

Projected life expectancy of people with HIV according to timing of diagnosis

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Background: Effective antiretroviral therapy (ART) has contributed greatly towards survival for people with HIV, yet many remain undiagnosed until very late. Our aims were to estimate the life expectancy of an HIV-infected MSM (men-who-have-sex-with-men) living in a developed country with extensive access to ART and healthcare, and to assess the effect of late diagnosis on life expectancy.

Methods: A stochastic computer simulation model of HIV infection and the effect of ART was used to estimate life expectancy and determine the distribution of potential lifetime outcomes of an MSM who becomes HIV positive in 2010 aged 30 years. The effect of altering the diagnosis rate was investigated.

Results: Assuming a high rate of HIV diagnosis (median CD4 count at diagnosis: 432 cells/mm³), projected median age at death (life expectancy) was 75.0 years. Therefore, 7.0 years of life were lost on average due to HIV; comparable to the effect of cigarette smoking. Cumulative risks of death by five and ten years after infection were 2.3% and 5.2%. The 95% uncertainty bound for life expectancy was (68.0,77.3) years. When a low diagnosis rate was assumed (diagnosis only when symptomatic; median CD4 count 140 cells/mm³), life expectancy was 71.5 years, implying an average 10.5 years of life lost due to HIV.

Conclusions: If low rates of virologic failure observed in treated patients continue, predicted life expectancy is relatively high in people with HIV who can access a wide range of antiretrovirals. The greatest risk of excess mortality is due to delays in HIV diagnosis.

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Introduction

Since the introduction of potent antiretroviral therapy (ART), the prognosis of people living with HIV has improved dramatically [1]. HIV is no longer considered a fatal disease, but one that can be controlled, provided good adherence to antiretroviral drugs can be maintained over the long term [2,3]. This leads us to ask how long

people currently infected with HIV can be expected to live. Most studies to date which have estimated life expectancy have projected current death rates in people with HIV [4–7]. However, this approach does not fully take into account that positive effects of therapy on death rates take years to be fully realised due to the slow increase in CD4 counts and that drugs have improved over time in their ability to induce and maintain viral suppression [8–

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10]. Consequently, life expectancy of HIV-positive people is likely to have been underestimated.

One factor that may increase mortality is late diagnosis of HIV [11], yet there are still many people who present for care at an advanced stage of infection. Calculating life expectancy of people with HIV allows us to quantify the improvement in prognosis and to also develop an understanding of the benefits of preventing and testing for HIV and the possible impact of delays in diagnosis. Incorporating current estimates of rates of virologic response to ART and subsequent long term increases in CD4 count relies on building a model that captures the processes underlying HIV progression and the effect of ART and then using this to predict the range of courses of infection and treatment over a long time period. This has been done for the United States for example, based on a model that predicted an average 24 year survival after entry into healthcare [12]. However, this estimate is now known to be too low, as since then, extensive data from routine clinic cohorts have provided increasingly robust estimates of long-term viral suppression rates [13–16].

We have previously developed a stochastic computer simulation model of HIV progression (HIV Synthesis) and used it to reconstruct the HIV-infected population in the UK and to predict future trends in key outcomes [13,17]. The aims of this study were to use this model to predict the course of infection of men-who-have-sex-with-men (MSM) who were infected with HIV in 2010, assuming that current standards of care are maintained, and to consider the effect of delays in diagnosis of HIV on life expectancy.

Methods

The HIV Synthesis model and its fit to various aspects of HIV progression and therapy outcomes have been described previously [13,17] and are shown in detail in the Supplementary Material. In brief, it is an individual-based stochastic model that generates data on the progression of HIV infection and effect of ART on simulated patients. Variables updated every three months include calendar date, age, viral load, CD4 count, clinical events, use of specific drugs, resistance and adherence. The effects of ART (on viral load, CD4 count and risk of resistance emergence) in any three month period depend on the current number of active drugs in the regimen, viral load and adherence level. If new resistance mutations arise, these lead to a reduction in the number of active drugs in the regimen and in turn, virologic failure of the regimen becomes more likely.

In our model, we considered the scenario of a 30 year old MSM infected in 2010 with drug-sensitive virus, followed over 80 years (to 2090) or until death. We

considered MSM because for people in other prevention groups, there may be other factors besides HIV itself which are associated with lower life expectancy. Outcomes were simulated for 10,000 men in this situation, resulting in a distribution of possible outcomes for such a person. We assumed that all individuals are never lost to follow-up at any stage in their lifetime. A relatively high rate of HIV diagnosis was assumed (4.5% chance of diagnosis in any three month period), given that the observed CD4 count at diagnosis for MSM in 2009 was 410.5 cells/mm³ [18]. It was assumed that the man has no hepatitis co-infections, and has a 40% chance of being a smoker for life. Smokers were assumed to carry a mortality risk which was 1.4-fold of that found in the general population, and non-smokers 0.7-fold (consistent with a two-fold increase in all-cause mortality associated with smoking [19]). We assumed most patients started on an NNRTI-based regimen, and a boosted PI-based regimen was then used if virologic failure occurred. Newer drugs such as raltegravir and maraviroc (used in absence of X4 virus) were assumed to be used only after regimens had virologically failed, or if the NNRTI and PI classes were exhausted due to toxicity. Adherence to ART was modelled such that people were assumed to have a fixed tendency to adhere, with period-to-period variability (see Supplementary Material). The tendency to adhere was correlated with the probability of treatment interruption, which was assumed to be 1.5-fold higher in those with lower adherence.

In addition, we considered the same scenario but instead assumed a much lower rate of diagnosis, such that patients were diagnosed only if symptomatic. Sensitivity analyses were performed to explore the effects on life expectancy of varying other key assumptions (e.g. rate of diagnosis and rate of interruption), as well as to comprehensively assess the robustness of the estimate of life expectancy to values of key parameters.

There is increasing evidence that people with HIV may have a raised risk of common clinical conditions such as renal, liver and cardiovascular diseases as well as non-AIDS cancers [20–25]. Data from observational studies suggest that there is a modest increase in the risk of death for HIV-positive people with CD4 count greater than 500 cells/mm³ compared to the general population; this is of the order of approximately 1.5 [26,27]. Hence, we also assumed a 1.5-fold increased risk of all non-AIDS deaths throughout life. As we used general population death rates for UK males for 2009 [28], the resulting estimates apply to MSM living in countries with similar general population death rates.

Results

Under the assumption of a high diagnosis rate, the projected median age at death (life expectancy) for the

10,000 simulated men infected at age 30 in 2010 was 75.0 years (Table 1). If they had not been infected with HIV, their life expectancy was estimated to be 82.0 years, implying 7.0 years of life lost due to HIV infection.

When a high diagnosis rate was assumed, 56.8%, 78.1% and 96.9% of men were diagnosed with HIV by three, five and ten years after infection, respectively. The median duration of time from infection to diagnosis was 2.8 years, and the median (IQR) CD4 count at diagnosis was 432 (244–593) cells/mm³ (Table 2). The mean time from infection to starting ART (assuming 98% probability of initiation at CD4 count < 350 cells/mm³) was 5.9 years. This led to individuals spending on average 39.1 years on treatment, of which all but 7.1 years were spent actually receiving ART (there was a predicted 85% chance of interrupting ART at least once). On average, 18.8 years was spent on first line regimens (97% chance that an individual starts ART in their lifetime), 7.2 years on second line (60% chance they will start second line) and 6.0 years on third line and beyond (32% chance they will start third line), where lines of therapy are based on virologic failure, not changes due to toxicity. Men were assumed over 80% adherent during 96% of the time spent on ART. In addition, there was a predicted 41% chance of at least one AIDS disease occurring before death. Amongst those projected to develop AIDS, 16% did so before or at diagnosis, a further 4% after diagnosis but without having started ART, 40% while on ART, and 40% while interrupting ART. However, only 14% of deaths were projected to be from AIDS-related illnesses. Only 10% of men estimated to die of AIDS were

predicted to have resistance to all three original drug classes and integrase inhibitors.

We also considered a scenario in which the rate of diagnosis in the absence of any HIV-related symptoms was negligibly low, such that the median CD4 count at diagnosis was 140 cells/mm³ (Table 2). Assuming this low diagnosis rate, 21.7%, 37.4% and 73.6% were diagnosed with HIV respectively, after three, five and ten years from infection. This low rate of diagnosis resulted in a higher risk of death by ten years from infection (Fig. 1; 12.6% compared to 5.2% in the high diagnosis situation) and a life expectancy of 71.5 years, i.e. 10.5 years of life lost. Figure 1 also shows results for other diagnosis rate scenarios.

The estimated cumulative probability of diagnosis by each year since HIV infection for both high and low diagnosis rate scenarios are given in Fig. 2. Likewise, the estimated probability of having various CD4 counts are also given for the two scenarios (Fig. 3), showing the extent of the CD4 count advantage at any one point in the high diagnosis rate scenario. The impact of late diagnosis on CD4 count is projected to be greatest in the first 15 years since infection. Both figures for the low diagnosis rate scenario (Figs 2b, 3b) demonstrate the considerable increase in the proportion of deaths throughout the entire time period compared to when a high diagnosis rate was assumed, representing an extended assessment of the data illustrated in Fig. 1. The proportion of deaths that are AIDS-related is also larger in the scenario with a lower rate of diagnosis.

Table 1. Estimated life expectancy (median age at death), according to diagnosis rate and scenarios.

Diagnosis rate ^a	Scenario	Life expectancy (Median age at death) ^b	IQR of age at death
High	–	75.0	(62.5, 83.3)
	10-fold increase in ART interruption in those with low tendency to adhere ^c	73.8	(60.3, 82.8)
	Rate of ART interruption reduced to 0	76.5	(65.8, 84.8)
	Men were less adherent in general ^d	73.5	(58.8, 82.8)
	0% of men smokers for life	78.0	(65.5, 86.0)
	SMR = 1.1 for CD4 > 500 cells/mm ^e	75.3	(63.0, 83.5)
	High uptake of ART following diagnosis ^e	75.0	(63.0, 83.5)
	Low uptake of ART following diagnosis ^f	75.0	(62.5, 83.5)
	Very low uptake of ART following diagnosis ^g	74.8	(62.5, 83.3)
Low	–	71.5	(51.8, 81.8)
	3-fold raised risk of AIDS-related deaths occurring at HIV diagnosis	68.0	(43.8, 80.5)
No HIV	–	82.0	(72.8, 89.3)
	0% of men smokers for life	84.8	(75.8, 91.3)
	100% of men smokers for life	77.8	(68.8, 84.8)
Very high	–	75.3	(63.5, 83.3)
Medium	–	74.5	(61.5, 83.3)

ART, antiretroviral therapy; IQR, interquartile range; SMR, standardised mortality ratio.

^aThe rate of diagnosis was altered such that the median CD4 cell counts at diagnosis were 140, 351, 432 and 509 cells/mm³ respectively for low, medium, high and very high diagnosis rates.

^bAge at death presented in years.

^ccompared to 1.5-fold in initial model.

^dwhereby they were over 80% adherent for only 57% of their time on ART and between 50–80% adherent for only 34% of the time (compared to over 80% adherent during 96% of the time spent on ART in initial model).

^e98% chance of initiation of ART if CD4 ≤ 500 cells/mm³.

^f80% chance of initiation of ART if CD4 < 350 cells/mm³ and 2% chance of initiation of ART if CD4 ≥ 350 cells/mm³.

^g50% chance of initiation of ART if CD4 ≤ 500 cells/mm³.

Table 2. Characteristics of the 10,000 simulated men-who-have-sex-with-men (MSM), according to the assumed diagnosis rates.

	Diagnosis rate	
	High	Low
Median (IQR) time from infection to diagnosis (years)	2.8 (1.0–4.8)	6.8 (3.5–10.3)
Median (IQR) CD4 count at time of diagnosis (cells/mm ³)	432 (244–593)	140 (43–307)
Median (IQR) viral load at time of diagnosis (log copies/ml)	4.4 (3.9–4.8)	4.9 (4.4–5.2)
Proportion of patients with AIDS before or at diagnosis	0.059	0.420
Probability of death before or at diagnosis (%)	1.3	9.4

IQR, interquartile range. *The rate of diagnosis was altered such that the median CD4 cell counts at diagnosis were 140 and 432 cells/mm³ respectively for low and high diagnosis rates.

In the scenarios considered above, the risk of death for a person with a given AIDS condition was assumed to be the same, regardless of whether the AIDS event occurred at diagnosis or under follow-up. We performed a sensitivity analysis to estimate the life expectancy if in the low diagnosis rate scenario, we instead assumed a three-fold raised risk of AIDS-related deaths occurring at HIV diagnosis (on the basis that delays in diagnosis can lead to more serious disease). This resulted in a life expectancy of 68.0 years (Table 1). In other sensitivity analyses, we altered the rate of ART interruption under the assumption of a high diagnosis rate. Increasing the rate by ten-fold in those with low tendency to adhere (compared to 1.5-fold in the initial model) resulted in a life expectancy of 73.8 years, whilst reducing the rate of interruption to zero (regardless of adherence level) resulted in a life expectancy of 76.5 years. Assuming a high diagnosis rate, we also altered the probability of initiation of ART. We assessed the effect of both a higher rate and lower rate of uptake than what we speculate is being observed, however both scenarios did not impact much on predicted life expectancy (Table 1).

In order to attempt to fully quantify the uncertainty associated with our life expectancy estimate, we investigated the effect of plausible variations in parameter values. A total of 10,000 runs of the model were made, each time sampling at random, values for a number of different key parameters in order to generate the distribution of life expectancy in the multivariable sensitivity analysis. The median life expectancy from this analysis was 73.8 years and the 95% uncertainty bound was (68.0,77.3) years. Further details are given in the Supplementary Material.

Discussion

We used a previously validated model of HIV infection and the effect of ART [17] to predict the life expectancy for a 30 year old MSM infected with drug-sensitive virus in 2010. The estimated life expectancy of 75.0 years assumes a 40% chance of being a smoker and no hepatitis co-infection. This compares with a life expectancy of

82.0 years had HIV infection not occurred, which is consistent with life expectancy projections in several western European countries. Hence, an average 7.0 years of life is lost due to HIV infection. This excess mortality is similar to that of other chronic illnesses such as diabetes [29]. In addition, taking a situation without HIV, we calculated that lifetime smoking reduces life expectancy from 84.8 years, as we would estimate it to be for never-smokers, to 77.8 years (i.e. 7 years loss, which is probably conservative [30]), similar to the estimated impact of HIV, providing diagnosis is early.

It was projected that a relatively high proportion (41%) will at some point in their lifetime develop an AIDS condition. This arises largely due to the fact that in our model, there is a small risk of AIDS occurring even at higher CD4 counts and because of our assumption that a high proportion of people will interrupt ART at least once. There are also rapid consequences in terms of viral load increase and CD4 count depletion in our model. Estimated life expectancy increased by 1.5 years when it was assumed that no treatment interruptions occurred. Our rates of interruption were based on observed proportions of ART-experienced people on ART [31].

In the initial model, we assumed a high rate of diagnosis, consistent with that currently observed in data on MSM in the UK [18]. When we instead assumed a much lower rate of diagnosis (such that the CD4 count at diagnosis was 140 cells/mm³ instead of 432 cells/mm³), this increased the death rate within ten years from diagnosis, but the effect on life expectancy after this period was more modest. This is due to the durable effects of ART, even in those who start ART when their CD4 count is low [32,33]. However, late diagnoses can and should be prevented by increased access and uptake of HIV testing. Figure 1 emphasises the importance of early diagnosis and the substantial difference it makes to the death rates, especially in the first 20 years after infection. Furthermore, under the assumption of a low diagnosis rate, we estimated that 42% would present with AIDS at diagnosis (Table 2). Late diagnoses not only reduce the life expectancy of the HIV-positive person, but also impact on the probability of onward transmission because treatment, which reduces infectivity, is also delayed.

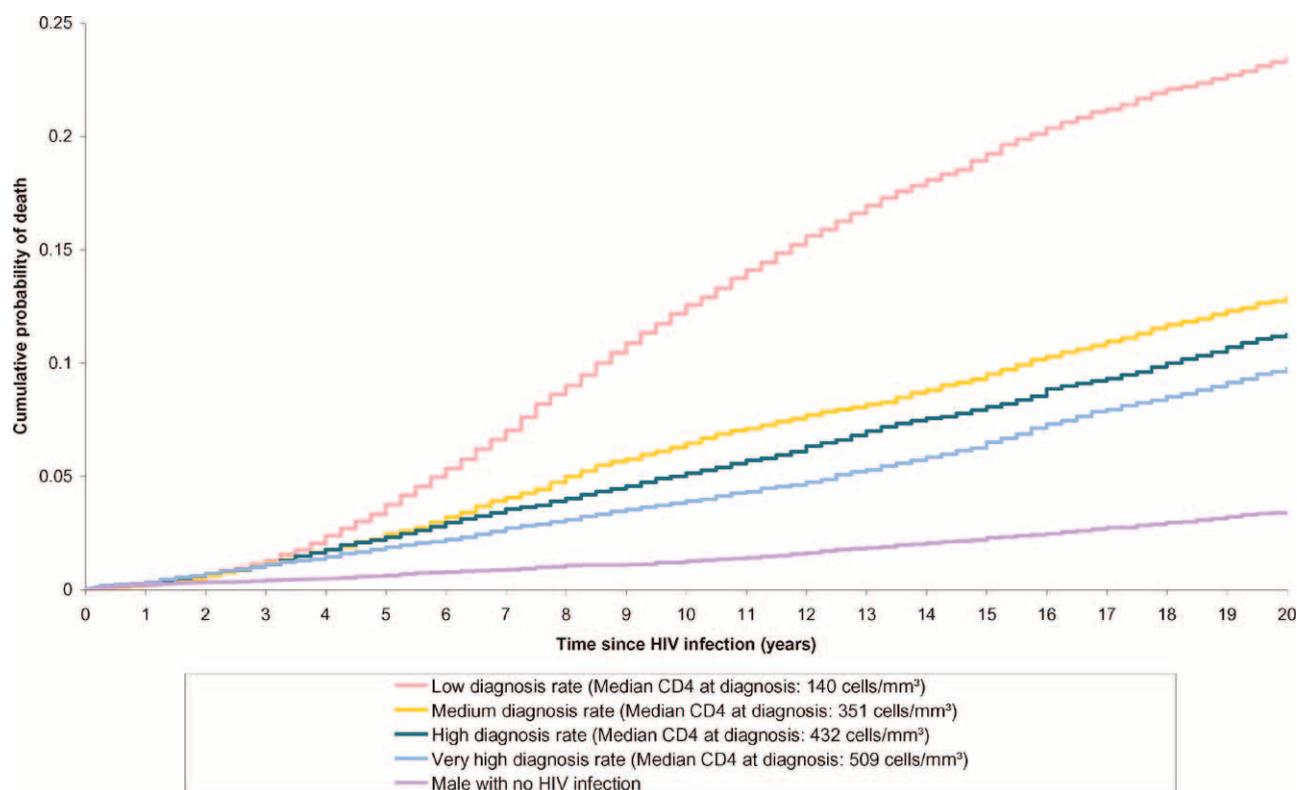


Fig. 1. Kaplan-Meier plots of time to death (all-cause mortality) from HIV infection by HIV diagnosis rate, and for people without HIV.

We did not assume an increased risk of death associated with the use of any specific antiretrovirals. Despite evidence that some drugs lead to an increased risk of myocardial infarction and possible impairment of liver and kidney functions [21,34–38], we assumed that the direct effect of antiretrovirals on mortality would be minimal, since drugs with severe adverse effects would probably not be used from 2010 due to the considerable choice of drugs available. However, we did assume a lifelong 1.5-fold increased risk of non-AIDS deaths compared with the general population, due to presence of HIV infection *per se*. Bearing in mind that most people are predicted to have viral suppression and high CD4 counts for most of their lives, this may well be a pessimistic assumption, resulting in underestimation of life expectancy.

Since our model takes into account the predicted durability of ART (using estimates of virologic failure and resistance emergence rates [32,39–41]), our approach to estimating life expectancy differs from that employed in analyses of cohort studies which have been based on the assumption that current death rates will remain unchanged [4,6,7]. The fact that risks appear to decrease as the CD4 count is increased with more durable viral load suppression means that such an assumption is also likely to be pessimistic [21]. Another key difference with some previous assessments is that we started on the

basis of a person being infected with HIV in 2010, rather than a person with HIV presenting for healthcare in 2010.

Our projected life expectancy after entry into healthcare (median 41.5 years) is much longer than the value of 24.2 years generated from the model used by Schackman *et al* [12] and values generated by many others [42–45]. It is also higher than those calculated from both cohort data and surveillance data in recent years; Lohse *et al* [4] calculated median survival to be 38.9 years among patients with HIV from age 25 years without hepatitis co-infection in the Danish HIV Cohort Study, whilst Harrison *et al* (5) estimated an average 22.5 years of survival after diagnosis in 2005 using US surveillance data. It is likely that this difference in life expectancy is partially due to the fact that data emerging from treated patient cohorts in recent years have shown still increasing prevalence of viral load suppression in treated patients and continuing very low rates of virologic failure in patients with viral suppression and increased regimen stability [13,14,46,47]. Walensky *et al.* [48] observed an increasing trend in life expectancy with growing numbers of antiretrovirals and increasing potency and tolerability. The higher life expectancy estimated by our model could also be explained by the fact that patients are assumed to start ART with combination therapy and because we also assumed that hepatitis co-infection is not present, nor are drugs injected. In fact, it has been estimated recently that

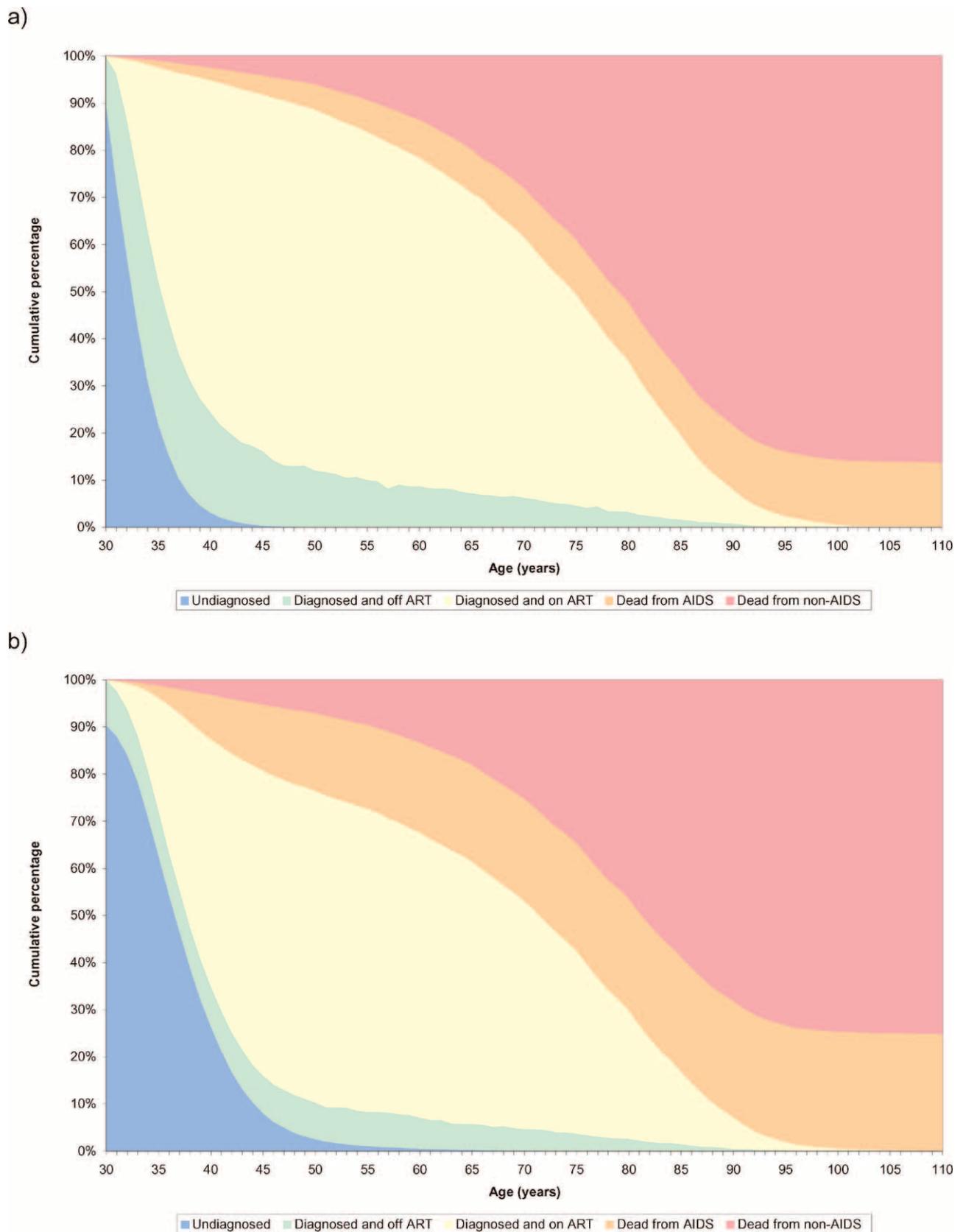


Fig. 2. Projected range of outcomes in terms of mortality and diagnosis status for 30 year old MSM infected in 2010. (a) Projected range of outcomes under the assumption of a high rate of diagnosis over 70 years. (b) Projected range of outcomes under the assumption of a low rate of diagnosis over 70 years. The rate of diagnosis was altered such that the median CD4 cell counts at diagnosis were 140 and 432 cells/mm³ respectively for low and high diagnosis rates. A table of the actual numbers used to generate these figures can be found in the Supplementary materials.

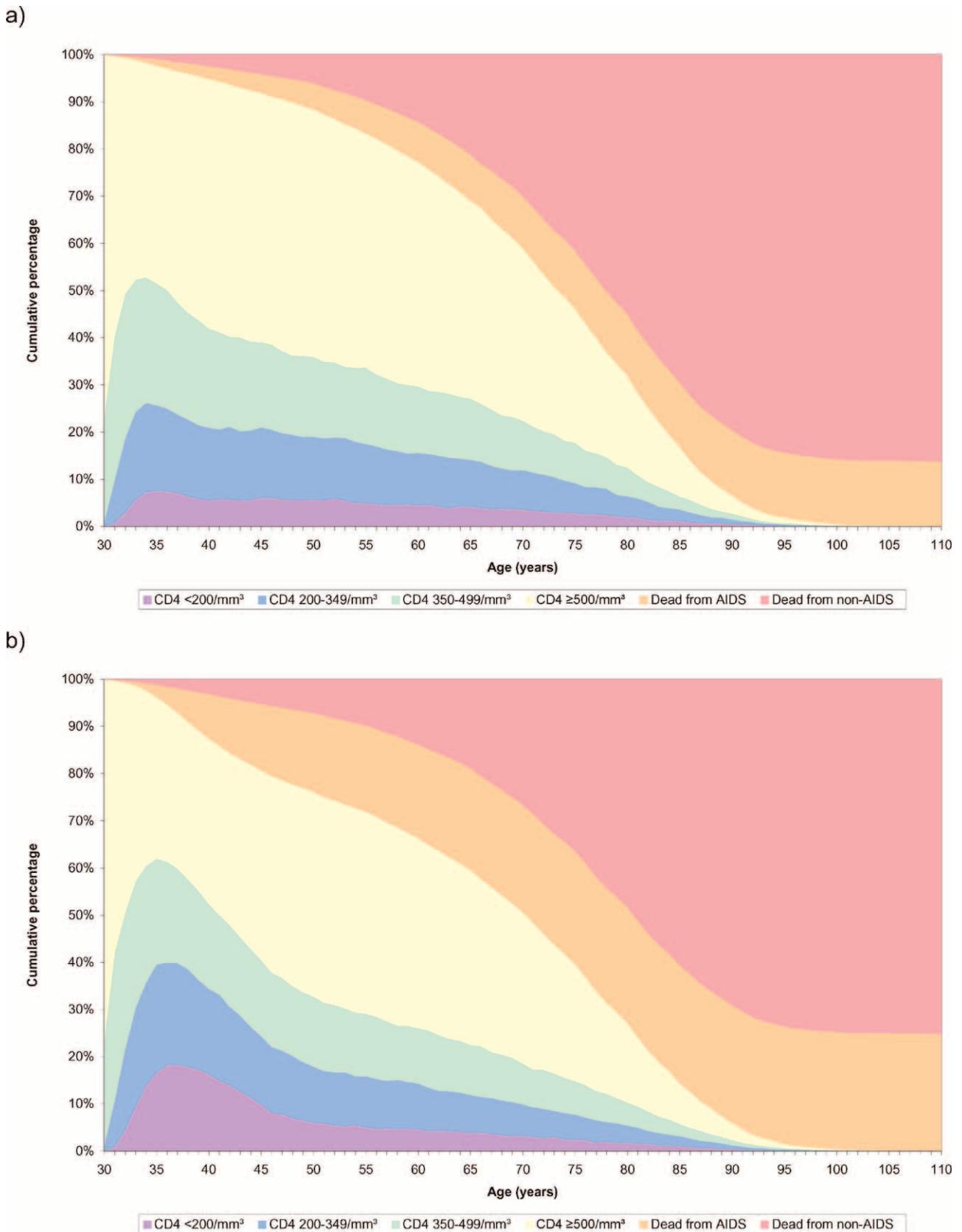


Fig. 3. Projected range of outcomes in terms of mortality status and CD4 cell counts for 30 year old MSM infected in 2010. (a) Projected range of outcomes under the assumption of a high rate of diagnosis over 70 years. (b) Projected range of outcomes under the assumption of a low rate of diagnosis over 70 years. The rate of diagnosis was altered such that the median CD4 cell counts at diagnosis were 140 and 432 cells/mm³ respectively for low and high diagnosis rates. A table of the actual numbers used to generate these figures can be found in the Supplementary materials.

asymptomatic treatment-naïve patients have near-normal life expectancy, based on their current death rates [7]. Our life-expectancy estimate is also somewhat higher than that found in a study by the ART-CC [6], which estimated that survival for a person age 20 initiating combination ART was 49.4 years, although the life expectancy of 69.4 years is within our uncertainty bounds of (68.0,77.3).

There are several limitations that should be considered. The main limitations relate to those inherent in modelling a process and then using that model to predict many years into the future. Our model has been shown to encapsulate the main features of HIV progression and the effect of ART as they are currently understood fairly closely ([13,17] and Supplementary Material). However, any model is at best an approximation to the truth and the effects of any model misspecification could be amplified due to the extremely long simulation period. We also make several assumptions in the model in order to make these projections. We assume that testing and treatment guidelines and the current standard of care will remain as they are now and we do not incorporate changes which may happen in the future. We assume that all-cause death rates will remain fixed at 2009 levels, instead of assuming that the current downward trend will continue [28]. We also assume that adherence to ART will remain stable over time and not decline. There is some recent evidence that this is the case for over ten years [49], but only time will tell whether this is the case for the 40–50 years that will be required by many. In addition as discussed above, we take no account of any increased risk of death associated with some antiretroviral drugs. With currently available drugs, such risks are likely to be small, but in the future as more data on the long-term effects of drugs become available, it will be possible to refine and update our model, incorporating new drugs and resistance mutations. We did not estimate life expectancy for females, which would require using death rates amongst females in the UK. However, as a large proportion of HIV-positive females living in the UK are not originally from the country (whereas a large proportion of MSM are), it is uncertain whether those rates apply. Finally, our estimates at this stage do not apply to people with hepatitis co-infection.

In summary, based on continuing low rates of virologic failure in treated patients, predicted life expectancy in people with HIV is high in settings with access to multiple antiretroviral drugs. Delays in diagnosis pose the greatest risk of excess mortality for people with HIV. Despite recent progress in the testing, treatment and care of HIV infected patients, there is still room for improvement such that life expectancy reaches the same as that of the non-infected population.

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FN and ANP were involved in model programming. ANP and JDL helped develop the original model. FN drafted the manuscript. All authors were involved in the conception of the paper, interpretation of results, critical revisions of the paper and approved the final version.

Conflicts of interest

None declared.

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