The assortativity parameter χ is varied in the calibration process.

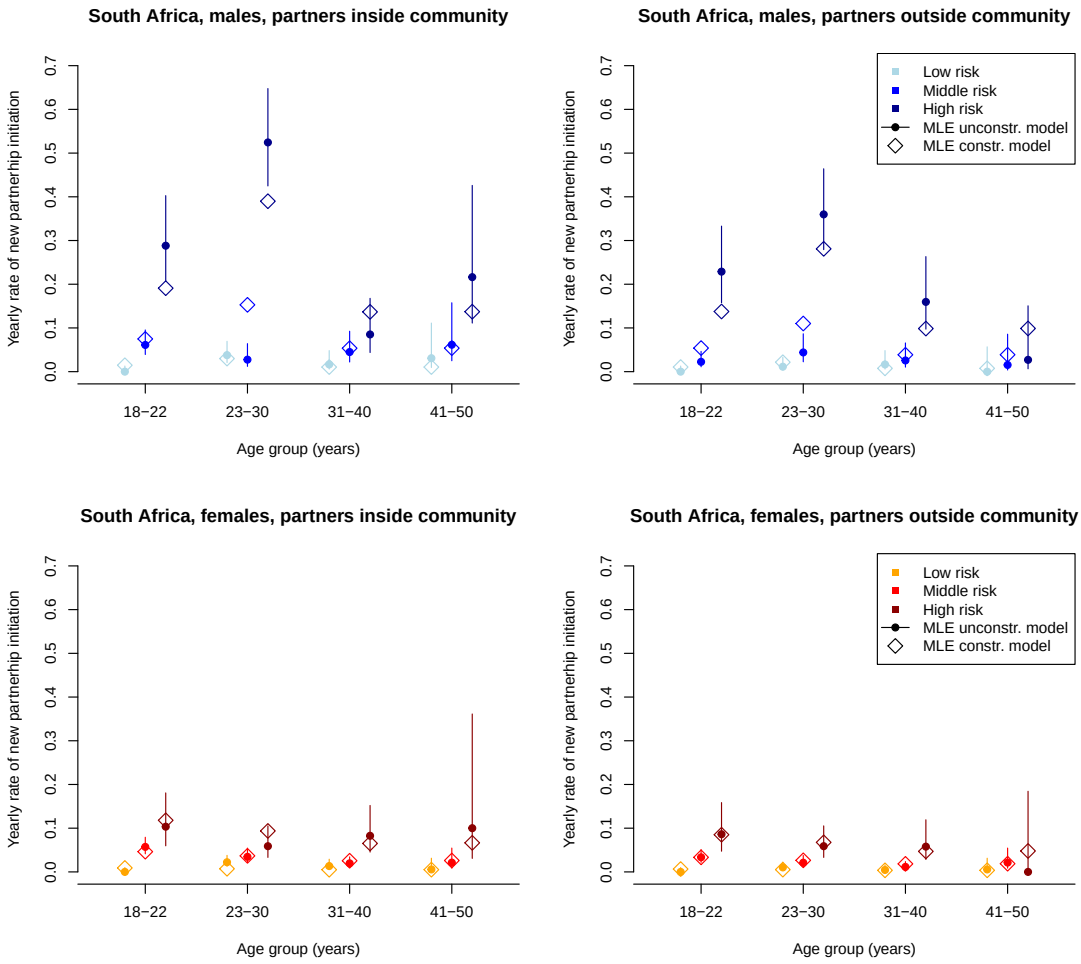

Figure 3.4: Rate of partnership formation inside (left) and outside (right) the community, by age, activity class and gender for South Africa. Age groups not shown had too few observations to provide a reliable estimate. The diamonds correspond to the maximum likelihood estimates of the rates in our model, where the effects of age, activity class and location (inside/outside) are modelled using multiplying effects on the partnership formation rate (see text for details). The dots and confidence intervals correspond to the likelihood for the unconstrained model where rates of partnership formation inside / outside the community and in each gender / age / activity class are estimated completely independently.

3.2.6 Condom use and frequency of sex acts

Surveyed individuals were asked to report the frequency of sex acts with their last up to 3 partners in the last year, and to report whether they were using condoms all the time, sometimes or never with each of these partners. Following exploratory analyses which

	13-17	18-22	23-30	31-40	41-50	51-60	61+
13-17							
18-22	0.41	0.56	0.04	0.00	0.00	0.00	0.00
23-30	0.07	0.59	0.33	0.01	0.00	0.00	0.00
31-40	0.01	0.07	0.56	0.34	0.02	0.00	0.00
41-50	0.00	0.02	0.09	0.64	0.23	0.02	0.00
51-60	0.00	0.00	0.02	0.09	0.64	0.23	0.02
61+	0.00	0.00	0.00	0.02	0.09	0.64	0.25

Table 3.3: Age mixing matrix for men in Zambia. Each row i shows $p^m_{age}[i,.]$, that is, for a surveyed man in age group i, the age distribution of the reported partners. Empty lines correspond to age groups with no data.

	13-17	18-22	23-30	31-40	41-50	51-60	61+
13-17							
18-22	0.01	0.14	0.72	0.09	0.03	0.00	0.00
23-30	0.01	0.01	0.35	0.50	0.13	0.00	0.00
31-40	0.00	0.00	0.02	0.39	0.53	0.05	0.01
41-50	0.01	0.01	0.01	0.02	0.60	0.31	0.04
51-60	0.00	0.01	0.01	0.01	0.02	0.60	0.35
61+	0.00	0.00	0.01	0.01	0.01	0.02	0.95

Table 3.4: Age mixing matrix for women in Zambia. Each row i shows $p^f_{age}[i,.]$, that is, for a surveyed woman in age group i, the age distribution of the reported partners. Empty lines correspond to age groups with no data.

suggested that sexual behaviours might be different with partners inside and outside the community, we used these data to compare condom use and frequency of sex acts in partnerships with partners inside versus outside the community.

For those reporting more than 3 partners in the last year, we inferred the location of (inside/outside the community) and condom use with the extra (>3) partners in the last year in a deterministic manner based on the last 3 partners. We considered condom use as consistent if individuals responded "always" to the question on condom use, and to be inconsistent if they reported "sometimes" or "never" using condoms with a partner.

We compared the proportion of partnerships in which condom use was reportedly used consistently among partners inside the community and partners outside the community, and found that reported condom use was higher with partners outside the community than inside. We therefore assumed that the risk or HIV transmission would be lower in serodiscordant partnerships between than within communities, with an estimated relative hazard of transmission for between versus within community partnership due to condom use of 0.73.

We also compare the frequency of sex acts reported for partners outside versus inside the community, this time only considering the last up to three partners, as it would

	13-17	18-22	23-30	31-40	41-50	51-60	61+
13-17							
18-22	0.23	0.73	0.05	0.00	0.00	0.00	0.00
23-30	0.03	0.46	0.45	0.06	0.00	0.00	0.00
31-40	0.01	0.06	0.51	0.36	0.07	0.00	0.01
41-50	0.02	0.02	0.10	0.52	0.32	0.03	0.00
51-60	0.00	0.02	0.02	0.10	0.52	0.32	0.03
61+	0.00	0.00	0.02	0.02	0.10	0.52	0.35

Table 3.5: Age mixing matrix for men in South Africa. Each row i shows $p^m_{age}[i, .]$, that is, for a surveyed man in age group i, the age distribution of the reported partners. Empty lines correspond to age groups with no data.

	13-17	18-22	23-30	31-40	41-50	51-60	61+
13-17							
18-22	0.01	0.28	0.63	0.06	0.02	0.00	0.00
23-30	0.01	0.02	0.48	0.37	0.12	0.01	0.00
31-40	0.00	0.01	0.05	0.43	0.47	0.04	0.00
41-50	0.02	0.00	0.02	0.10	0.68	0.15	0.04
51-60	0.00	0.02	0.00	0.02	0.10	0.68	0.19
61+	0.00	0.00	0.02	0.00	0.02	0.10	0.87

Table 3.6: Age mixing matrix for women in South Africa. Each row i shows $p^f_{age}[i, .]$, that is, for a surveyed woman in age group i, the age distribution of the reported partners. Empty lines correspond to age groups with no data.

be difficult to accurately infer a continuous variable from only three observations. We found that reported frequency of sex act was lower with partners outside the community than inside. We therefore assumed that the risk of HIV transmission would be further decreased in serodiscordant partnerships between compared to within communities, with an estimated relative hazard of transmission for between versus within community partnership due to frequency of sex acts of 0.602.

Overall, we therefore assumed that the risk of HIV transmission within a serodiscordant partnership with partners from different communities was 0.44 that in a serodiscordant partnerships with partners from the same community.

3.2.7 Partnership duration

Estimating the distribution of partnership duration from PC0 data is complex because of two main issues. First, there is right censoring, i.e. we observe partnerships which may be ongoing and we don't know when in the future they might end. Second, there is selection bias through which longer partnerships are more likely to be observed, precisely because they are longer.

These issues have been described elsewhere, for instance in [7], but to our knowledge no method has been proposed to estimate partnership duration from cross sectional data which would account for these issues.

Here, we propose a simulation-based approach, in which we simulate the longitudinal process of partnerships formation and dissolving as well as the cross sectional survey process, and compare the simulated survey data to the observed data. We assume that duration of partnerships are exponentially distributed.

Simulation process

We design a simulation study, completely independent from the individual based model. In this study, we simulate the formation and dissolution of partnerships, without keeping track of specific individuals involved in these partnerships. We simulate partnerships forming according to a Poisson process with constant rate c during a time interval $[t-\tau; t]$ (with time measured in years). Here c denotes the rate of partnership formation at the population level, not the individual level (since here we don't model specific individuals). Each formed partnership has a random duration, drawn from an exponential distribution with mean μ. We assume that a survey is conducted at time t, collecting data about all partnerships which were still "active" in the last year, i.e. which started before t and ended after $t - \tau$. For each of these partnerships, we record the time elapsed from partnership formation to t, the time for the survey. This forms a sample from the simulated distribution of partnership duration "so far" (i.e. up to the survey time), which closely mirrors the data collected in the extended PC0 survey on sexual behaviours.

Comparison with data

We propose to compare this simulated distribution to the observed distribution of partnership duration "so far" in PC0 using the Jensen Shannon divergence as a measure of dissimilarity between the two distributions. We use an optimization algorithm to find the set of values of μ and τ which minimise this divergence, for a fixed value of c.

Validating the method

To validate the method, we assessed its ability to accurately recover parameters μ and τ from data obtained through the simulation process described above. For the simulation, we used a partnership formation rate of $c = 2000$ (meaning that in the overall population on average 2000 partnerships are formed per year), a mean duration of partnership $\mu =$ 1, 5 or 10 years and a time interval of length $\tau = 10$ years (three simulated datasets). Because c was not estimated in the estimation method, but fixed, as a sensitivity analysis we assessed the method's ability to reestimate μ and τ when c was fixed to its 'true' value (i.e. that used for simulation), and when it was fixed to half or twice its true value (sensitivity analysis only performed on one of the three simulated datasets). Results are shown in Table 3.7 and suggest that this method is able to accurately re-estimate parameters.

c (simulated)	μ (simulated)	τ (simulated)	c fixed	μ (estimated)	τ (estimated)
2000.00	5.00	10.00	2000.00	4.80	10.25
2000.00	1.00	10.00	2000.00	1.01	9.59
2000.00	10.00	10.00	2000.00	9.65	10.17
2000.00	10.00	10.00	1000.00	9.88	10.27
2000.00	10.00	10.00	4000.00	9.65	10.17

Table 3.7: Results of the validation study for estimating mean duration of partnerships. Each line corresponds to one simulation and one set of estimates for that simulation. The first three columns show the parameter values used in the simulation. The fourth column shows the values of parameter c used in the estimation procedure (c was usually fixed to the value used for simulation but in the last two lines we show example where we c was fixed to a value different to that used in the simulation. The last two columns show the estimated values of parameters μ and τ, to be compared with the values used in simulation, shown in the second and third columns.

Estimated duration of partnerships based on PC0 data

We applied this method to estimate the average partnership duration from PC0 data. There are two additional complications with these data. First, individuals only report details of partnerships with their up to last three partners, not more. Second, it is unclear whether these partnerships are still ongoing or not at the time of the survey. Here, we only consider the details reported on the last partner. We consider the reported time between first and last sex with the last partner as the observed duration of partnership so far. We then estimate the mean duration of partnership μ as well as the parameter τ, with c fixed to 2000. We perform the analysis for the two countries together, but stratified by activity class. The estimated mean duration of partnership is 11.9, 6 and 3.5 for the low, medium and high activity classes respectively. Figure 3.5 shows the observed data along with data simulated using these estimates and indicate a good fit of the model to the data, supporting the assumption of an exponentially distributed duration of partnership.

We further observed that the reported time since first sex act was shorter with partners outside (3.18 years) than inside (6.94 years) the community, which suggests that partnerships are much shorter when between compared to within a patch. To account for this effect, we adjusted the above estimates so that partnerships between patches are twice shorter on average than those within a patch.

Where we had previously found a mean partnership duration of x, we assumed instead that it is $3x/5$ in between-patch partnerships and $6x/5$ in within patch partnerships. Indeed, assume we had estimated an overall duration of partnership of x. Now we want this to become x_{in} and x_{out}. Accounting for how many there are of each type (roughly 2/3-1/3 for Zambia), $x = (2/3 * x_{in} + 1/3 * x_{out})$ and $x_{in} = 2x_{out}$. So $x = 5x_{out}/3$ and so $x_{out} = 3x/5$ and $x_{in} = 6x/5$.

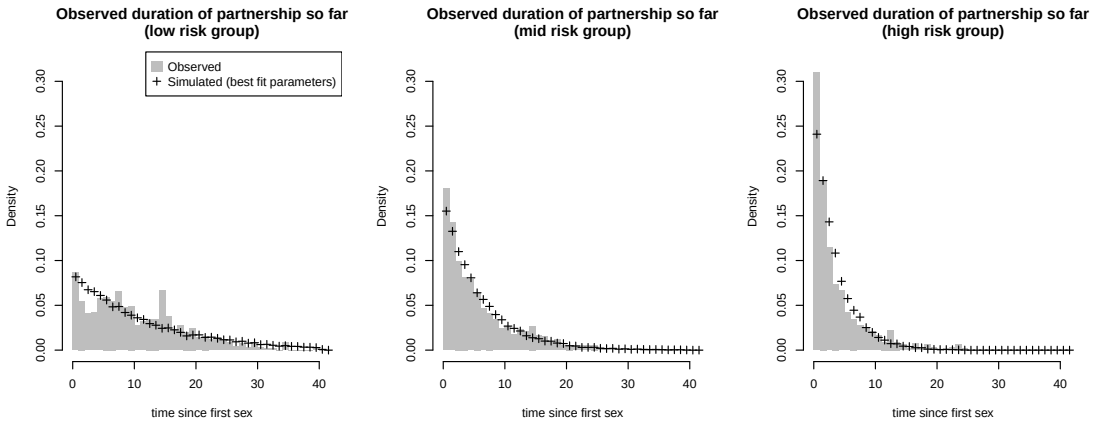

Figure 3.5: Observed and simulated duration of partnerships so far, by activity class.

3.3 Allowing flexibility around reported behaviours

To allow some flexibility around parameters estimated directly from reported data on sexual behaviours we used two 'multiplier' parameters; one for the rate of partnership formation, and one for the mean duration of partnerships. These two parameters are varied in the calibration process.

3.4 Checking partnership formation and dissolution

To check for bugs in the partnership formation and dissolution, we performed a series of checks which are described in this section.

3.4.1 Lists of individuals available for partnership formation

Each individual has a fixed maximum number of partners which they can't exceed at any point in time. If they have not reached this maximum, they are available for partnership formation and appear in a list of available partners (stratified by patch, gender, age and activity class), as many times as appropriate, e.g. once if they have reached their maximum number of partners minus one. The list is initialised at the start of the simulation with all individuals (as there are no partnerships initially), and then updated every time someone enters or leaves the population, and every time a partnership is formed or dissolved. To check this updating is done correctly, we perform the following check. Each year, we sweep through all individuals in the population and count their partners and check their maximum number of partners. Based on this information, we check that each individual appears in the list of available partners as appropriate. This is done in function `sweep_through_all_and_check_lists_serodiscordant_and_available_partners` in debug.c.

3.4.2 Number of partners outside the community

For each individual we record the number of partners outside the community at any time point. This is updated every time a partnership is made or broken as appropriate. To check this updating is done correctly, we perform the following check. Each year, we sweep through all individuals in the population and loop through their partners and count how many are outside the community. We then check that this is consistent with the recorded number of partners outside the community for that individual. This is done in function `sweep_through_all_and_check_n_partners_outside_n_HIVpos_partners_and_n_HIVpos_partners_out` in debug.c.

3.4.3 Rates of partnership formation

- **Partnership formation by activity class.** Output, each year, the average number of new partners made by individuals in that year, disaggregated by activity class. Check that this is consistent with the relative rates of partnership formation in each activity class (given by `relative_number_partnerships_per_risk`). Note this average number of new partners needs some time to reach equilibrium, and then equilibrium is affected by HIV, so checking is done between reaching equilibrium and HIV starting. Also note that because of balancing issues we may not expect exactly the same results. This is done in output.c function `store_annual_partnerships_outputs`.

- **Partnership formation by age group.** Output, each year, the average number of new partners in the last year made by individuals in the low activity class, stratified by gender and age, and check this is consistent with the parameters `c_multiplier` $\times$ `c_f` $\times$ (1+`rel_rate_partnership_formation_between_patches`) and `c_multiplier` $\times$ `c_m` $\times$ (1+`rel_rate_partnership_formation_between_patches`) . Note this may not be exactly the same as the input because of balancing issues, in particular we may expect the observed rates to be higher than the input in females, and lower than the inputs in males because of the balancing. This is done in output.c function `store_annual_partnerships_outputs`.

- **Partnership formation with partners inside vs outside the community.** Output, each year, the average number of new partners in the last year made by individuals in the low activity class, with partners in a different community, stratified by gender and age, and check this is consistent with the parameters `c_multiplier` $\times$ `c_f` $\times$ `rel_rate_partnership_formation_between_patches` and `c_multiplier` $\times$ `c_m` $\times$ `rel_rate_partnership_formation_between_patches` . Note this may not be exactly the same as the input because of balancing issues, in particular we may expect the observed rates to be higher than the input in females, and lower than the inputs in males because of the balancing. This is done in output.c function `store_annual_partnerships_outputs`.

3.4.4 Assortativity of partnerships

- **Assortativity by age (at partnership formation)** Every year, we output the age of all newly formed partnerships, building an age assortativity matrix which we can then compare to the PC0 data. Again note there may be some differences because of balancing. This is outputted in a file called `Age_assortativity_at_partnership_formation_`
  Note this includes all partnerships between and within patches without distinction between the two, since the age assortativity matrices used are independent of partners location

- **Assortativity by age (partners at a given time point)** Every year, we sweep through all alive individuals and check their age group and the age group of their partners, and compare with PC0. This is done in function sweep_through_all_and_check_age_of_p
  in debug.c

- **Assortativity by risk (at partnership formation)** Every year, we output the activity class of all newly formed partnerships, building a risk assortativity matrix which we can then compare to the input assortativity parameter. Again note there may be some differences because of balancing. This is outputted in a file called `Risk\_assortativity\_at\_partnership\_formation\_run\_i.csv`. Note this includes all partnerships between and within patches without distinction between the two, since the risk assortativity used is independent on partners location

- **Assortativity by risk (partners at a given time point)** Every year, we sweep through all alive individuals and check their activity class and the activity class of their partners. This is done in function sweep_through_all_and_check_age_of_partners
  in debug.c

Validity of assortativity by age is checked visually by comparing the input age mixing matrices with the age mixing matrix obtained in the IBM at partnership formation, and cross-sectionally as described above. Validity of assortativity by risk is checked visually by comparing the input assortativity parameter with the risk mixing matrix obtained in the IBM at partnership formation, and cross-sectionally as described above.

3.4.5 Partnership duration by activity class and within vs between communities, as drawn at partnership formation.

We output all duration of partnerships (as drawn at partnership formation so ignoring premature dissolution due to death) between two high-high, individuals in the same community (community 0), or in different communities (communities 0 and 1). We check that the distribution of the duration is what it should be, i.e., for high risk-high risk partnerships, Gamma distributed with scale `breakup_scale_lambda_high_within_patch` × `breakup_scale_multiplier_overall` and shape `breakup_shape_k_high` (within community partnerships) and scale `breakup_scale_multiplier_between_vs_within_patch` × `breakup_scale_lambda_high_within_patch` × `breakup_scale_multiplier_overall`

and shape `breakup_shape_k_high` (between community partnerships). We do the same for med-med and low-low partnerships. We output the observed versus expected distributions in the main knitr document summarising the outputs of the IBM.

Chapter 4

HIV and ART

In this section we describe the HIV component of the PopART IBM, which we take to consist of HIV transmission, HIV progression, emergency ART (individuals starting ART at low CD4 due to symptoms - in other words initiation of ART outside the normal HIV testing route), and AIDS-related death. AIDS-related death and emergency ART are included in this component as they are in a sense 'HIV progression' events (and furthermore competing events), albeit progressing either to initiating ART or death. We also describe HIV-testing and ART-related events, including initiating ART and loss-to-follow-up.

Individuals have several characteristics related to HIV and the ART cascade. These are HIV status (negative, early infection, chronic infection), CD4 category (CD4 $>$ 500, 350-500, 200-350 or $\leq$ 200 cells/mm^3), ART status if HIV-positive (not aware of status, aware of status but not yet on ART, early ART (started ART recently), on ART and virally suppressed, on ART but not virally suppressed, dropped out prior to starting ART, and dropped out when previously on ART) and set-point viral load (the viral load of the individual during the period 6-24 months post infection). These characteristics get updated over time and can mutually interact - for example CD4 and set-point viral load influence infectivity.

4.1 Seeding HIV

At a given time (`start_time_hiv`) HIV is introduced for the first time. This is a parameter sampled uniformly from 1970-1980 for communities in Zambia and from 1976-1986 for communities in South Africa. Over the next 5 years, at the start of each year, a percentage of the population is seeded to be HIV-positive, with a higher percentage amongst individuals in higher sexual risk groups. The percentage seeded is governed by a multiplicative parameter ranging from 1-100, sampled on a log scale, between runs, to try to ensure that epidemics can be in different phases and have different values of R_0.

4.2 HIV transmission

HIV transmission occurs between individuals who are in a sexual partnership in the IBM, and where one partner is HIV+. At each timestep any HIV-negative individual who has at least one HIV-positive partner is at risk of HIV infection. The model keeps track of every individual who has at least one serodiscordant partner at the time. The list is updated as serodiscordant partnerships are created or break up, when either individual in the partnership dies, or when one partner in a previously concordant seronegative partnership gets infected.

The hazard of infection of an HIV-negative partner in a serodiscordant partnership depends on the following behavioural and biological factors:

- gender of the HIV-negative partner;
- set point viral load and stage of HIV infection of the HIV-positive partner (either early HIV infection or CD4 stage if the infection is chronic);
- whether the partner is on ART;
- the circumcision status of the HIV-negative individual if male (reduced susceptibility, depending on type of circumcision - i.e. medical or traditional);
- the type of partnership (inside/between patches), as in PC0 individuals who reported having a partner outside the community reported lower coital frequency and higher condom use than those inside.

Each of these factors acts via a multiplicative cofactor on a baseline hazard, with all factors multiplying together. Individuals with more than one HIV-positive partner are exposed to a total hazard that is the sum of the hazards from each partner.

4.2.1 Immediately post-infection

Once an individual becomes HIV infected, the following events happen to them:

- They enter the early (acute) phase of HIV infection, and are scheduled to end early infection 1-3 months later. The time of the end of early infection is drawn uniformly between that range, separately for each individual.
- They are assigned a set-point viral load.
- Based on their set-point viral load, they are assigned a CD4 category (> 500, 350-500, 200-350 or ≤ 200) which they will enter once they reach chronic (non-early) infection. The category is drawn randomly for each individual, with the probability of being in a given CD4 category is based on an analysis in Cori et al.[12] of data from the ATHENA cohort in the Netherlands.

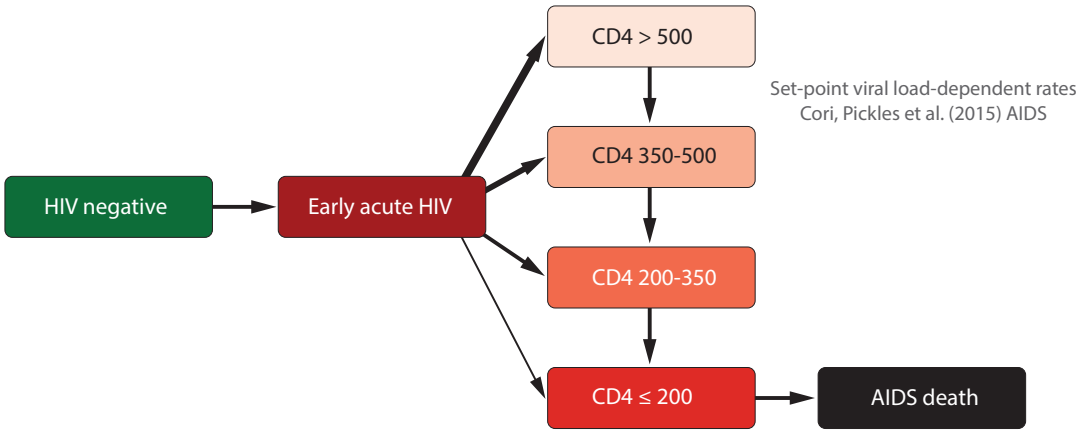

Figure 4.1: Schematic of HIV progression in the model.

- Note that seeded infections (those introduced at the start of the epidemic) are assumed to not enter early infection but to start in a random CD4 category with the same probability distribution as an individual leaving early infection, with duration chosen as for that given CD4 stage.
- Their seronegative partners are added to the list of serodiscordant partnerships (as they are now in serodiscordant partnerships with those people), while the list of serodiscordant partnerships is updated to remove the newly infected individual's partnerships that have become seroconcordant positive.
- We increment the counter of new HIV infections in the population, to count total population incidence.

4.3 HIV progression in the absence of ART

Once an individual leaves early infection, they enter a CD4 category ($>$ 500, 350-500, 200-350 or $\leq$ 200) drawn at random as described above (see Figure 4.1). They will then progress sequentially to lower CD4 categories until they reach CD4$\leq$ 200. After that compartment the next stage is AIDS-related death; individuals are assumed to only die from AIDS-related illness in the model once their CD4 is below 200cells/mm^3.

Each individual in the model, upon entering a given CD4 category is assigned a time at which they will progress to the next CD4 category (or death if CD4 is below 200cells/mm^3) if they do not start antiretroviral therapy (or die from non-AIDS causes) beforehand. This time is drawn from an exponential distribution with mean time based on the analysis in Cori et al. [12], which analysed the rate of CD4 progression of the ATHENA cohort of HIV-positive individuals in the Netherlands, by set point viral load. Individuals with higher set-point viral load progress more quickly on average. Compared to the mean time an individual with $\log_{10}$ SPVL$\leq$4 would spend in a given compart-

ment $t_{baseline}$, an individual with $\log_{10}$ SPVL>4 would spend a shorter time on average $t_{baseline}/\text{SPVLfactor}_{CD4}^{(\log_{10} SPVL-4.0)}$, where the SPVLfactor_{CD4} is a factor varying by CD4 category.

4.3.1 Emergency ART

Hallett et al. have hypothesized that individuals with low CD4 may start ART outside of the standard HIV testing care cascade, since data suggests that a large percentage of patients initiate treatment at late stages of infection [16]. In the PopART IBM there is a process which we term 'emergency ART' in the model, whereby individuals who have CD4 below 200 cells/mm^3 can quickly start ART without having had a prior HIV test once they have clinical symptoms. An individual who reaches the CD4< 200 category in the absence of ART will have had a time to AIDS-related death assigned to them. They will then have a second time drawn from the same distribution, the time to start emergency ART, in effect a competing hazard. At the population level an individual therefore has a 0.5 probability of starting emergency ART rather than dying, but individuals who have a longer time to AIDS-related death will be more likely to start emergency ART before dying.

4.3.2 Set-point viral load

Based on Fraser PNAS 2007 [14] we assume that the average annual hazard of transmitting HIV $\beta(v)$ of an individual with set-point viral load v (not logSPVL) is well described by the formula

$$\beta(v) = \frac{\beta_{max} * v^{\beta_k}}{(v^{\beta_k} + \beta_{50}^{\beta_k})}$$

where the parameters $\beta_k = 1.02$ and $\beta_{50} = 13,938$ copies per ml, and β_{max} is the average annual hazard of (uncircumcised) man getting HIV from a HIV+ partner who has maximal SPVL, which is a parameter varied in the calibration uniformly from 0.2 to 0.6 yr^{-1}. By way of comparison, in [14] a value of $\beta_{max} = 0.317$ yr^{-1} was found for Zambia.

As described in 4.3, in addition to modifying infectivity, SPVL also affects the rate of CD4 progression, and the initial CD4 category of a new infectee.

Initializing set-point viral load

Each individual, on seroconversion or when seeded HIV-positive, is assigned a set-point viral load, where $\log_{10}\text{SPVL} \sim N(4.74, 0.61)$, based on [6]. Future versions of the model will allow for inheritance of SPVL.

4.4 HIV testing

HIV testing is divided into two testing routes, similar to the division used in Cori PLOS One 2013 [11]: 'background' HIV testing, and 'PopART' HIV testing. The former rep-

resents the testing that takes place outside the trial: testing through clinics, as part of antenatal care, etc. The latter is the household-based CHiPs testing in the trial. These two different testing routes are treated separately in the PopART IBM, and have different parameter values, reflecting that these are different processes and may have different outcomes: the home-based CHiPs testing will, by design, reach individuals who may have been less inclined to actively seek out healthcare; however CHiPs actively re-visit known HIV-positives which may facilitate individuals initiating ART.

In this section we focus on describing the 'background' HIV testing. The 'PopART' HIV testing is described in detail in chapter 6.

4.4.1 Background HIV testing scheduling

"Background" HIV testing means testing external to the trial. We assume that in fixed periods each person, apart from HIV-positives who already know their status, has a probability of having an HIV test. This probability differs by gender, being higher for women, and varies over time. The first period is 2000-2006, when HIV testing rates were low, after which yearly intervals are used.

Between 2000-2006, men have a probability of 0.075 and women 0.158 of receiving an HIV test, based on the 2007 Zambia DHS, excluding those who reported having an HIV test in the most recent year (2007). Since 2006 the probability of being tested within an annual period was calibrated to get similar knowledge of serostatus to that given by CHiPs data on knowledge of serostatus just prior to visit (see report 4 Figure 2 on calibration of model runs to communities), using a baseline probability that assumes that everyone who reported testing in the most recent survey tested once, and a multiplier $m^{backgroundtest}$ to scale up this probability.

4.4.2 CHiPs HIV testing scheduling

CHiPs trial data includes the proportion of people enumerated by age and gender who are successfully visited by CHiPs (a successful visit meaning that they either accept an HIV test and receive the result, self-report that they are HIV-positive or refuse a test because they report having had an HIV-negative test in the past 3 months). This data is used, on a community-by-community basis, to give the proportion of individuals by age and gender visited each timestep, and converted in the model into a number of individuals who are to be visited that timestep.

At the beginning of the round, the population is divided up by age, gender. The total number of people in each group $n_{g,a}$ scheduled to be visited throughout that round is calculated based on the data, and the model draws $n_{g,a}$ individuals and puts them into a shuffled list, which is then split up so that the correct number of people at each timestep for that age and gender group are visited.

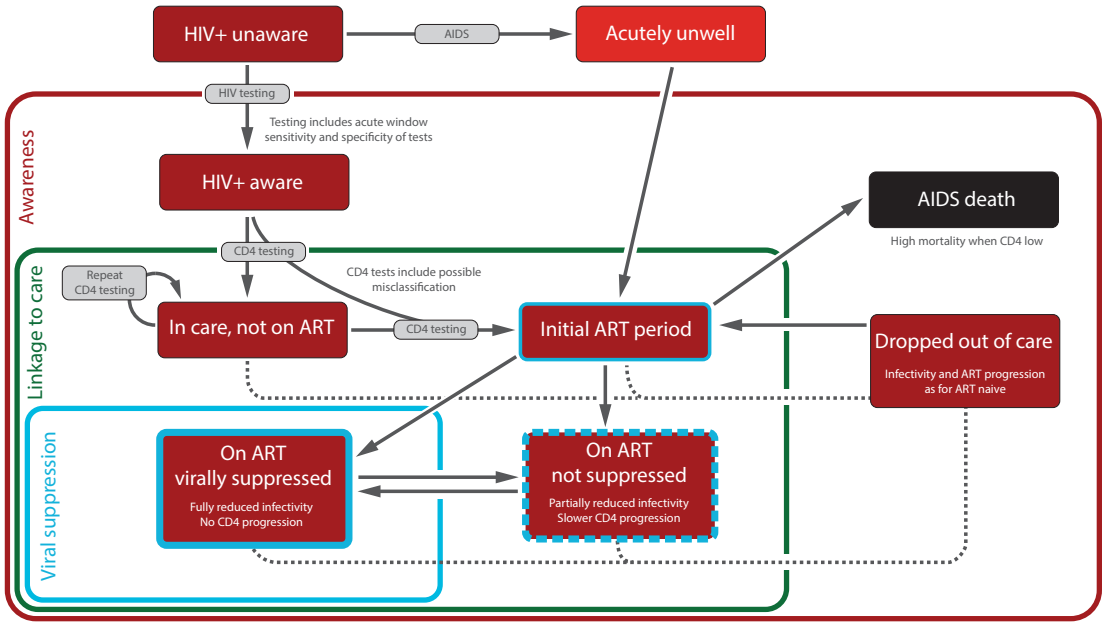

Figure 4.2: Schematic of the HIV care cascade in the model.

4.4.3 An individual's HIV test process

Upon having an HIV test, whether through CHiPs or background testing, an individual may receive a positive or negative test result. This test is assumed to be 100% sensitive and specific, except during a window period in early infection when the necessary antibodies/antigens may not yet be present for detection. Individuals who receive a negative HIV test can have new future HIV tests scheduled either by CHiPs testing (if in arms A or B) or by background testing (and HIV-negative men may then undergo voluntary male medical circumcision, as described later).

HIV test window period Individuals who test during very early infection may not get a positive test result [9], a 'window period' which has reduced over time as improved HIV tests have been adopted within country. Within the PopART IBM, the window period for the test is taken to be 60 days until 2006, roughly the window period for first or second-generation HIV antibody tests, and 30 days from then onwards, with the latter corresponding to the window period of more recent antigen/antibody tests.

4.5 The care cascade

Figure 4.2 presents a schematic overview of the HIV care cascade as it is represented in the model.

Report 4 Figures 21 and 22 show respectively the distribution of HIV-positive individuals over time and the transitions that they undergo.

Dropping out of the care cascade Individuals who receive a positive test may at that point drop out of the care cascade. In background testing, in order to remain in care, an individual must first collect their HIV test results, and then have a CD4 test and collect those results. Data from the Zambia 2013 DHS survey shows that about 3% of respondents had ever had an HIV test but did not collect their test results, so the probability of collecting HIV test results is set to 0.97. A systematic review by Mugglin et al. in sub-Saharan Africa found that CD4 cell count was measured in 77.6% of patients, and in the PopART IBM the probability of an individual receiving their CD4 test results $p^{cd4}_{background}$ is informed by this. In CHiPs testing, CHiPs data from the trial provides information on the average time taken to initiate ART after a CHiPs visit, and in the PopART IBM an HIV positive individual visited successfully by CHiPs (subject to the HIV test window period) has a time to start ART drawn from a biexponential distribution parameterised from the data as described above. This time may be after their CHiPs visit in the following round, and if that occurs, then during the following round the time to start ART is redrawn, effectively meaning that the individual "dropped out" during the earlier round, only to be able to relink in the following round.

ART eligibility Over time the eligibility criteria for initiating ART have changed over time. Within the PopART IBM, the CD4 categories used reflect the different CD4 thresholds that have been in place at different periods, and the rules for initiating ART mirror the changes in national guidelines, apart from in arm A communities where since the beginning of the trial ART has been available regardless of CD4 count: ART becomes available to HIV-positive individuals with CD4<200 cells/mm^3 in 2004, with eligibility changing to <350 in 2011, and <500 in 2014.5. Clinics in Zambia have transitioned to ART regardless of CD4 count during April-May 2016, and within the IBM, in arm B and C communities, this changes in 2016.33. In arm A communities in the PopART IBM it is assumed that ART has been available regardless of CD4 count since the beginning of the trial - taken to coincide with the start of CHiPs visits in the community.

Remaining in the cascade but ineligible for ART Prior to the trial, and in arms B and C during the trial until the adoption of universal ART guidelines, in the model an individual whose CD4 category was above the guidelines were ineligible for ART. They would then have their CD4 retested periodically (at an approximately yearly schedule) until either they were eligible or they dropped out of care. In background testing the probability of remaining in care after another ineligible CD4 test result is assumed to be $p^{cd4}_{background}$, while in PopART arm B communities it is assumed to be 1 due to the more active linkage to care facilitated by CHiPs.

Initiating ART Individuals who are eligible to start ART, and are in care, are scheduled to start ART shortly afterwards. For background testing this time is exponentially distributed with mean $t^{ART}_{background}$ years, while for PopART it is drawn from a biphasic exponential that depends on the CHiPs round.

Upon starting ART, an individual firstly enters a state of 'early ART' during which they are not yet virally suppressed, lasting 2 months. During this time they have a reduced infectivity $RR^{\text{early ART}}$. Individuals may subsequently end up in one of three states: they may remain adherent and on ART and become virally suppressed; they may remain on ART but with poor adherence and be virally unsuppressed; or they may die, due to complications from immune reconstitution inflammatory syndrome, which is assumed in the model to occur only in individuals with CD4$\leq$ 200 (with probability $p_{die}^{\text{early ART}}$). We assume that, of those who do not die during early ART, a proportion $p^{\text{become VS}}$ of individuals become virally suppressed afterwards. This parameter governs outputs on viral suppression in the model.

Becoming virally suppressed An individual who is virally suppressed is assumed to keep their CD4 at the time of initiating ART without progressing any further or increasing their CD4 through the benefits of ART, provided they remain on ART and virally suppressed. They are also assumed to have very reduced transmissibility of HIV. However over time they may become virally unsuppressed, or drop out of ART.

Data from a Zambian cohort in Lusaka [23] shows that over about 8 years roughly 30% of those successfully initiated on ART have dropped out, while around 13% have poor adherence. In the PopART IBM, on becoming virally suppressed an individual has a next event drawn. The possible next events are: remain virally suppressed for life with probability $p^{remainVS}$; become virally unsuppressed in the future (with probability $p^{VSbecomeVU}$); or drop out from care (with probability $p^{VSdropout}$). If either of the latter, a time to that event happening is drawn uniformly from 0.01-6 years, roughly corresponding to the timescale observed in [23].

Becoming virally unsuppressed An individual who is virally unsuppressed is assumed to undergo CD4 progression but at a rate reduced by a factor $f^{VUprogression}$ than someone not on ART, an assumption also previously made in [11]. They also have reduced infectivity compared to someone not on ART. The reduction in infectivity is by half. Individuals who are virally unsuppressed are assumed to eventually drop out, ceasing ART, as they are already poor adherers, at a time drawn uniformly from 0.01-6 years, the same timescale as for virally suppressed individuals who drop out.

Dropping out Individuals who have dropped out can re-enter care in one of two ways. In PopART they may receive a CHiPs visit (or if they dropped out in a previous round, they may successfully link in the current round). Outside of PopART they may start emergency ART when their CD4 is low, as described in 4.3.1.

Chapter 5

Circumcision

5.1 Types of circumcision

In the PopART IBM we assume that there are two types of circumcision: traditional circumcision and voluntary male medical circumcision (VMMC). Traditional circumcision is assumed to occur in individuals prior to entry to the IBM adult population, while VMMC can occur after a man receives an HIV-negative test. VMMC is assumed to reduce susceptibility to HIV in men by RR_{VMMC}, but not affect infectivity of an HIV-positive man. Traditional circumcision is assumed to be ineffective in reducing susceptibility ($\text{eff}^{TMC} = 0$), following an analysis of PC0 data [19]. It is assumed in the model that traditionally circumcised men will not receive VMMC in addition.

5.1.1 Traditional circumcision

From PC0 we use the proportion of men who report being circumcised by a traditional practitioner for the parameter p^{TMC}. Individuals receive traditional circumcision in the model prior to entering the adult population age 14. This is similar to what is found in PC0 in Zambia, where the mean age at circumcision of those who underwent traditional circumcision was 9 years.

5.1.2 VMMC

VMMC is assumed to occur only in adult men who have received an HIV-negative test (either through background testing or via CHiPs testing). After the test, the probability of receiving circumcision is $p_{circ}^{background}$ and p_{circ}^{CHiPs} respectively depending on whether the HIV test is a background test or CHiPs test. However since not every man tests in a given year the proportion of all men who receive VMMC will be smaller per year. Report 1 Figure 10 shows uptake of VMMC in PopART communities. If an individual in the model chooses to receive VMMC, a time for the VMMC is scheduled a time $t_{VMMC}^{background}$ in the future for individuals coming from background testing and a time t_{VMMC}^{CHiPs} for CHiPs testing.

Upon getting VMMC an individual initially undergoes a healing period of about 2 weeks, during which they have a modified risk of HIV acquisition, from both the increased susceptibility of the open wound and the reduced coital frequency, resulting in an overall $RR_{\text{circ unhealed}}$, as in [11]. After the end of the healing period they become circumcised with reduction in susceptibility to HIV of RR_{VMMC}.

Chapter 6

CHiPs data analysis

In this section we describe the analyses of the CHiPs data performed as a basis to parameterize the CHiPs intervention in the model. First, we describe the process of CHiPs enrolling individuals into the interventions and delivering HIV testing and counseling. Then, we describe the process of ART initiation for HIV positive individuals after they have been visited by CHiPs.

6.1 Uptake of universal testing

Several steps have to occur before an adult either receives an HIV test delivered by CHiPs or self reports HIV+ not in care or HIV- according to a test performed within the last 3 months; we grouped these steps as follows:

- Household steps (h):
  - Household visited by CHiPs
  - Household enumerated
- Individual steps (i):
  - Adult is contacted
  - Adult consents to participate
  - Adult accepts HIV testing by CHiPs or self reports being HIV+ not in care or HIV- according to a test performed within the last 3 months

In this chapter, we refer to a "successful CHiPs visit" when all of these steps have happened for an individual. We compute, for each time step t (designed so that there are 48 timesteps in a year), the proportion of individuals who get a successful CHiPs visit, by community (c), age (a), and gender (g), as $p_{c,a,g}(t) = p_c^{(h)} p_{c,a,g}^{(i)}(t)$, where $p_c^{(h)}$ is the proportion of households visited and enumerated in community c and $p_{c,a,g}^{(i)}$ is the proportion of individuals in community (c), age (a), and gender (g), among those enumerated, who have received a successful CHiPs visit during time step t.

We computed these for round 1, for round 2 and round 3 from anonymised data on the timing and outcome of CHiPs visits, stratified by community, age and gender (see Figures 6.1 and 6.2 for Zambia). For this analysis we used 1-year age groups. Note that for round 3 the dataset was from October 2017, so this did not correspond to a full round.

The schedule of CHiPs "successful visits" for rounds 1, round 2 and round 3 in the model is based on these data, but taken at the community level. Specifically, the proportion of individuals in the community who receive a CHiPs visit with an HIV test within a given time step is taken to match the observations, by gender and age. For the DSMB report in 2016 data in round 3 and round 4 were assumed to be equally spread, as no CHiPs data was available for round 3 and round 4 at this time (October 2016). For the coverage at the end of the round, a set of three assumptions were made for the DSMB report in 2016: pessimistic, central, and optimistic. Based on the observation that the average proportion of individuals successfully visited by CHiPs in a time step generally increased by about 25% between rounds 1 and 2, the scenarios assumed that in rounds 3 and round 4, this proportion is increased compared to round 1, by 25% (so similar to round 2) in the pessimistic scenario, by 50% in the central scenario, and by 75% in the optimistic scenario. We further assumed that rounds 3 and 4 will be shorter, with round 3 lasting one year, and round 4 a third of the year (until the end of 2018). Although for rounds 1 and 2, we used community-level data, rounds 3 and 4 scenarios were constructed based on national level data (i.e. pooled across all communities in a given country). Data were also smoothed across ages to define the rounds 3 and 4 scenarios. Figure 6.4 summarises the community-level coverage of the CHiPs successful visits by age and gender, in all four rounds. The green line and shaded area in Figure 6.4 show the CHiPs schedule under the three assumpiton sets, based on the analysis in 2016. The red points in Figure 6.4 illustrate the observed data for round 3 as available in October 2017. The central assumption set for round 4, yellow line in Figure 6.4, together with the observed round 3 data were used in the model analysis for the DSMB report in October 2017.

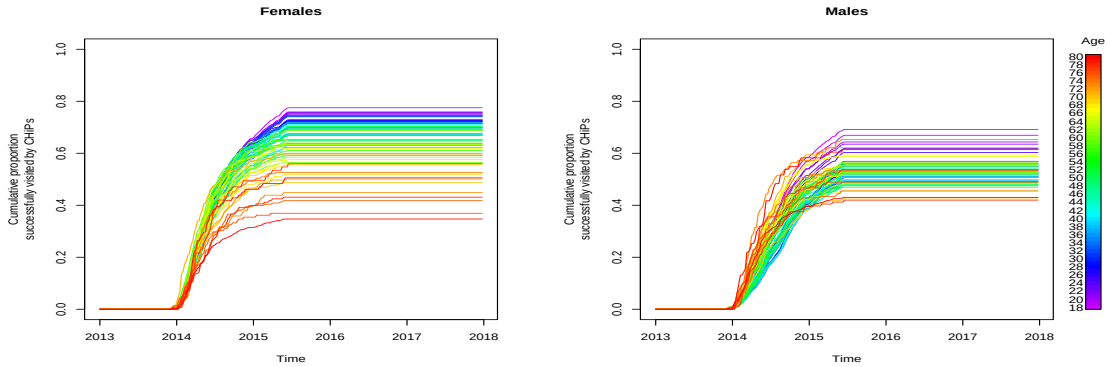

Figure 6.1: Cumulative proportion of females (left) and males (right) successfully visited by CHiPs in round 1, over time, in Zambia.

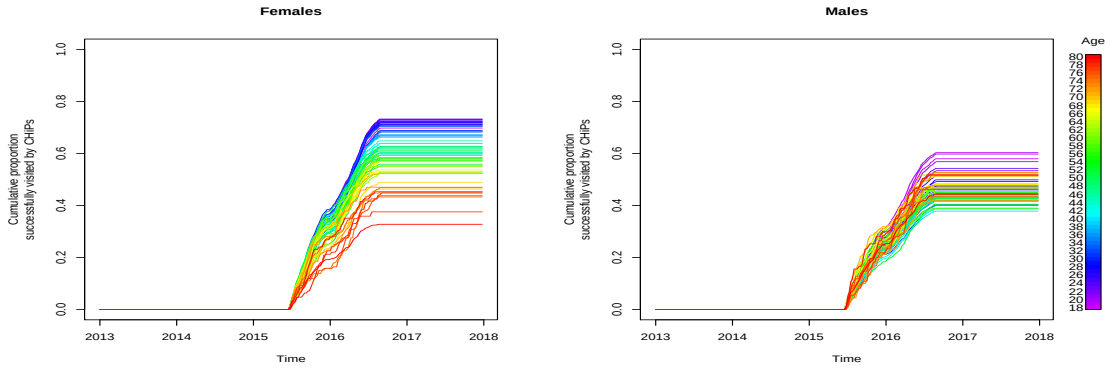

Figure 6.2: Cumulative proportion of females (left) and males (right) successfully visited by CHiPs in round 2, over time, in Zambia.

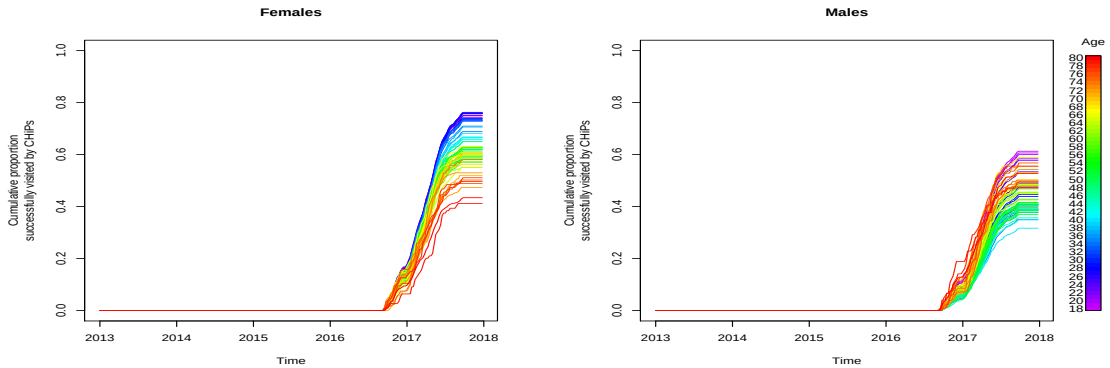

Figure 6.3: Cumulative proportion of females (left) and males (right) successfully visited by CHiPs in round 3, over time, in Zambia (data up to October 2017).

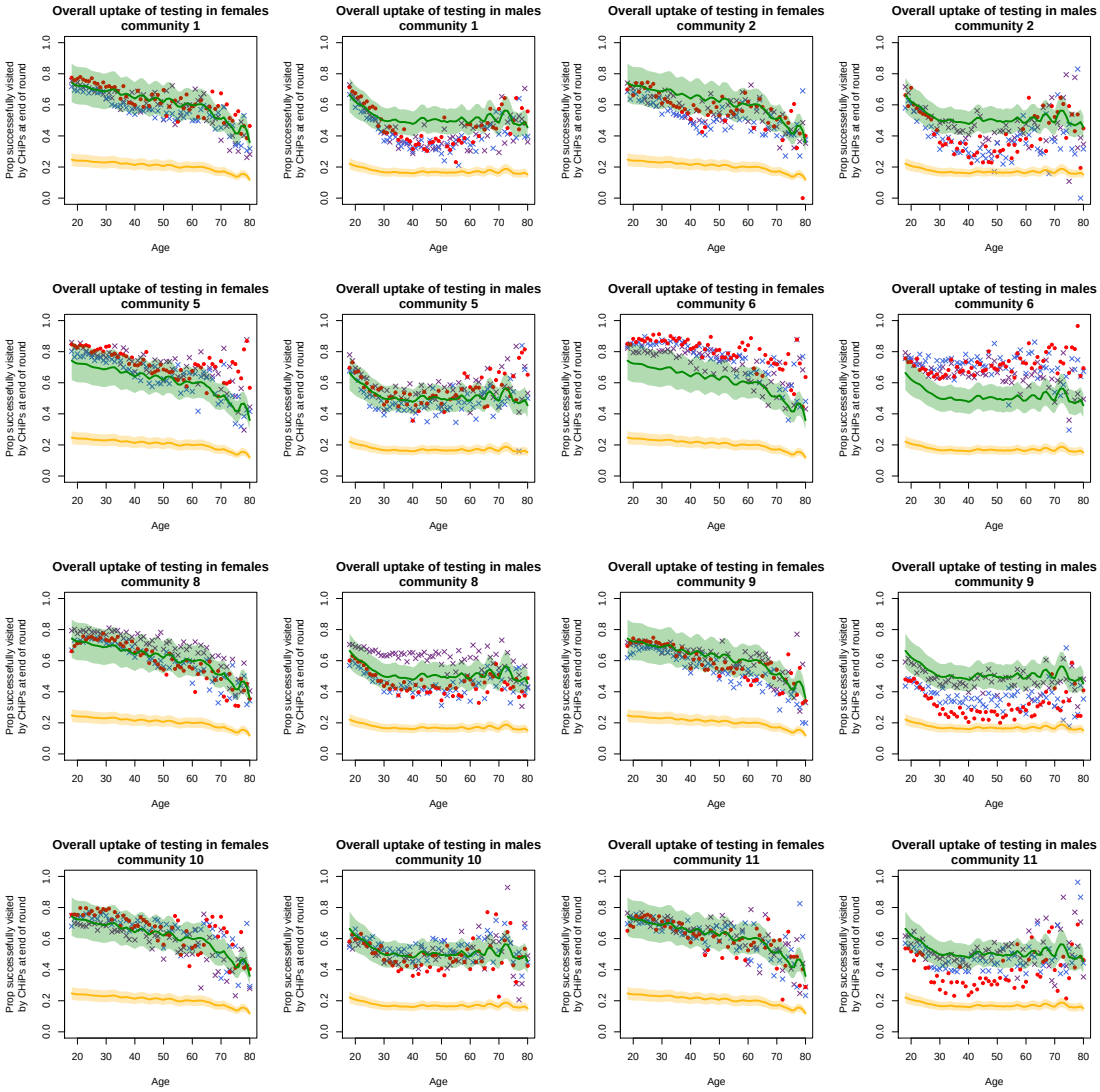

Figure 6.4: Proportion of individuals successfully visited by CHiPs, by community, age and gender, at the end of each round, for Zambia. The purple crosses show data for round 1, the blue crosses data for round 2 and the red dots data from round 3. The green and yellow lines show the central scenarios for rounds 3 and 4 respectively, which were used for predictions in October 2016. The green and yellow shaded areas show the corresponding range of scenarios from pessimistic to optimistic as per October 2016. Note the range of scenarios for round 4 is narrow, as the coverage at the end of the year is mostly determined by the short duration of the round.

6.2 Uptake of ART

Uptake of ART after a CHiPs visit is modelled using a mixture of two constant hazards: we assume that among HIV+ individuals not on ART identified by CHiPs, a proportion q will initiate ART fast (at rate ν_{fast}) and a proportion $1-q$ will initiate ART slowly (at rate ν_{slow}). Hence, the proportion who initiate ART by time t after a CHiPs visit is given by $q\left(1-e^{-\nu_{fast}t}\right)+(1-q)\left(1-e^{-\nu_{slow}t}\right)$.

Note that individuals who have not yet initiated ART when they receive the CHiPs visit of the subsequent round get 'reset' that is their time of ART initiation is assumed to be driven by the latest CHiPs visit. In the individual based model, this means that occasionally, an individual can get rescheduled his/her start of ART to a later date following a new round of CHiPs visit. This assumption may seem odd but is closest to the way the data was analysed. We fitted this biexponential model, using a maximum likelihood approach, to the CHiPs intervention data from round 1, with analyses stratified by country, and year quarter, in order to get round 1 estimates. For round 2, follow-up data up to October 2017 was used, and as only a limited amount of data was available, the analysis was stratified by country, but not by quarter.

The biexponential model presented above was favoured over a saturated exponential model (similar to the biexponential model but with $\nu_{slow}=0$, i.e. a proportion $(1-q)$ never initiate ART), as it produced a much better fit to the data.

Figure 6.5 show the fits for Zambia and Figure 6.6 for Sout Africa. In Figure 6.5 the estimates based on CHiPs data available per September 2016, which was the time at which the DSMB report 2016 was produced, are shown in the right column. In September 2016 the CHiPs round 2 was not complete. The left column shows the estimates for the same model but based on CHiPs data available in October 2017, incldluing the complete round 2 data and the non-completed round 3 data.

For rounds 3 and 4, we defined pessimistic, central and optimistic scenarios. These were defined based on the estimated parameters of the biexponential distribution for round 1 (across the 6 quarters) and round 2. The parameters of the biexponential distribution for the pessimistic scenario were taken as the central estimates for round 2. The parameters for the central scenario were taken as being slightly higher (10% higher for the proportion of fast intiators and 25% higher for the rates). Finally, the parameters for the optimistic scenarios were taken as the maximum upper bound of the 95%CI of parameters across all past estimates (i.e. round 2 and all quarters in round 1). Figure 6.7 shows these parameters, and figure 6.8 shows the corresponding survival curves.

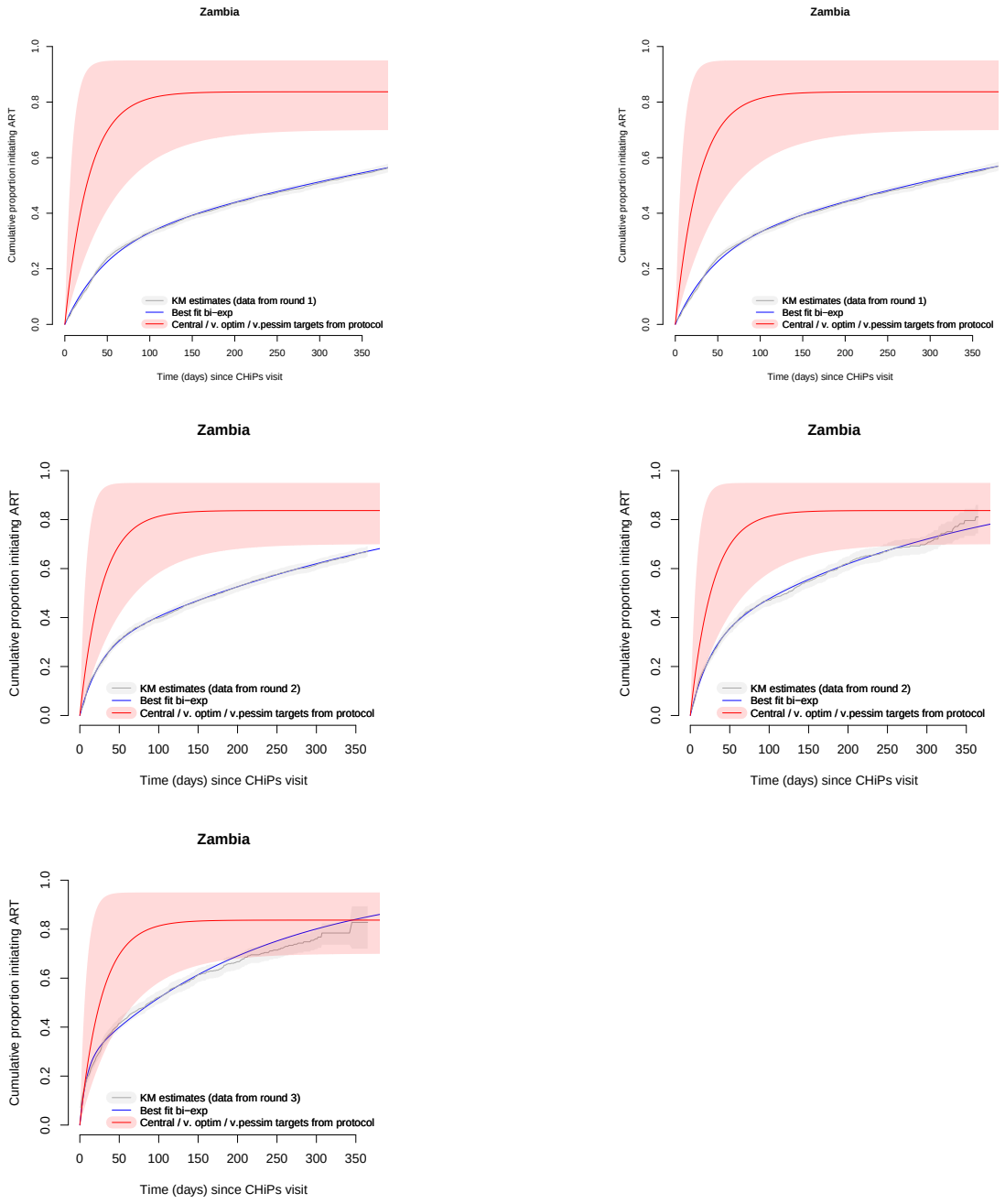

Figure 6.5: ART uptake in Zambia after a CHiPs visit in round 1, 2 and 3 as per October 2017 in the left column and for round 1 and 2 as per September 2016. The grey line and shaded area show the Kaplan-Meyer (KM) survival curves and 95%CI; the blue line shows the best fit bi-exponential model; the red line and shaded area show the central and extreme (pessimistic and optimistic) scenarios defined in the protocol.

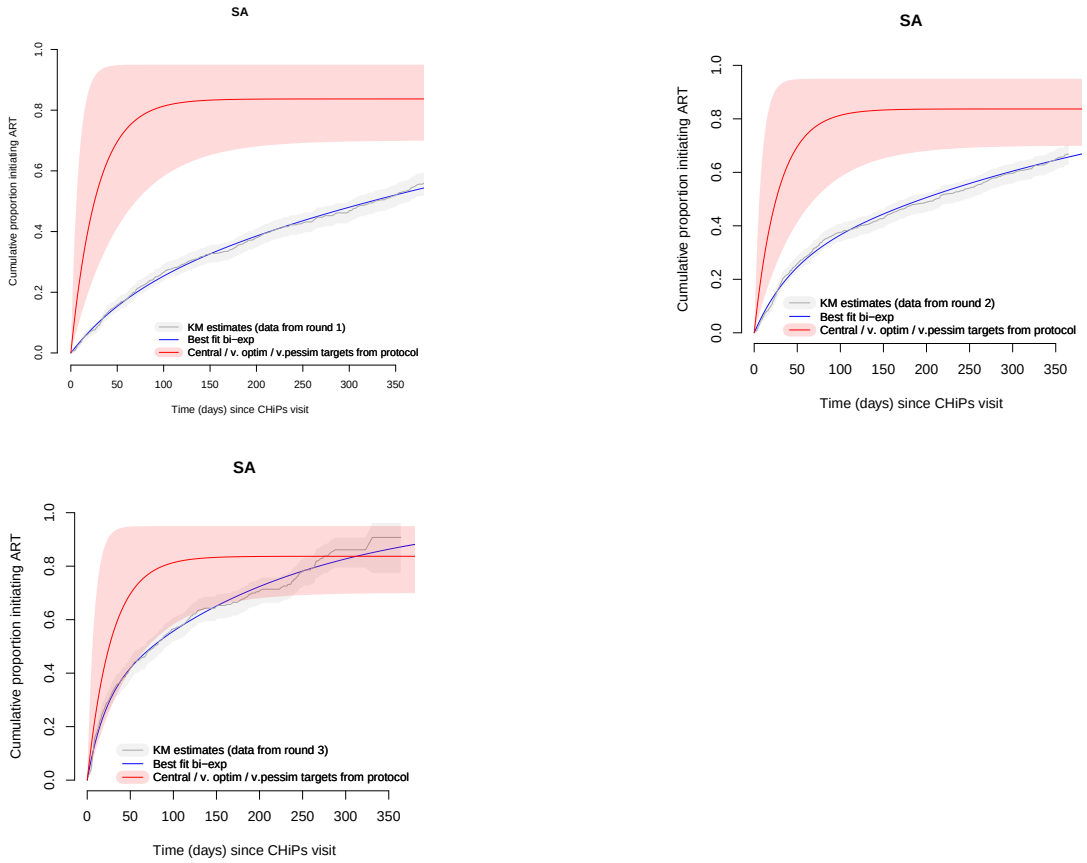

Figure 6.6: ART uptake in South Africa after a CHiPs visit in round 1, 2 and 3 as per October 2017. The grey line and shaded area show the Kaplan-Meyer (KM) survival curves and 95%CI; the blue line shows the best fit bi-exponential model; the red line and shaded area show the central and extreme (pessimistic and optimistic) scenarios defined in the protocol.

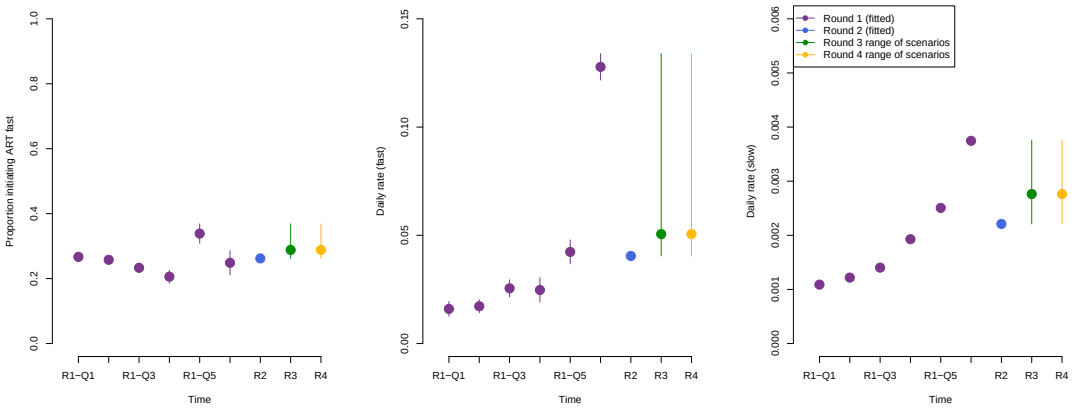

Figure 6.7: Parameters of the biexponential distribution used to model the time between CHiPs visit and ART initiation, for various rounds (Zambia). The left panel shows the proportion of fast initiators. The middle panel shows the rate of initiation for fast initiators. The right panel shows the rate of initiation for slow initiators. In each panel, the six purple dots show central estimates based on data for each quarter in round 1; the blue dot shows central estimates based on data for round 2. In both cases the vertical lines show the 95%CI. The green and yellow dots show the central assumptions for rounds 3 and 4 respectively. The green and yellow vertical lines show the range of scenarios for rounds 3 and 4, from pessimistic to optimistic

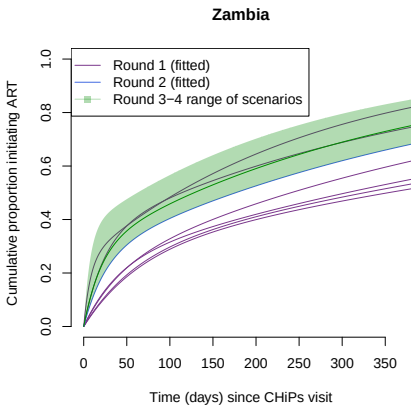

Figure 6.8: Biexponential cumulative distributions used to model the uptake of ART following a CHiPs visit, for various rounds (Zambia). The curves shown in this figure are based on the parameters shown in figure 6.7. The six purple curves show the fits based on data for each quarter in round 1; the blue curve shows the fit based on data for round 2. The green curve shows the central assumption for rounds 3 and 4. The green shaded area shows the range of scenarios from pessimistic to optimistic for rounds 3 and 4

Chapter 7

Population Cohort

Within the PopART IBM there is a population cohort, a group of individuals enrolled at baseline (PC0) and whose HIV status is then checked in the model at 3 subsequent rounds. PC trial impact is estimated from the IBM by looking at cumulative HIV incidence in this cohort.

The cohort is generated such that we match exactly the data on number of people in specified subpopulations who were enrolled in the real PC0 at each timestep with a baseline HIV test result. The subpopulations we use are divided by age (one year age groups), gender and HIV status (HIV-negative, HIV-positive and unaware at baseline PC, HIV-positive and aware at baseline PC). For each category we draw that number of individuals plus some 'reserves' (individuals who have the same characteristics in case one of the individuals drawn dies or leaves the specified group - for example if an HIV-negative individual gets HIV prior to enrolment.

The number of reserves is taken to be 25% of the number in a given group, with a minimum of 15 people. In cases where the model cannot find enough people, it continues with as many people in that given group as possible. Enrolments for the chosen individuals are then carried out throughout the baseline PC round, following the data on date of specimen collection from PC0. At enrollment each individual's HIV, ART and viral suppression status are recorded. Subsequent PC visits occur in the same order, but at a different rate to allow for the whole cohort to be revisited over a different timescale. The duration of each PC round is based on what occurred in each community for PC0, and times provided by SCHARP for PC12 onwards. At this time there is no PC12N, and retention in PC is assumed to be 100% at each round. In each subsequent round HIV, ART and viral suppression status at that time are recorded again.

Chapter 8

Model calibration and computation of trial impact

In the previous chapters, we have described the structure of the model, as well as the values used for many parameters (for a list of parameters and their values see chapter 9).

However, a number of parameters in the model are not directly informed by data but instead are calibrated as follows. For each community, we draw a large number of parameter sets (50,000) within pre-specified ranges using latin hypercube sampling. For each run, we simulate an epidemics trajectory until 2020 using the central uptake scenario (see chapter 6 for description of uptake scenarios). For each of these simulations for a Zambian community, we compute the likelihood of the following 'data' given the model parameters:

- regional DHS prevalence estimates by age (5-year age groups) and gender for all available DHS surveys,
- community-specific CHiPs prevalence data by age (5-year age groups) and gender for CHiPs rounds 1, 2, 3.
- community-specific CHiPs data on proportion of HIV positive individuals aware of status by age (5-year age groups) and gender for CHiPs round 1, 2, and 3 (the first UNAIDS 90).
- community-specific CHiPs data on proportion of those aware of status who are on ART by age (5-year age groups) and gender for CHiPs round 1, 2, and 3 (the second UNAIDS 90).

For simulations of South African communities we compute the likelihood of the following 'data' given the model parameters:

- community-specific CHiPs prevalence data by age (5-year age groups) and gender for CHiPs round 3.

- community-specific CHiPs data on proportion of HIV positive individuals aware of status by age (5-year age groups) and gender for CHiPs round 3 (the first UNAIDS 90).
- community-specific CHiPs data on proportion of those aware of status who are on ART by age (5-year age groups) and gender for the CHiPs round 3 (the second UNAIDS 90).

The CHiPs Round 1 and Round 2 data from South Africa are used for estimates of the time to start ART after referral by CHIPs to HIV care, but otherwise are not used for model calibration. For Round 1 data, this is because there was under-recording of individuals who were not contacted, refused to participate, participated and self-reported HIV-positive, or participated and did not accept the offer of HIV testing from CHiPs; i.e. the total population, the proportion of the total population who were contacted, and the proportion of the total population who knew they were HIV-positive, are underestimated and the uptake of HIV testing is over-estimated. For Round 2 data, this is because it was established in early 2016 that from early in Round 2 some CHiP teams sometimes (1) recorded that a person had tested HIV-negative when in fact they had declined the offer of HIV testing (2) did not record a person on the electronic register, or recorded them as having self-reported or tested as HIV-negative, when in fact they self-reported they were HIV-positive.

We then select the 10 parameter sets with highest likelihood (see report 1 for details on calibration and examples on one community). Note that in all mentions of round 3 data above, the data were only available until October 2017.

For each community, we then rerun the model using these 10 parameter sets, but using a central scenarios for the uptake parameters for round 4 (see chapter 6 for definitions scenarios). For each of those, the model is run with 10 different stochastic realisations of the model after the trial start, and for each with 10 different stochastic realisations of the PC sampling. Hence for each community and each uptake scenario we consider $1,000$ model runs, corresponding to 10 different background epidemics $\times$ 10 different versions of the the model after the trial start (with the same uptake level) $\times$ 10 different versions of the PC sampling.

We also run the model using the 10 parameter sets obtained through calibration under the counterfactual scenario where there are no CHiPs visits at all. Again, for each of these we consider 10 different stochastic realisations of the model after the trial start, and for each with 10 different stochastic realisations of the PC sampling, leading to a total of $1,000$ model runs for the counterfactual.

For each pair of runs with and without intervention, we then compute the trial impact as the relative difference in population HIV incidence between 2014.5 (the midpoint of PC0) and 2018 (the projected midpoint of PC36). The impact is calculated overall, and by gender. We also compute the weighted mean between the impact in each gender, with weights given by the proportion of men and women in PC0, to account for gender imbalance in PC. Note that for the impact calculation we effectly use 100 pairs of runs, not $1,000$, as the PC sampling does not affect the impact in the population. Report 2 shows

an example of comparison between one run and its counterfactual for one community. Report 3 shows the range of predicted trial impacts based on all runs and all communities.

The full sets of runs including variability in PC sampling were used to produce model outputs which could be directly compared to data available to the DSMB (see report 4).

Chapter 9

Model parameterization

9.1 Mortality

The natural (non-HIV) mortality rate used in the model is derived from UNPD WPP 2015 estimates in the given country [21]. UNPD provides estimates of the number of deaths that occur in a given 5 year age group (0-4, 5-9,...) during the five year time periods 1950-55, 1955-60, 1960-65,...2010-2015 for each gender. UNPD also publishes the estimated size of each 5 year age group during that period. Projections of future number of deaths and population sizes are also published, and we use the 'medium fertility' variant as described in [22].

UNPD deaths include deaths from AIDS-related illness as well as non-HIV mortality. We therefore carry out several steps to derive the natural (non-HIV) mortality rate used in the PopART IBM. Firstly we obtain the UNPD annual mortality rate for a given gender g and age group a. As UNPD publishes estimates over 5 year time periods we take this to correspond to the mortality rate at the mid-point of the period, in other words at times $t = 1952.5, 1957.5$, etc.

$$\text{UNPD\_mortality\_rate}^{a,g}(t) = \frac{\text{(No. of deaths in gender } g \text{ and age } a \text{ over } t\text{-2.5 to } t\text{+2.5)}}{\text{(5 years)} \times \text{(No. of people of gender } g \text{ in age group } a \text{ at time } t)}.$$

For each gender g and age group a we fit a linear regression to the natural log of the mortality rate. We merge all UNPD data from ages 80+ into a single age group for simplicity. HIV-related mortality only affects mortality over a certain time period, which from visual inspection of data is after 1980, and varies by age group (see Figures 9.1-9.4 to see the regression fits). HIV-related mortality appears to have an effect that is projected to last longer in South Africa than in Zambia for the model used by UNPD (EPP/Spectrum). In Zambia, future mortality is overestimated if data is restricted to 1950-1980 only.

We therefore fit the regression model to a restricted dataset as follows:

Country	Population	Data
Zambia	Men <80	1950-1980 and 2050-2100
Zambia	Men 80+	1950-2100
Zambia	Women <80	1950-1980 and 2050-2100
Zambia	Women 80+	1950-2100
South Africa	Men <80	1950-1980 only
South Africa	Men 80+	1950-2100
South Africa	Women <80	1950-1980 only
South Africa	Women 80+	1950-2100

Figures 9.1-9.4 show the UNPD estimates and the regression fit to these estimates. Table 9.1 shows the results of the regression, which are used as parameters in the PopART IBM.

	Zambia				South Africa			
	Men		Women		Men		Women	
Age group	Intercept	Slope	Intercept	Slope	Intercept	Slope	Intercept	Slope
0-4	40.212	-0.022	40.705	-0.022	42.293	-0.023	54.690	-0.030
5-9	44.032	-0.025	46.709	-0.026	42.586	-0.025	68.215	-0.038
10-14	35.333	-0.021	40.583	-0.023	40.871	-0.024	69.069	-0.038
15-19	24.761	-0.015	33.245	-0.020	38.144	-0.022	71.719	-0.039
20-24	22.432	-0.014	30.933	-0.018	37.628	-0.022	71.849	-0.039
25-29	20.435	-0.013	30.743	-0.018	37.291	-0.022	68.580	-0.037
30-34	17.019	-0.011	31.502	-0.019	36.825	-0.021	63.583	-0.035
35-39	15.467	-0.010	30.226	-0.018	34.332	-0.020	56.239	-0.031
40-44	16.937	-0.011	27.039	-0.016	30.516	-0.018	47.610	-0.027
45-49	17.651	-0.011	23.513	-0.014	26.053	-0.015	40.423	-0.023
50-54	16.497	-0.010	21.266	-0.013	21.867	-0.013	35.665	-0.020
55-59	15.642	-0.010	20.786	-0.013	17.916	-0.011	31.795	-0.018
60-64	14.097	-0.009	19.762	-0.012	15.110	-0.009	27.901	-0.016
65-69	12.925	-0.008	18.136	-0.011	13.182	-0.008	24.094	-0.014
70-74	12.310	-0.008	16.554	-0.010	11.254	-0.007	21.628	-0.012
75-79	11.378	-0.007	14.728	-0.009	9.395	-0.006	20.417	-0.012
80+	7.562	-0.005	9.202	-0.006	6.229	-0.004	8.480	-0.005

Table 9.1: Country, gender and age-group specific mortality parameters.

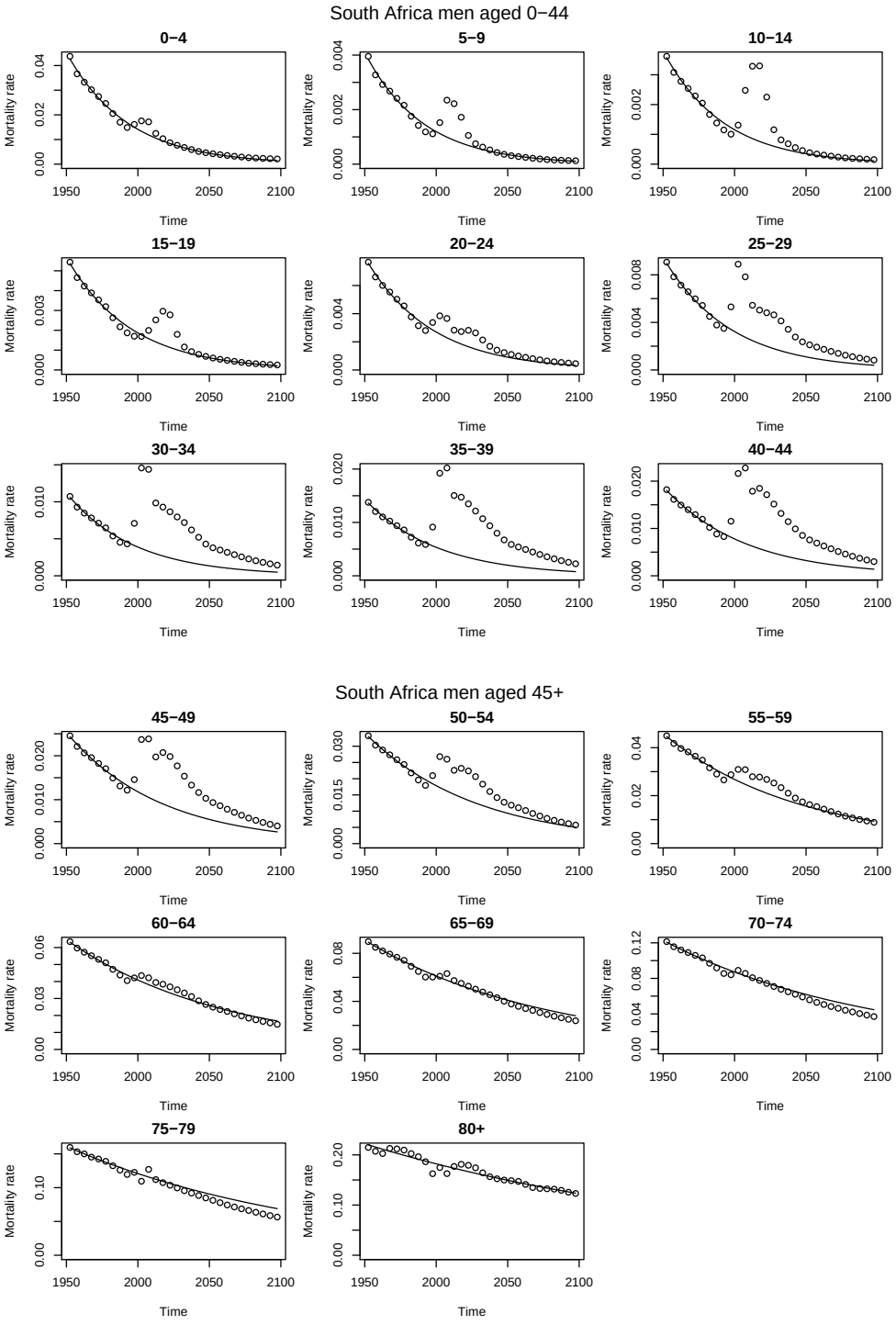

Figure 9.1: Annual mortality for men in South Africa by age group. Circles show UNPD estimates of mortality including HIV-related mortality. Lines show fitted regression estimates of non-HIV mortality as used in the PopART IBM.

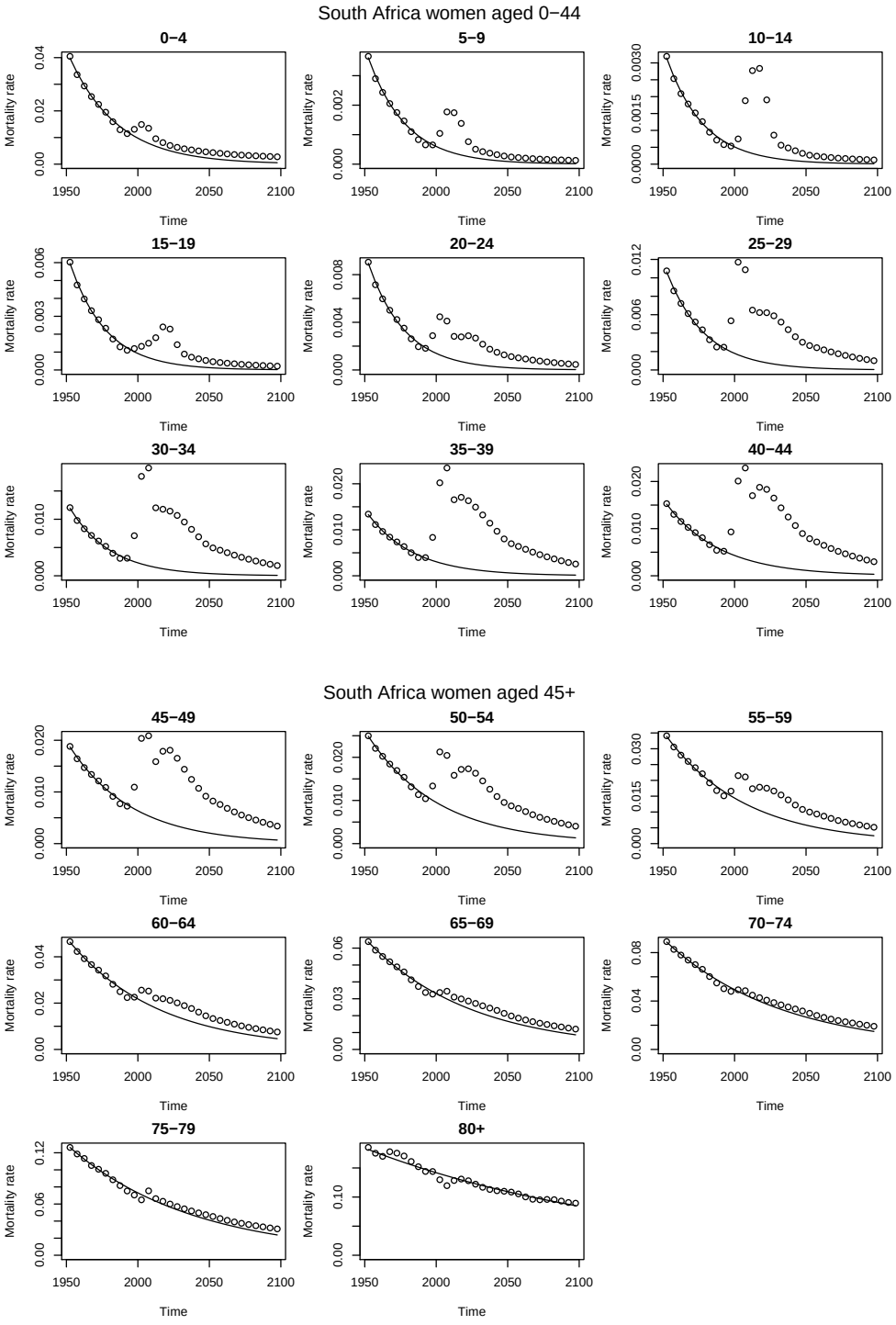

Figure 9.2: Annual mortality for women in South Africa by age group. Circles show UNPD estimates of mortality including HIV-related mortality. Lines show fitted regression estimates of non-HIV mortality as used in the PopART IBM.

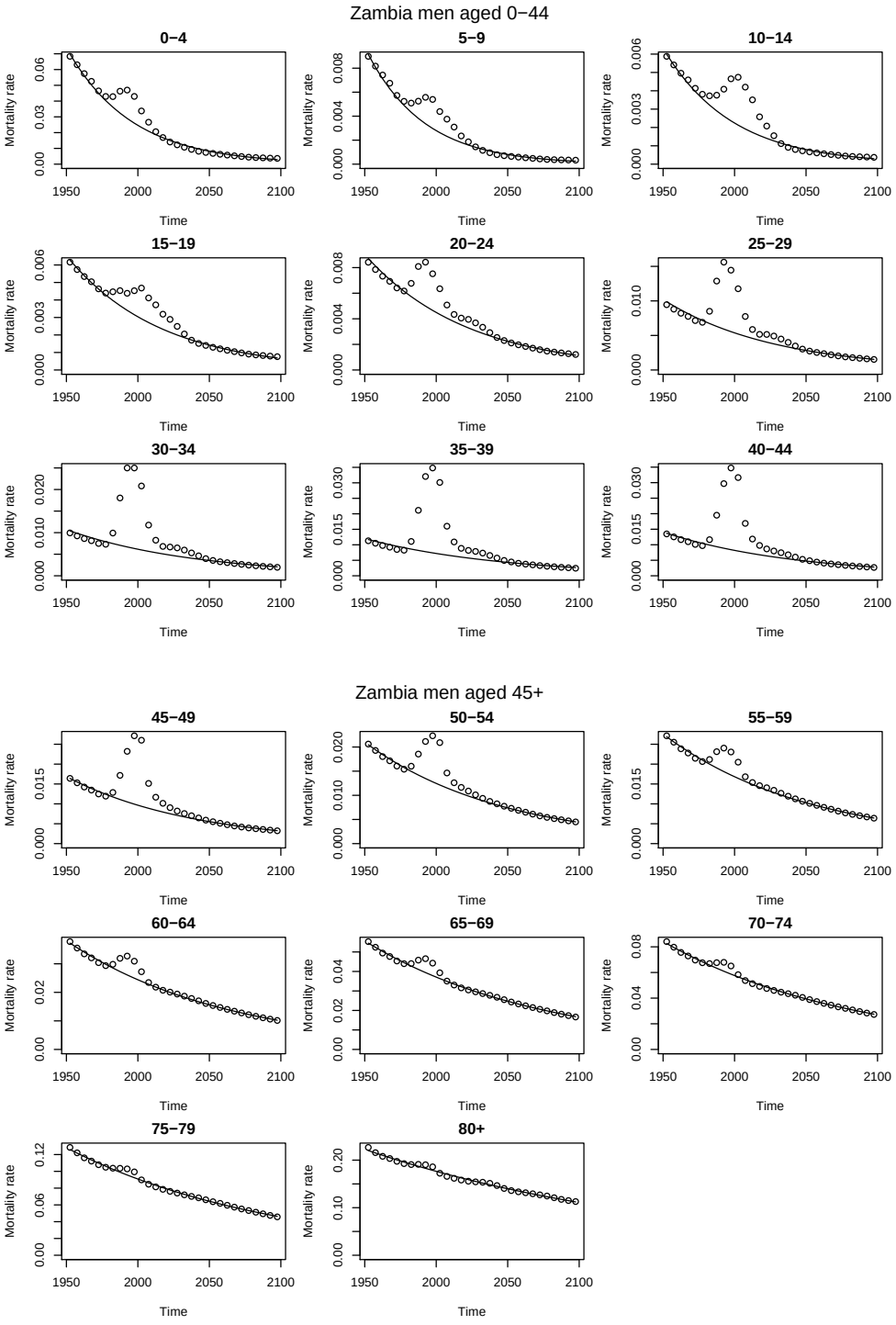

Figure 9.3: Annual mortality for men in Zambia by age group. Circles show UNPD estimates of mortality including HIV-related mortality. Lines show fitted regression estimates of non-HIV mortality as used in the PopART IBM.

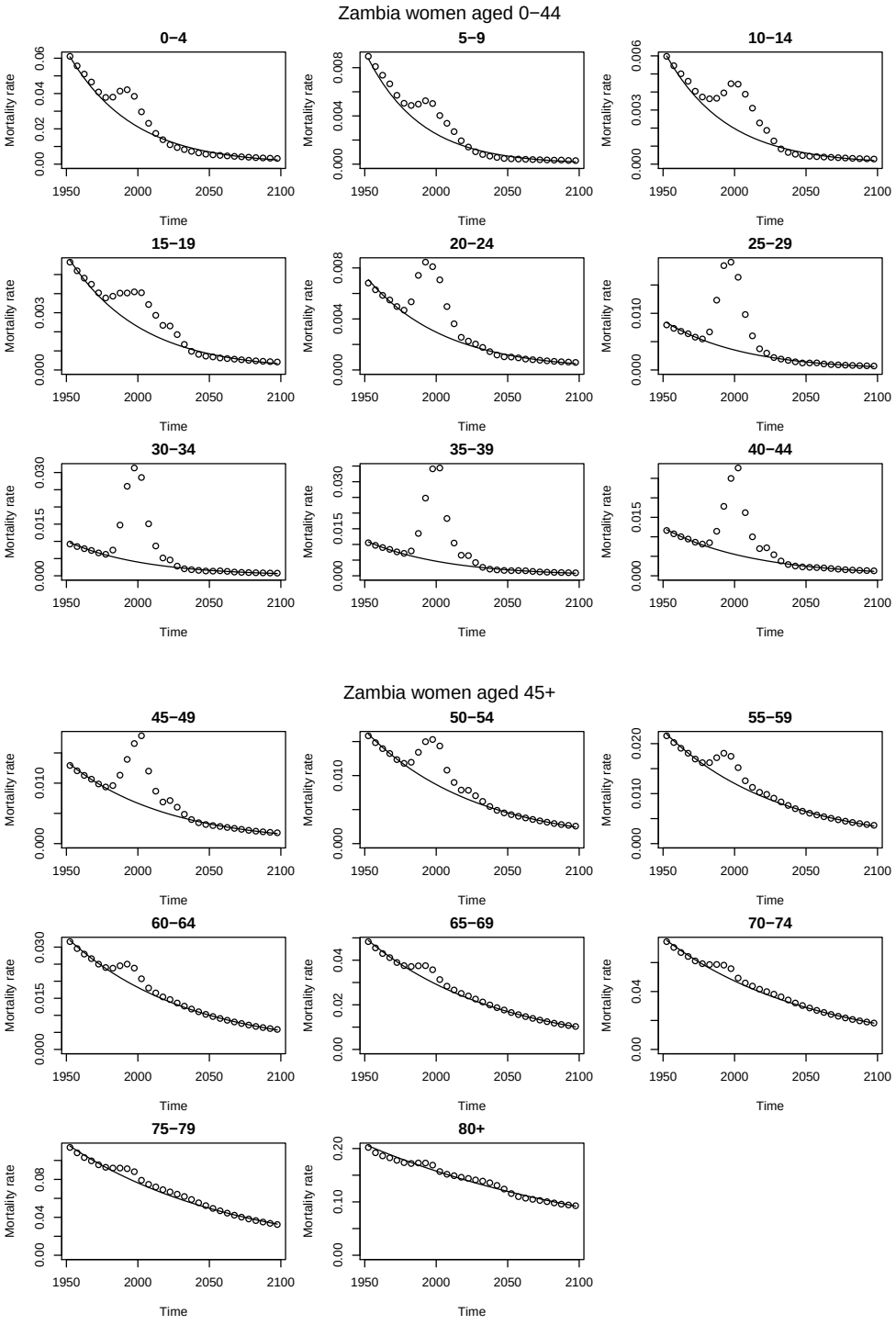

Figure 9.4: Annual mortality for women in Zambia by age group. Circles show UNPD estimates of mortality including HIV-related mortality. Lines show fitted regression estimates of non-HIV mortality as used in the PopART IBM.

9.2 Fertility

Fertility estimates come from UNPD WPP 2015 estimates in the given country [21]. As described in the main document, these are subsequently adjusted for childhood mortality, using the data given in 9.1 so that the IBM model fertility parameters represent the number of children who will survive to adulthood.

	Fertility rate per 1000 women by age group													
	Zambia							South Africa						
Period	15-19	20-24	25-29	30-34	35-39	40-44	45-49	15-19	20-24	25-29	30-34	35-39	40-44	45-49
1950-1955	171.9	282.0	261.3	240.7	211.5	140.4	42.1	66.8	265.0	291.9	242.2	189.8	132.0	72.3
1955-1960	175.8	288.3	267.2	246.1	216.2	143.5	43.0	65.7	260.8	287.3	238.3	186.7	130.0	71.2
1960-1965	182.1	298.7	276.8	255.0	224.0	148.7	44.6	64.7	256.6	282.7	234.5	183.7	127.9	70.0
1965-1970	188.5	309.1	286.5	263.9	231.9	153.9	46.2	60.4	239.7	264.1	219.1	171.7	119.5	65.4
1970-1975	189.1	310.2	287.5	264.8	232.6	154.5	46.3	76.1	233.9	253.6	211.0	160.2	105.1	54.0
1975-1980	187.9	308.1	285.5	263.0	231.1	153.4	46.0	86.1	217.3	231.8	193.6	142.3	87.4	41.5
1980-1985	178.3	292.4	271.0	249.6	219.3	145.6	43.7	93.6	201.1	211.3	177.0	125.9	71.7	30.5
1985-1990	171.0	312.4	295.9	253.2	190.7	83.3	28.5	95.4	179.4	185.7	155.9	107.3	56.0	20.4
1990-1995	162.7	297.2	281.5	240.9	181.4	79.2	27.1	90.8	152.2	155.2	130.8	86.9	41.0	11.7
1995-2000	143.7	282.3	274.1	236.4	178.3	84.6	30.6	80.6	140.5	142.5	111.5	74.4	31.0	10.3
2000-2005	143.3	268.9	258.1	235.5	187.4	88.3	28.5	70.7	139.0	141.8	105.6	67.4	27.1	8.8
2005-2010	122.0	273.3	267.3	229.0	176.9	86.8	24.6	59.2	131.7	135.1	95.9	58.4	22.6	7.1
2010-2015	103.3	267.3	265.0	210.3	152.4	71.8	19.9	50.9	129.0	133.1	90.2	52.3	19.4	5.9
2015-2020	77.5	272.4	278.7	195.2	129.2	60.7	14.6	40.2	129.4	136.0	85.6	45.4	15.5	4.3
2020-2025	65.5	264.8	275.4	182.9	115.9	54.3	12.1	35.0	125.3	133.8	82.3	42.0	13.8	3.6
2025-2030	55.5	256.4	271.0	171.8	104.4	48.6	10.1	30.6	121.1	132.0	80.1	39.4	12.4	3.1
2030-2035	47.3	247.2	265.7	161.7	94.5	43.6	8.5	26.9	116.6	130.0	78.7	37.4	11.3	2.6
2035-2040	40.5	237.9	260.0	152.8	86.0	39.3	7.1	23.8	112.0	128.5	78.1	36.1	10.4	2.2
2040-2045	35.0	228.5	254.1	145.0	78.7	35.5	6.0	21.3	107.4	127.3	78.4	35.3	9.8	1.9
2045-2050	30.4	219.3	248.1	138.4	72.6	32.3	5.1	19.1	102.7	126.5	79.5	35.0	9.3	1.7
2050-2055	26.6	210.0	242.0	132.6	67.4	29.5	4.4	17.2	97.8	125.7	81.5	35.3	8.9	1.4
2055-2060	23.5	201.1	236.1	127.9	63.0	27.1	3.8	15.6	92.8	125.2	84.3	36.0	8.7	1.3
2060-2065	20.8	192.1	230.0	123.8	59.3	25.0	3.3	14.2	87.5	124.7	87.8	37.1	8.6	1.1
2065-2070	18.7	183.7	224.3	120.6	56.3	23.2	2.9	12.9	82.0	124.1	92.1	38.7	8.6	1.0
2070-2075	16.8	175.1	218.4	117.8	53.7	21.5	2.5	11.8	76.2	123.3	97.0	40.8	8.7	0.9
2075-2080	15.3	167.1	212.9	115.9	51.7	20.2	2.2	10.8	70.1	122.0	102.5	43.2	8.8	0.8
2080-2085	14.0	159.0	207.2	114.4	50.0	19.0	2.0	9.9	63.8	120.3	108.5	46.2	9.0	0.7
2085-2090	12.9	151.2	201.9	113.4	48.7	17.9	1.7	9.0	57.3	118.1	114.9	49.5	9.3	0.6
2090-2095	12.0	143.5	196.5	112.9	47.8	17.0	1.6	8.2	50.8	115.1	121.4	53.3	9.6	0.5
2095-2100	11.3	135.9	191.1	112.8	47.1	16.1	1.4	7.4	44.4	111.7	128.2	57.6	10.0	0.5

Table 9.2: *Fertility rate for Zambia over time, using UN population world population projection 2015 estimates*

Parameter	Value	Source
Annual transmission hazard in individuals with maximal SPVL	0.05-0.3 yr^{-1}	Hazard is adjusted down via a Hill function for lower SPVL. [14] estimated 0.313 yr^{-1} for individuals with SPVL 1 million copies/ml. Lower limit chosen to be more consistent with observed values in serodiscordant couples.
Relative infectivity by HIV stage (compared to CD4>500):		
Early HIV	5.3 (HIGH) 2.65 (LOW)	[3] gives 20% of infections due to acute at present. For low acute assumption assume RR is halved so that only 10% of new infections come from acute stage.
350-500	1.0	Assume no difference.
200-350	1.0-1.5	Range no difference to [13]
<200	2.0-4.0	Range informed by [11] to [13]. Upper range increased compared to [11] to be closer to [5].
Relative infectivity of male-to-female transmission	1.0-3.0	Lower limit no difference, upper limit is mean of low and high-income country estimates from [5].
$RR^{\text{early ART}}$, relative infectivity on early ART compared to no ART	0.5	Assumption
RR^{VS}, relative infectivity on ART and VS compared to no ART	0.0	No infections in [8] when VS.
RR^{VU}, relative infectivity on ART and VU compared to no ART	0.7	Assumption to get overall effectiveness of 0.93 in [8] if 90% on ART are VS.
Relative HIV transmission risk for partnerships between patches, compared to partnerships within same patch	0.45	Pooled PC0 analysis for Zambia and SA together. Partnerships between patches are assumed to have different unprotected coital frequency.
Distribution of initial CD4 category after HIV infection, by $\log_{10} SPVL$ category:		
$\log_{10}$SPVL$\leq$ 4.0:		
CD4>500:	0.864	Analysis in [12]
CD4 350-500:	0.113	
CD4 200-350:	0.023	
CD4$\leq$200:	0.000	
$\log_{10}$SPVL 4.0-4.5:		
CD4>500:	0.780	
CD4 350-500:	0.190	
CD4 200-350:	0.030	
CD4$\leq$200:	0.000	
$\log_{10}$SPVL 4.5-4.0:		
CD4>500:	0.740	
CD4 350-500:	0.210	
CD4 200-350:	0.050	
CD4$\leq$200:	0.000	
$\log_{10}$SPVL >5.0:		
CD4>500:	0.710	
CD4 350-500:	0.250	
CD4 200-350:	0.040	

CD4≤200:	0.000	
t_{acute}, Duration of early infection	0.08-0.25 yrs	[3]
For individuals with $log_{10}SPVL < 4.0$:		
Mean time spent in CD4 > 500 category	4.56-6.37 yrs	[12]
Mean time spent in CD4 500-350 category	2.98-4.53 yrs	[12]
Mean time spent in CD4 350-200 category	5.04-13.69 yrs	[12]
Mean time spent in CD4 ≤ 200 category	1.8-2.8 yrs	[11]
Factor adjusting time in each CD4 category per 10-fold increase in SPVL		
CD4 > 500	1.89-2.49	[12]
CD4 500-350	1.61-2.19	[12]
CD4 350-200	1.41-2.73	[12]
CD4 ≤ 200	0.77-3.44[1]	[12]
$f^{VUprogression}$, multiplier for increased duration in each CD4 stage when on ART but virally unsuppressed	1.0-2.0	[11]
$\log_{10}$ set-point viral load of new infectee	$\sim$N(4.74, 0.61^2)	[6]

Table 9.4: HIV-related parameters used in the PopART IBM. *HIGH*=high set of assumptions (high acute, high contamination). *LOW*=low set of assumptions (low acute, low contamination).

[1] values <1 are set to 1

Parameter	Values	Notes
χ, risk assortativity	0.05-0.95	Large range to reflect uncertainty.
θ, proportion of compromise from males	0.01-0.5	Assumption that women underreport more than men.
$c_a^{m,in}$, within community partnership formation rates for men		Units are 10^{-3} yr^{-1}
13-17	17.4(Z) 50.6(S)	No PC data. Assumed same as 18-22.
18-22	34.8(Z) 101(S)	PC0 analysis
23-29	40.8(Z) 162(S)	PC0 analysis
30-39	25.1(Z) 64.6(S)	PC0 analysis
40-49	24.4(Z) 50.5(S)	PC0 analysis
50-59	5.1(Z) 15.2(S)	No PC data available, roughly consistent
60-79	2.5(Z) 7.6(S)	decline with UK Natsal data
$c_a^{f,in}$, within community partnership formation rates for women		Units are 10^{-3} yr^{-1}
13-17	8.9(Z) 26.0(S)	No PC data. Assumed same as 18-22.
18-22	17.7(Z) 52.0(S)	PC0 analysis
23-29	14.7(Z) 28.6(S)	PC0 analysis
30-39	10.2(Z) 30.3(S)	PC0 analysis
40-49	13.1(Z) 39.1(S)	PC0 analysis
50-59	6.5(Z) 19.6(S)	No PC data available, roughly consistent
60-79	3.3(Z) 9.8(S)	decline with UK Natsal data
Relative number of partnerships by risk group		
Low risk δ^{low}	1.0	
Medium risk δ^{med}	7.1	
High risk δ^{high}	12.4	
$c_{multiplier}$, multiplier to account for misreporting of number of sexual partners	0.5-4.0 (H) 0.625-5.0 (L)	1.0 means that people report the correct number of partners, > 1 means people are underreporting. Lower range taken to ensure 1 is sampled well and to allow over-reporting.
Relative rate of formation of partnerships between patches compared to within patches	0.56 (H,Za), 0.66 (H,SA) 0.2 (L)	PC0 analysis. Lower value used for analysis with lower contamination at levels of previous modelling for DSMB.
Unscaled duration of low risk partnerships within patch	15.4(Za) 9.8(SA)	PC0 data (units of years)
Unscaled duration of medium risk partnerships within patch	6.1(Za) 7.0(SA)	PC0 data (units of years)
Unscaled duration of high risk partnerships within patch	3.8(Za) 4.2(SA)	PC0 data (units of years)
Multiplier scaling duration of all partnerships	1.0-2.0	Assumption
Multiplier scaling duration of partnerships between patches compared to within patch	0.46 (Za), 0.58 (SA)	PC0 data
Maximum number of concurrent partners by risk group:		
Low	1	Assumption - over 90% of PC have 0 or 1
Medium	3	partners in the last year.
High	10	

Table 9.3: Partnership-related parameters used in the PopART IBM. *H*=high set of assumptions (high acute, high contamination). *L*=low set of assumptions (low acute, low contamination). *Z,Za* = Zambia. *S,SA* = South Africa.

Parameter	Value	Source
Time when background HIV testing begins	2000	Assumption
Time when ART first available	2004	Assumption
Time when ART guidelines changed to CD4<350	2011	
Time when ART guidelines changed to CD4<500	2014.5(Za) 2015.0(SA)	
Time when ART guidelines changed to immediate treatment	2016.33	As reported by trial community clinics .
$p^{background}_{collectHIVresults}$, probability collect background HIV test results	0.97-1.0	Lower limit from Zambia DHS 2013. Upper limit assume all collect.
$m^{backgroundtest}$ increase in annual probability of background testing from 2006 onwards.	1-3	Assumption.
$p^{background}_{collectCD4results}$, probability collect background CD4 test results	0.75-0.95	Lower limit [18]. Upper limit assumption that most collect.
$p^{\text{early ART}}_{die}$, probability die while on early ART	0.08	[23]
$p^{\text{become VS}}$, probability become VS after early ART if do not die	0.9	To get observed values of viral suppression in PC0.
$p^{\text{become VU}}$, probability become VU after early ART if do not die	0.1	So probabilities sum to 1.
$p^{\text{remains VS}}$, probability that someone VS remains VS for life	0.6	[23]
$p^{\text{VS becomes VU}}$, probability that someone VS eventually becomes VU	0.3	[23]
$p^{\text{VS dropout}}$, probability that someone VS eventually drops out	0.1	[23]
$t^{earlyART}$, duration of early ART phase	2 months	Comparable with analysis of ATHENA cohort data from Netherlands (unpublished)
$t^{\text{CD4 retest}}$, time between successive CD4 tests when not eligible for ART	0.9-1.1 yrs	Assumption
$t^{ART}_{background}$, mean time to start ART through background HIV testing (of those who decide to start ART)	0.4-0.7 yrs	Range from analysis of CHiPs data by country.
t^{ART}_{CHiPs}, mean time to start ART through CHiPs testing	See table below	Analysis of CHiPs follow-up data.

Table 9.6: Cascade-related parameters used in the PopART IBM. Times for initiating ART following a CHiPs visit are in Table 9.7. *VS=virally suppressed, VU=virally unsuppressed.*

Round/period	**Mean time to start ART fast (yrs)**	**Mean time to start ART slow (yrs)**	**Probability of being a fast starter**
Round 1, period 1	0.177	2.55	0.276
Round 1, period 2	0.160	2.17	0.258
Round 1, period 3	0.103	1.84	0.224
Round 1, period 4	0.106	1.41	0.202
Round 1, period 5	0.063	1.00	0.328
Round 1, period 6	0.021	0.69	0.254
Round 2	0.070	0.89	0.296
Round 3	0.070	0.89	0.296
Round 4	0.070	0.89	0.296

Table 9.7: Parameters for time to ART initiation after CHiPs visits used in the PopART IBM. These parameters give a biphasic exponential distribution from which a time to initiate ART is drawn for individuals who receive a positive result from a CHiPs HIV test.

Parameter	**Value**	**Notes**
Time when VMMC first became available nationally	2010	
p^{TMC}, probability of being traditionally circumcised	0.094(Za) 0.561(SA)	PC data
Eff^{VMMC}, effectiveness of VMMC in reducing susceptibility	0.6	[20]
Eff^{TMC}, effectiveness of TMC in reducing susceptibility	0.0	PC analysis [19]
$RR_{\text{circ unhealed}}$, relative risk of HIV during VMMC healing phase	0.330	[11]
$p_{circ}^{background}$, probability of being circumcised following background HIV- test	0.22(Za) 0.06(SA)	Arm C PC0 data
p_{circ}^{CHiPs}, probability of being circumcised following CHiPs HIV- test	0.4	Based on CHiPs uptake data analysis from DSMB November 2015
$t_{VMMC}^{background}$, time between background HIV- test and getting VMMC	0.25-1.0 yrs	Assumption
t_{VMMC}^{CHiPs}, time between CHiPs HIV- test and getting VMMC	0.08-1.0 yrs	Assumption
$t_{VMMC}^{Healing}$, time for VMMC wound to heal	2 weeks	[11]

Table 9.8: Circumcision-related parameters used in the PopART IBM

Parameter	Value	Notes
Start of simulation	1900	Assumption to give demographics and partnerships time to burn in
Start of HIV epidemic	1970-1980 1976-1986	Zambia South Africa
Proportion by age group at start of simulation		
14-17	0.1583(Za) 0.1339(SA)	All based on UNPD WPP 2015
18-22	0.1613(Za) 0.1420(SA)	*http://esa.un.org/wpp/Excel-*
23-29	0.1885(Za) 0.1724(SA)	*Data/population.htm*
30-39	0.1983(Za) 0.2046(SA)	(downloaded 12 May 2016)
40-49	0.1353(Za) 0.1498(SA)	
50-59	0.0828(Za) 0.1045(SA)	
60-79	0.0755(Za) 0.0928(SA)	
80+	0.0000(Za) 0.0000(SA)	
Proportion by activity group when entering population		
Low-activity men	10-50%	Based on variability between
Low-activity women	10-50%	communities from PC0
Medium-activity men (of those not in low activity group)	50-99%	
Medium-activity women (of those not in low activity group)	50-99%	
Proportion of new adults who are male	0.507(Za) 0.505(SA)	CIA world factbook
Number of years of HIV seeding after start of HIV epidemic	5	Assumption
Unscaled % of population seeded HIV+ each year by risk group		
Low	0.002%	These are scaled by $F_{initial}$ below to
Medium	0.008%	get the actual % of the population
High	0.008%	seeded HIV+.
$F_{initial}$, factor multiplying seeded % at the start of the HIV epidemic	1-100	Sampled on log scale

Table 9.9: Parameters related to initialization in the PopART IBM

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