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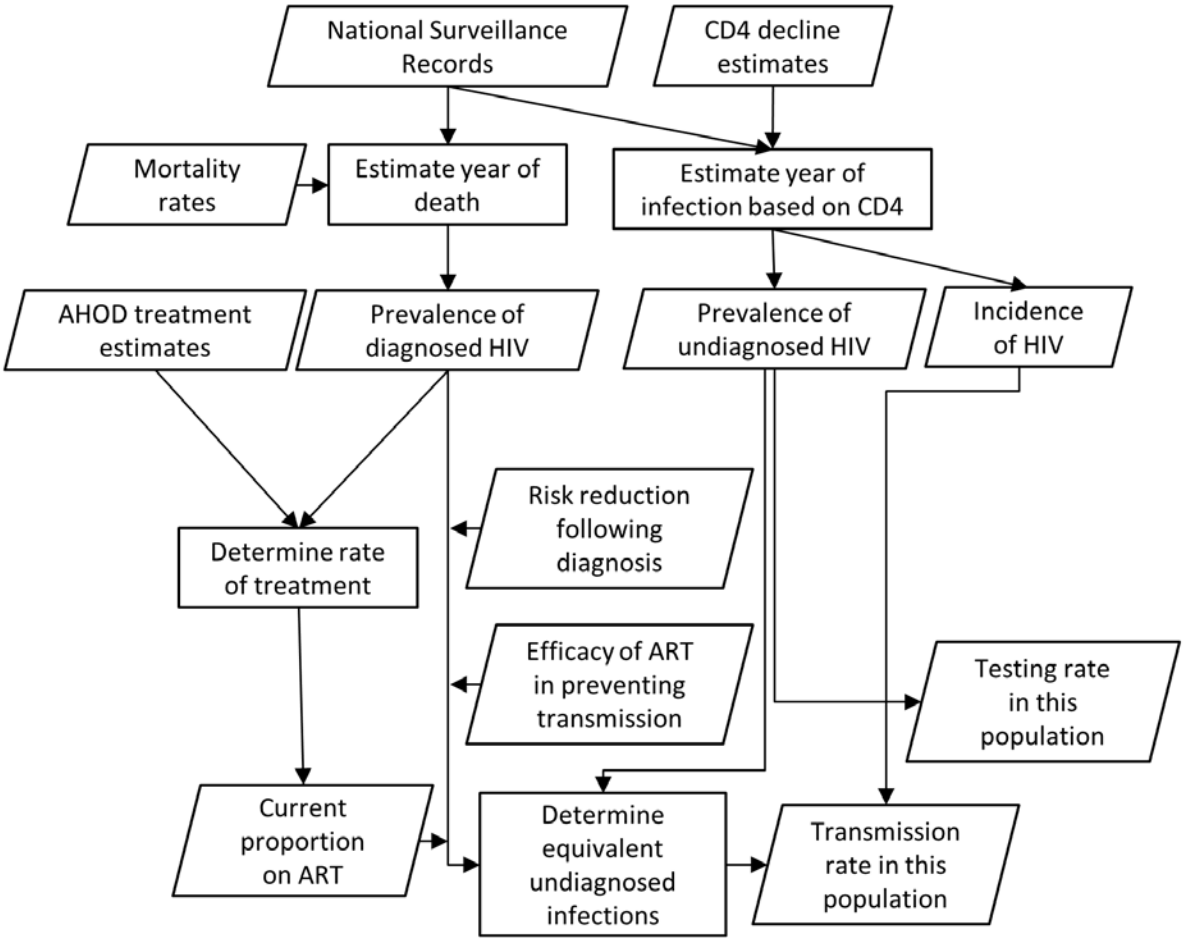
Appendix

Section 1

Establishing baseline characteristics in the model

A schematic diagram describing how the model was calibrated to baseline Australian data is shown in Figure A1. This method is described in detail below.

Figure A1: Process diagram of the establishment of baseline characteristics in the model.



Collection of data

National surveillance records of registered HIV diagnosed cases include sex, age, date of diagnosis and CD4 count at diagnosis of all 31,651 people who were diagnosed with HIV in Australia between 1980 and the end of 2011. To correct for missing data, a Markov chain Monte Carlo multiple imputation was performed over the variables of sex, age, diagnosis date, age and CD4 count to fill missing records.

AIDS progression

Progression to AIDS was calculated for diagnoses prior to 1997. Individuals were assigned viral load counts in the proportion found in Mellors et al[1]. The results of Mellors et al. were used to fit AIDS survival curves which were used to determine the time until AIDS.

Mortality calculation

Life tables from the Australian Actuary[2] and standardised mortality ratios of PLHIV in Australia[3] were used to calculate the simulated date of death of each individual in the database, and are shown in Tables A1 and A2.

Table A1: Standardised mortality ratios in people with an HIV diagnosis (no AIDS diagnosis) by year

Age range	1980-1989	1990-1996	1997 onwards
0-24	4.89 (2.9-8.26)	2.76 (1.92-3.98)	3.79 (2.39-6.01)
25-34	4.21 (3.13-5.65)	1.89 (1.63-2.19)	2.69 (2.35-3.07)
35-44	4.04 (2.97-5.51)	1.52 (1.63-2.19)	2.16 (1.96-2.38)
45-54	1.15 (0.58-2.32)	1.08 (0.89-1.31)	1.56 (1.39-1.76)
55-64	1.36 (0.65-2.86)	0.46 (0.33-0.65)	1.05 (0.89-1.24)
65+	0.83 (0.27-2.58)	0.49 (0.34-0.72)	1 (0.8-1.25)

Table A2: Standardised mortality ratios in people with an AIDS diagnosis by year

Age range	1980-1989	1990-1996	1997 onwards
0-24	310.4 (219.5-439)	78.1 (61.6-99.1)	20.0 (11.1-36.0)
25-34	256.4 (229.4-286.6)	59.9 (56.5-63.4)	14.1 (12.3-16.2)
35-44	209.5 (190.7-230.2)	46.0 (43.9-48.2)	8.12 (7.43-8.87)
45-54	95.6 (83.2-109.8)	24.9 (23.5-26.5)	4.25 (3.81-4.472)
55-64	39.7 (30.4-51.8)	9.25 (8.24-10.32)	2.43 (2.08-2.84)
65+	37.8 (26.8-53.1)	4.44 (3.6-5.47)	1.19 (0.94-1.5)

Back-projection of date of infection

To determine the incidence of HIV, it was necessary to determine an estimate for the date of infection for each individual in the model. Each individual has a record of their date of diagnosis and their CD4 count at diagnosis (or an imputed value where this does not exist).

Using the CD4 count at diagnosis and diagnosis date, as well as estimates of CD4 count prior to infection[4-20], CD4 decline following infection [21] and, CD4 stochasticity[22], we produced multiple back-projected estimates the date of diagnosis for all individuals.

The first step of this calculation is to determine what would happen to a theoretical population of people who are infected with HIV. We re-created the distributions of the populations in a number of publications[4-20], weighted the samples according to population size, then combined all the populations together into a single distribution. The median CD4 of this combined population was 892 (95% CI 455-1718)

Primary HIV infection in the model lead to a decrease in CD4 count to a median nadir of 418, followed by a rebound to a median of 756 [23]. Based on a median of 892 from the weighted average above, the fractional decline to the lowest CD4 point of the primary infection was calculated to be 46.9% of the median healthy CD4 and occurred in the first time step ($1/10^{th}$ of a year). The peak of the rebound in CD4 was calculated to be 84.8% of the healthy CD4 count and occurred in the second time step ($2/10^{th}$ of a year). We applied these fractional declines to the uninfected distribution to give a distribution of CD4 counts at the 2 stages of primary HIV infection.

From the second time step onwards, CD4 counts declined at a rate proportional to the square root of their CD4 count (a decrease of -2.418 (95% CI -2.887 to -1.948) per year in the square root of the CD4 count)[21].

It was assumed that CD4 counts had a high level of variability. Malone et al. [22] calculated that daily variability in CD4 count was 62.3 cells/μL (s.d. 30.5). The mean of the CD4 counts in this study was 409 cells/μL. Hence the median variability in CD4 was estimated to be 15.2% (s.d 7.45%). This variability was then applied to the smooth declines in CD4 count calculated in previous steps.

At this stage, we have a trajectory of all people who are infected with HIV and are never diagnosed. The next stage is to determine at what point they are tested and hence diagnosed with HIV. In our model, people are tested at a constant rate in time, however testing increases as CD4 decreases. The testing probability per step is of the form

$$P = A_1 + A_2\, e^{-(A_3 C)},$$

where C is the CD4 count of each individual at each time step, and A_1, A_2, and A_3 are parameters that are fit such that the distribution of the CD4 at diagnosis of the ideal population matches the CD4 at diagnosis of the population in the real data set.

Once these values are optimised, we have a set of theoretical CD4s attached to corresponding theoretical times until diagnosis. By selecting theoretical CD4 counts that are similar to the real CD4 counts in our data set, we can produce a distribution of likely times between infection and diagnosis, and hence a distribution of the expected dates at which infection likely occurred.

Calculation of incidence, undiagnosed infected and diagnosed infected

The above calculations and the original data set have provided the date of diagnosis, the date of infection and the date of death for all individuals. Using this information we could calculate the number of new infections per time step, the total number of diagnosed cases of HIV and the total number of undiagnosed cases of HIV.

Calculation of treatment rates

The treatment rate was determined by comparing the estimates of the size of the currently living HIV-infected population with the estimates of the total number of people on ART[24], as shown in Table A3.

Table A3: Number of people on ART in each year.

Year	Estimated number of patients prescribed antiretroviral therapy (by end of year)	Sourced from AHOD annual report
1996	5617	2001
1997	6087	2002
1998	6099	2004
1999	6082	2004
2000	6413	2005
2001	6113	2010
2002	6440	2010
2003	7173	2010
2004	7,598	2012
2005	8,453	2012
2006	9,463	2012
2007	9,933	2012
2008	10,596	2012
2009	11120	2012
2010	11523	2012

2011	11920	Linearly projected value
2012	12317	Linearly projected value

Treatment was assigned at random to those who were currently diagnosed to maintain the level of treatment observed in the data.

The average rate of treatment in 2012 was calculated by dividing the estimated number of treated in 2012 by the estimated number of people living with diagnosed HIV. This was used as the baseline rate for treatment at all point in the future, and was calculated to be 49.5% on average.

Calculation of infectivity

To determine the probability of infectivity in the population, we calculated the number of 'equivalent undiagnosed infections' (EUI) in each time step.

In the model, an HIV diagnosis results in a reduction in the risk behaviour of the individual. We sampled uniformly between 0.5 and 0.8 to provide what we consider a reasonable estimate of and uncertainty in the reduction in risk behaviours following HIV diagnosis in Australia based on established studies[25-29]. This means that the contribution of a diagnosed but untreated individual to the infected pool was weighted as 0.5-0.8 (median 0.65) of a person who is infected but undiagnosed.

We used the HTPN 052 estimates[30] for risk reduction (96% [95% CI: 74%-99%]) in the model, as the proportion of people with undetectable viral load in the study (89%) matched closely to the proportion of people in Australia who have undetectable viral load (87%-90%)[31]. The confidence intervals of the HTPN 052 were used to estimate uncertainty in the model. This means that the contribution of a diagnosed and treated individual to the infected pool was weighted as (1-0.96) x (1-0.65) = 0.014 of a person who is infected but undiagnosed where no risk compensation occurs, or (1-0.96) = 0.04 of a person who is infected but undiagnosed where 100% risk compensation occurs.

Calculating the size of the EUI population allowed us to determine the probability with which current infections generate new infections. The number of new infections at each time step over the period 2007-2011(calculated earlier) was divided by the total number of EUI to determine the number of new infections per EUI.

The above model was run 200 times, sampling across the uncertainty in the estimates of each parameter.

Calculation of baseline testing probability

The probability at which individuals are tested for HIV infection was re-calculated as the required per-step probability of testing multiplied by the current number of undiagnosed PLHIV to produce the observed number of diagnoses.

Previously diagnosed overseas cases

Australia collects records of all notifications of HIV, include a number which are previously diagnosed overseas. In our model, PLHIV who have been previously diagnosed overseas were assumed to not be responsible for any transmissions prior to their appearance in the surveillance database. However, following the date of entry into the database, PLHIV with a previous overseas diagnosis were assumed to contribute to the transmission of HIV, as would any other person with a diagnosed HIV infection in the model.

Forward simulation of interventions

The baseline values for the future were established by running the model without any adjustment of any of the parameters. The model was then run using a range of treatment and testing scenarios whose ultimate impact was to vary the number and proportion of people who are undiagnosed, diagnosed untreated, and diagnosed treatment, and hence change the infectivity of the population as a whole.

Testing rates in the model

The best-fitting model testing rates may appear to be quite low but these represent population rates. For example, of the estimated 3148 locally originated undiagnosed infections, 856 are diagnosed within one year, or 26%. However, at an individual-level, it is estimated that ~35% of PLHIV are diagnosed with their HIV infection in the first year. The reason for this discrepancy occurs because time until diagnosis is not an exponential plot; it is much steeper initially, because testing rates are not constant in time.

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