Can Australia reach the World Health Organization Hepatitis C elimination goal by 2025 among HIV-positive gay and bisexual men?

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Summary: HCV incidence among Australia's HIV-positive GBM population is likely to decline sharply with DAA use, even with increases in risk behavior. Our model suggests reaching the WHO HCV elimination target ahead of time among this population is achievable.

ABSTRACT

Background: HIV-positive gay and bisexual men (GBM) in Australia are well engaged in clinical care. We hypothesized that the World Health Organization's hepatitis C virus (HCV) elimination target of an 80% reduction in incidence by 2030 may be reachable ahead of time in this population.

Methods: We predicted the effect of treatment and behavioral changes on HCV incidence among HIV-positive GBM up to 2025 using a HCV transmission model parameterized with Australian data. We assessed the impact of changes in behavior that may facilitate HCV transmission in the context of different rates of direct-acting antiviral (DAA) use.

Results: HCV incidence in our model increased from 0.7 per 100 person years in 2000 to 2.5 per 100 person years in 2016, and had the same trajectory as previously reported clinical data. If the proportion of eligible (HCV RNA positive) patients using DAAs stays at 65%/year between 2016-2025, with high-risk sexual behavior and injecting drug use remaining at current levels, HCV incidence would drop to 0.4 per 100 person years (85% decline from 2016). In the same treatment scenario but with substantial increases in risk behavior, HCV incidence would drop to 0.6 per 100 person years (76% decline from 2016). If the proportion of eligible patients using DAAs dropped from 65%/year in 2016 to 20%/year in 2025 and risk behavior did not change, HCV incidence would drop to 0.7 per 100 person years (70% reduction from 2016).

Conclusions: Reaching the World Health Organization HCV elimination target by 2025 among HIV-positive GBM in Australia is achievable.

Keywords: Hepatitis C virus; HIV; gay and bisexual men; Australia

INTRODUCTION

Hepatitis C virus (HCV) is a major contributor to morbidity and mortality in people with HIV.[1-3] In Australia, which has one of the highest rates of HCV screening globally,[4] it is estimated that around 3,000 individuals are HIV/HCV co-infected.[4, 5] Recently, HCV incidence has increased among Australia's population of HIV-infected gay and bisexual men (GBM).[6] This increase was mirrored by an increase in injecting drug use (IDU) [6, 7] and may also be associated with an increase in high-risk sexual behaviors such as fisting, use of recreational drugs, and group sex.[8, 9]

Direct-acting antiviral agents (DAAs), which rapidly reduce HCV viral load and achieve high cure rates, offer an unprecedented opportunity to prevent transmission. Their introduction has led the World Health Organization (WHO) to set the ambitious target of achieving an 80% reduction in global HCV incidence by 2030.[10] In Australia, the first DAAs became available under government subsidy to all HCV-infected adults in March 2016.[11] With rapid upscale of DAAs, we hypothesize that it may be possible to meet the WHOs HCV elimination target ahead of time in Australia's population of HIV-positive GBM as this group is well engaged in clinical care. Importantly however, changes in the rate of high-risk sexual practices and IDU could jeopardize the anticipated benefits of DAAs.[9]

We developed a mathematical model of HCV transmission among HIV-positive GBM in Australia to investigate the extent of DAA treatment uptake required to reach the WHO target in this population by 2025 and identify behavioral changes that could compromise this outcome.

METHODS

HCV incidence and prevalence

HCV incidence among Australia's HIV-positive GBM population was estimated by sub-analysis of recent work on the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) project.[6] ACCESS is a HIV/sexually transmitted infection sentinel surveillance network of sexual health clinics, general practice clinics, infectious disease hospital outpatient clinics, community-run health services, and pathology laboratories.[12] In the original analysis, demographic, behavioral, and clinical data were extracted from the patient management systems of 42 sexual health services for patients who attended between 2007 and 2015. In Australia, sexual health services frequently manage the care of GBM and people living with HIV. The ACCESS sexual health services network is broadly representative of sexual health services across the country. Rates of HCV testing among people living with HIV increased between 2007-2015. However, the most notable increase in testing rates occurred between 2013-2015 when HCV incidence plateaued. This indicates that the current rate of testing is picking up most incident HCV infections.

The past prevalence of active HCV infection among Australia's HIV-positive GBM population (with and without a history of IDU) was estimated from the HIV, viral hepatitis and sexually transmissible infections Annual Surveillance Report [13, 14] and the Australian HIV Observational Database.[5] Thereafter it was projected by our HCV transmission model.

HCV transmission model

We adopted a system of ordinary differential equations to model HCV transmission among HIV-infected GBM (see Supplementary Material - System of ordinary differential equations). This was based on the model previously developed by Salazar-Vizcaya *et al* [9] for the Swiss GBM population with the addition of IDU as a means of HCV transmission. We adapted the Swiss model to reflect HCV transmission dynamics and risk-taking behavior among Australian HIV-positive GBM.

Supplementary Figure 1 summarizes the model structure. The population was classified into compartments distributed by stage of infection, risk group and enrollment in care. Risk groups included: 1) individuals who do not engage in high-risk sexual practices associated with HCV transmission and do not inject drugs; 2) individuals who do not engage in high-risk sexual practices associated with HCV transmission but do inject drugs; 3) individuals who do engage in high-risk sexual practices associated with HCV transmission but do not inject drugs; and 4) individuals who do engage in high-risk sexual practices associated with HCV transmission and do inject drugs. Each risk group included five compartments: 1) two HCV uninfected (susceptible) in and out of HIV care; 2) two HCV-infected in and out of care; and 3) one on HCV treatment only accessible for individuals in care. HCV infection could occur through sexual practices, drug injection within sexual contexts or outside sexual contexts. The model assumed that the incidence of HCV infections acquired through drug injection outside sexual contexts (εIDU) reflects HCV incidence in the general population of injecting drug users. The main analysis assumed that rollout of DAAs will be successful and result in a 90% reduction in this incidence. Our sensitivity analyses assessed this assumption. HCV could also be acquired in all risk groups by means of an external force of infection independent of risk behavior. GBM could transition

between risk groups. Testing rates were not explicitly included in the model but were assumed consistent with those that led to the incidence rate reported in Boettiger *et al*.[6] Treatment rates in the model reflect transitions from infection to treatment start, and therefore time to HCV diagnosis and treatment delay. Individuals who cleared HCV infection were considered susceptible.

Model parameterization and calibration

Model parameters were estimated using the Australian HIV Observational Database,[5] the Australian Gay Community Periodic Surveys,[7, 15] the Australian Needle and Syringe Surveys,[16] or from other published literature (Supplementary Table 1). Rates of transition to sexual practices associated with HCV transmission, IDU, and enrolment in HIV care were set to reproduce data on the frequency of such practices and coverage of antiretroviral therapy, as well as the fraction of GBM injecting who did this within sexual contexts. The infection rate through sexual practices (β_{sex}), the prevalence of active HCV infection among GBM who did and did not inject drugs in the year 2000, and the baseline transition rate to IDU were fitted to HCV incidence between 2007 and 2015, and the prevalence of HCV antibodies in 2007 (4.7% for non-IDU and 32.5% for IDU [5, 13]) by comparing these data with model outcomes for the HIV diagnosed population. The model fit was obtained by minimizing the sums of squared distances between model outputs and data points. These distances were calculated as the differences between modelled and observed values weighted to reflect measurement errors in the data. The infection rate through IDU (β_{idu}) in the context of sex parties was estimated by assuming that, at the beginning of the simulation, the incidence of HCV in GBM engaging in this practice equaled that in HIV-positive GBM engaging in IDU outside the context of sex parties.

Between 2007 and 2015, the number of HCV RNA negative GBM newly diagnosed with HIV ranged between 610 to 809/year.[4] The proportion of HIV-positive GBM using antiretroviral therapy, our proxy for being engaged in care, increased from 60.3% in 2005 to 86.5% in 2015 (Figure 1A).[4, 7, 8] The percentage of HIV-positive GBM injecting drugs after HIV diagnosis was estimated to increase from 13.9% in 2010 to 17.9% in 2015 (Figure 1B).[7] The proportion of individuals engaging in condomless anal intercourse (CLAI) with casual partners after HIV diagnosis increased from 41.4% in 2005 to 51.7% in 2015 (Figure 1C).[8, 17] Among those engaging in CLAI with casual partners, 65% were assumed to be engaging in high-risk sexual behavior though this value was varied in our sensitivity analyses. This assumption was based on the proportion of HIV-positive GBM included in the 2011 Sydney Gay Community Periodic Survey who reported CLAI with casual partners in the past 6 months and either recent fisting, recent group sex, recent use of party drugs for sex, or any combination of the three.[18] The percentage of IDU taking place in the context of high-risk sex was estimated to be 90% between 2007-2016 (Figure 1D).[7]

The percentage of individuals treated for HCV between 2007-2015 was assumed to vary between 13.6% and 27.3% among non-injecting HIV/HCV co-infected GBM, and between 7.1% and 17.6% among injecting HIV/HCV co-infected GBM.[19] Treatment success in the interferon era was greater for HCV genotypes 2 and 3 (69.0%) compared with genotypes 1 and 4 (32.4%).[19] The exit rates for non-injecting HIV-positive GBM (3.7 per 100 person years) and injecting HIV-positive GBM (5.7 per 100 person years) were based on the number of individuals who died or were lost to follow-up in the Australian HIV Observational Database.[5]

Model scenarios

We projected future HCV incidence and prevalence of active HCV infection based on a range of hypothetical changes in IDU, high-risk sexual behavior, and rates of DAA treatment uptake. Incidence and prevalence contour plots explored the consequences of changes in risk behavior under three different treatment scenarios. These were: 1) 65% of eligible (HCV RNA positive) patients/year start a DAA regimen (based on data from the Control and Elimination within Australia of Hepatitis C from people living with HIV (CEASE) study [20]) increasing exponentially to 100% of eligible patients/year by 2025; 2) 65% of eligible patients start a DAA regimen every year between 2016 and 2025; and 3) 65% of eligible patients/year start a DAA regimen decreasing exponentially to 20% of eligible patients/year by 2025. Treatment with DAAs was assumed to last 3 months on average and to result in 95% sustained virologic response, independent of HCV genotype.[21-24]

Uncertainty analyses were performed by sampling combinations of the fitted parameters and iteratively solving the equations for all scenarios. Outcomes were reported as a 95% range around the median of these model solutions.

Sensitivity analyses

The high-risk sex/CLAI with casual partners ratio used in the main analyses (0.65, Supplementary Table 1) may not accurately reflect reality as the available data suggested a wide range of possible values for this parameter. We therefore performed further model fits and projections for all scenarios, where this ratio varied between 0.5 and 0.8.

Since the scale-up of DAAs is ongoing for HCV-infected persons who inject drugs in Australia, and the model assumes that HIV-positive GBM who inject drugs outside the context of high-risk sex could become infected with HCV via contact with this population, we assumed reductions in HCV incidence in the general population of injecting drug users of 90% (main analysis), 50% and 10%.

Software

Statistical analyses were performed with Stata 14 (Stata Corp., College Station, Texas). All algorithms were implemented in R [25], using the deSolve package [26, 27] for solving the differential equations, the optim package [28] for model fitting, and the FME package [29] for sampling model parameters to produce uncertainty estimates.

RESULTS

HCV incidence in our model increased from 0.7 (95%CI 0.5-0.8) per 100 person years in 2000 to 2.5 (95%CI 1.4-3.5) per 100 person years in 2016. The model accurately represented previously reported clinical data (Figure 1E).[6] The prevalence of active HCV infection in 2016 was estimated to be 15.4% (95%CI 10.1-21.7).

High treatment uptake scenario: DAA regimen used by 65%/year of eligible individuals in 2016 increasing to 100%/year by 2025

Figures 2 shows the projected changes in HCV incidence and prevalence of active HCV infection with differing levels of behavior change in the high treatment uptake scenario. If the proportions of HIV/HCV co-infected GBM engaging in high-risk sex and IDU remained at current levels, the

continued upscale of DAA use would cause HCV incidence to drop to 0.3 (95% range 0.3-0.4) per 100 person years by 2025 (an 88% reduction from 2016) and the prevalence of active HCV infection to 0.6% (95% range 0.5-0.8); this is illustrated in Figure 3A and Figure 4. Figure 3B show that with substantial increases in the proportions engaged in high-risk sex and IDU (both increasing to 80%), the upscale of DAA use would lead to HCV incidence dropping to 0.4 (95% range 0.4-0.6) per 100 person years by 2025 (an 82% reduction from 2016; Figure 4) and the prevalence of active HCV infection dropping to 0.8% (95% range 0.6-1.1). Importantly, changes in the proportion engaging in IDU had a bigger impact on HCV incidence and active HCV infection prevalence than changes in the proportion engaging in high-risk sex as illustrated in Figure 2 by the more dramatic changes along the x-axes than the y-axes. This was consistent across all three scenarios.

Stable treatment uptake scenario: DAA regimen used by 65%/year of eligible individuals in 2016 remaining stable to 2025

With rates of high-risk sex, IDU and DAA use remaining at current levels, HCV incidence would drop to 0.4 (95% range 0.3-0.5) per 100 person years (85% reduction from 2016; Figure 4) and the prevalence of active HCV infection would decline to 0.9% (95% range 0.7-1.3; Figures 2 and 3A). If rates of high-risk sex and IDU were both to increase substantially while DAA use remained stable, HCV incidence and active HCV infection prevalence would drop to 0.6 (95% range 0.5-0.8) per 100 person years (76% reduction from 2016; Figure 4) and 1.2% (95% range 0.9-1.9), respectively (Figures 2 and 3B).

Low treatment uptake scenario: DAA regimen used by 65%/year of eligible individuals in 2016 decreasing to 20%/year by 2025

In the low treatment uptake scenario, it was estimated that by 2025 HCV incidence would drop to 0.7 (95% range 0.4-1.3) per 100 person years (70% reduction from 2016; Figure 4) and the prevalence of active HCV infection would fall to 2.6% (95% range 1.6-4.3) if high-risk sexual behavior and IDU did not change (Figures 2 and 3A). If the proportion engaged in high-risk sex reached 80% by 2025 and the proportion engaged in IDU reached 80% over the same period, HCV incidence would drop to 1.5 (95% range 0.7-2.6) per 100 person years (38% reduction from 2016; Figure 4) and active HCV infection prevalence would be 3.8% (95% range 2.1-6.5) (Figures 2 and 3B).

Sensitivity Analyses

Figure 5 shows that the reductions in HCV incidence associated with each treatment scenario did not vary substantially when assuming extreme values for the high-risk sex/CLAI with casual partners ratio. Figure 6 shows that smaller reductions in the assumed HCV incidence of the general population of people who inject drugs led to slightly smaller reductions in HCV incidence among HIV-positive GBM.

DISCUSSION

We reconstructed the HCV epidemic among HIV-positive GBM in Australia between 2007-2015 using a mathematical transmission model based on four risk groups. We used this model to predict the future course of HCV incidence and active HCV infection prevalence in HIV-positive GBM. With treatment uptake >40% and stable risk behavior between 2016-2025, the WHO HCV

elimination target is likely to be reached ahead of time. However, the WHO target may not be met if DAA coverage declines or risk behavior increases substantially.

These results are consistent with earlier work. Findings from Switzerland found that stabilization of high-risk behavior combined with an increase in DAA uptake could effectively reduce national HCV incidence and prevalence among HIV-positive GBM.[9] Importantly, the HCV epidemic among HIV-positive GBM in Switzerland has followed a similar trend to that in Australia.[6, 9] In the UK, where HIV/HCV incidence among GBM has been stable for over a decade, it has been shown that scaling up DAAs among this population could substantially reduce active HCV infection prevalence without behavioral intervention.[30]

There are several key differences between our study and the work from Switzerland. Firstly, we added IDU as a means of HCV transmission. HCV transmission among HIV-positive GBM in Australia is largely driven by IDU.[6] In contrast, the fraction of reported IDU among GBM in Switzerland is low.[9] This proved to be critical in our model as increased rates of IDU had a greater potential to jeopardize the benefits of DAAs compared with increased rates of high-risk sex. Another key difference is that our projections were based on an increasing HCV incidence that was beginning to decelerate, whereas the Swiss model was based on a rapidly accelerating increase in HCV incidence. This could have had a profound impact on the projected effects of scaling up DAAs in our model. Finally, we specifically designed our analysis to evaluate whether HCV transmission could be reduced sufficiently to reach the WHO HCV elimination target by 2025. With stable treatment uptake and stable risk behavior between 2016-2025, the WHO HCV elimination target is likely to be reached early but this could be compromised by a decline in DAA

coverage or a substantial increase in risk behavior. Of note, it was recently reported that the rapid increase in uptake of pre-exposure prophylaxis, a highly effective HIV preventative intervention, among GBM in Australia was accompanied by an equally rapid decrease in consistent condom use.[31] Whether significant behavioral changes will also result from the introduction of DAAs is an active area of investigation.

This study has benefited from the extensive, high quality clinical and behavioral data available on people living with HIV in Australia. However, unlike earlier models [9, 30], we had to estimate many parameters using published literature rather than a single national HIV database. This may have reduced the internal consistency of our parameter estimates. We did not investigate alternative explanations for increased HCV transmissions over time, such as the emergence of more transmissible HCV strains or an increase in unsafe injecting practices. Phylogenetic analyses have revealed that many strains were involved in the early spread of HCV among HIV-positive GBM [32, 33] hence the emergence of a particularly transmissible HCV strain seems unlikely. In Australia, approximately 10% of GBM who inject drugs report recent sharing of needles; this percentage varied little between 2015-2017.[34] Ensuring injecting drug users continue to have good access to clean injecting equipment is likely to be critical to the success of DAAs as increased sharing of equipment could be more detrimental than an increase in the number of injecting drug users.

Our model shows that HCV transmission among Australia's HIV-positive GBM population will decline sharply with DAA use, even with substantial increases in rates of risk behavior. Achieving the WHO HCV elimination target by 2025 among this population appears to be achievable. The

validity and scope of these findings are being further investigated through the ongoing monitoring of treatment uptake and behavior in the CEASE study.

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Conflicts of interest

DCB is supported by a National Health and Medical Research Council Early Career Fellowship. LSV is supported by a Swiss National Science Foundation grant (#324730 179567). GJD is an advisory board member and receives honorarium from Gilead Sciences, Merck Sharpe & Dohme, Abbvie, and Bristol-Myers Squibb, has received research grant funding from Gilead Science, Merck Sharp and Dohme, Abbvie, and Bristol-Myers Squibb, and travel sponsorship from Gilead Science, Merck Sharp and Dohme, Abbvie, and Bristol-Myers Squibb, outside the submitted work. RTG's institution has received funding for his research on HCV elimination from the NSW Department of Health, Australia, and RTG has provided project advice to Gilead Sciences. MGL has received unrestricted grants from Boehringer Ingelhiem, Gilead Sciences, Merck Sharp & Dohme, Bristol-

Myers Squibb, Janssen-Cilag, ViiV HealthCare, and consultancy fees from Gilead Sciences, and DSMB sitting fees from Sirtex Pty Ltd. TL has received personal fees from Bayer Australia, outside the submitted work. AR reports support for advisory boards and/or travel grants from Janssen-Cilag, MSD, Gilead Sciences, Abbvie, Pfizer, and Bristol-Myers Squibb, and an unrestricted research grant from Gilead Sciences. All remuneration went to his home institution and not to AR personally, outside the submitted work. GVM has received research funding and consultancy fees for Gilead Sciences and Abbvie; GVM is also supported by a National Health and Medical Research Council Career Development Fellowship. DC reports no conflict of interest.

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Figure 1. Trends in A) antiretroviral therapy use, B) intravenous drug use, C) high-risk sex, D) intravenous drug use in the context of high-risk sex, and E) hepatitis C virus incidence

A)-D), red dots represent parameter data with error bars representing 95% confidence intervals and black lines represent trends inputted into the model. E), black dots with 95% confidence intervals are from [6] and the blue line is the modelled trend with shaded region representing the modelled 95% range. ART, antiretroviral therapy; IDU, injecting drug use; HCV, hepatitis C virus; py, person years

Figure 2. Projected hepatitis C virus incidence and prevalence of active hepatitis C virus infection in 2025 with high, stable and low rates of direct-acting antiviral uptake

High treatment uptake defined as an increase from 65%/year of eligible patients using DAAs in 2016 to 100%/year in 2025. Stable uptake defined as remaining at 65%/year of eligible patients using DAAs between 2016 and 2025. Low uptake defined as a decrease from 65%/year of eligible patients using DAAs in 2016 to 20%/year in 2025. IDU, injecting drug use; HCV, hepatitis C virus; DAA, direct-acting antiviral

Figure 3. Projected hepatitis C virus incidence between 2016 and 2025 with A) stable and B) increasing proportions engaging in high-risk sex and intravenous drug use

Black dots with error bars representing 95% confidence intervals are from [6]. Colored lines are the modelled trends with shaded regions representing the modelled 95% range. Stable high-risk sex behavior and IDU defined as remaining at 35% and 20%, respectively. Increasing proportion of high-risk sex behavior defined as increasing from 35% in 2016 to 80% in 2025. Increasing proportion of IDU defined as increasing from 20% in 2016 to 80% in 2025. High treatment

uptake defined as an increase from 65%/year of eligible patients using DAAs in 2016 to 100%/year in 2025. Stable uptake defined as remaining at 65%/year of eligible patients using DAAs. Low uptake defined as a decrease from 65%/year of eligible patients using DAAs in 2016 to 20%/year in 2025. HCV, hepatitis C virus; py, person years; IDU, injecting drug use

Figure 4. Percentage reduction in hepatitis C virus incidence between 2016 and 2025 with different rates of direct-acting antiviral uptake and stable risk behavior (solid line) or increasing proportions engaging in high-risk sex and intravenous drug use (dashed line)

Stable high-risk sex behavior and IDU defined as remaining at 35% and 20%, respectively. Increasing proportion of high-risk sex behavior defined as increasing from 35% in 2016 to 80% in 2025. Increasing proportion of IDU defined as increasing from 20% in 2016 to 80% in 2025. Horizontal dashed line represents World Health Organization hepatitis C virus elimination target. IDU, injecting drug use

Figure 5. Sensitivity analysis with high-risk sex/CLAI with casual partners ratio of A) 0.5 and B) 0.8

Unchanged high-risk sex behaviour and IDU defined as remaining at 35% and 20%, respectively. Very high proportion of high-risk sex behaviour defined as increasing from 35% in 2016 to 80% in 2025. Very high proportion of IDU defined as increasing from 20% in 2016 to 80% in 2025. High treatment uptake defined as an increase from 65%/year of eligible patients using DAAs in 2016 to 100%/year in 2025. Stable uptake defined as remaining at 65%/year of eligible patients using DAAs. Low uptake defined as a decrease from 65%/year of eligible patients using DAAs in 2016 to 20%/year in 2025. Error bars represent 95% range. Dotted grey line represents the World Health Organization HCV elimination target for 2030. CLAI, condomless anal intercourse; HCV, hepatitis C virus; IDU, injecting drug use; DAA, direct acting antiviral

Figure 6. Sensitivity analysis with an A) 50% and B) 10% reduction in HCV incidence in the population of people who inject drugs

Unchanged high-risk sex behaviour and IDU defined as remaining at 35% and 20%, respectively. Very high proportion of high-risk sex behaviour defined as increasing from 35% in 2016 to 80% in 2025. Very high proportion of IDU defined as increasing from 20% in 2016 to 80% in 2025. High treatment uptake defined as an increase from 65%/year of eligible patients using DAAs in 2016 to 100%/year in 2025. Stable uptake defined as remaining at 65%/year of eligible patients using DAAs. Low uptake defined as a decrease from 65%/year of eligible patients using DAAs in 2016 to 20%/year in 2025. Error bars represent 95% range. Dotted grey line represents the World Health Organization HCV elimination target for 2030. HCV, hepatitis C virus; IDU, injecting drug use; DAA, direct acting antiviral.

Figure 1

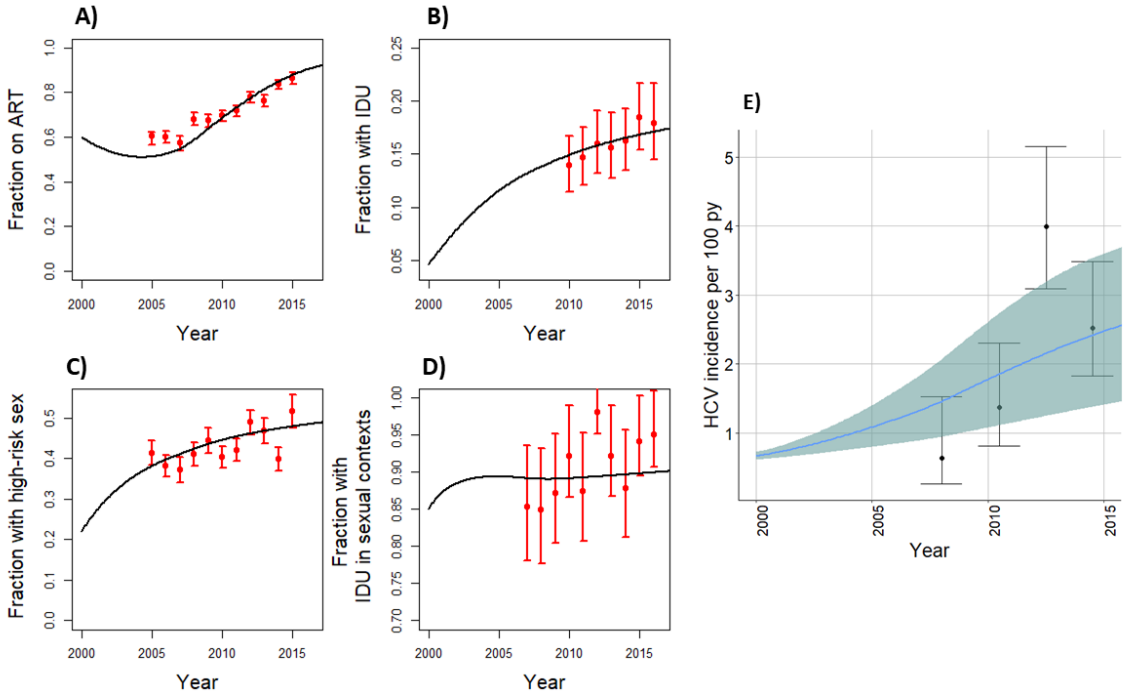

Figure 2

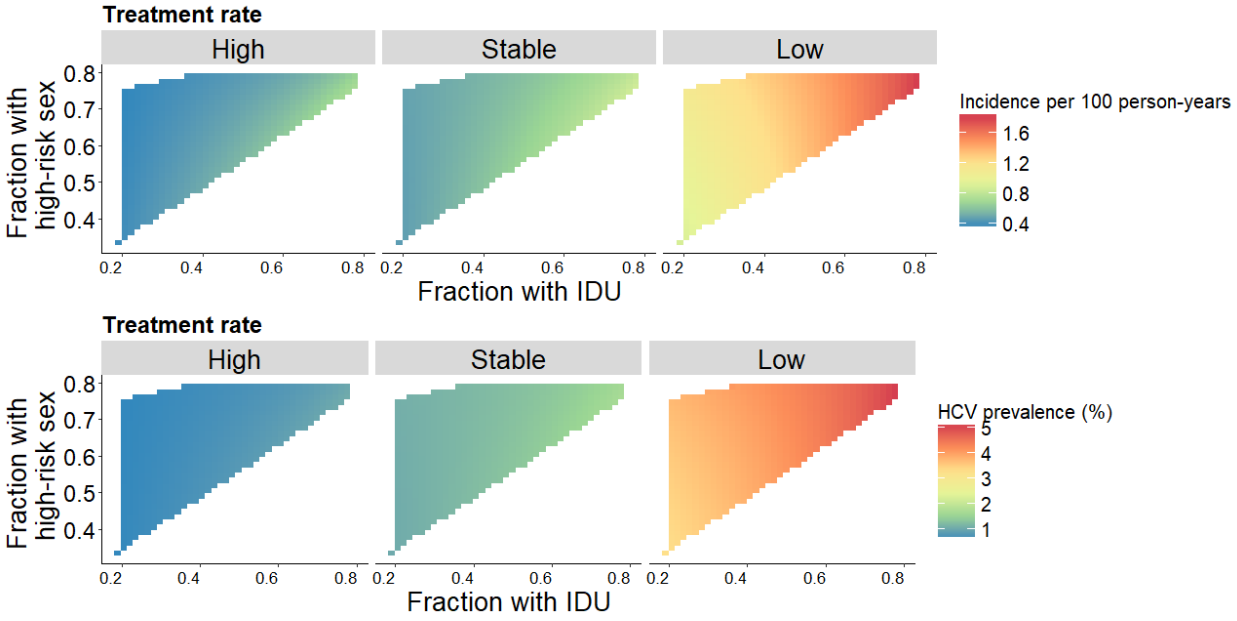

Figure 3

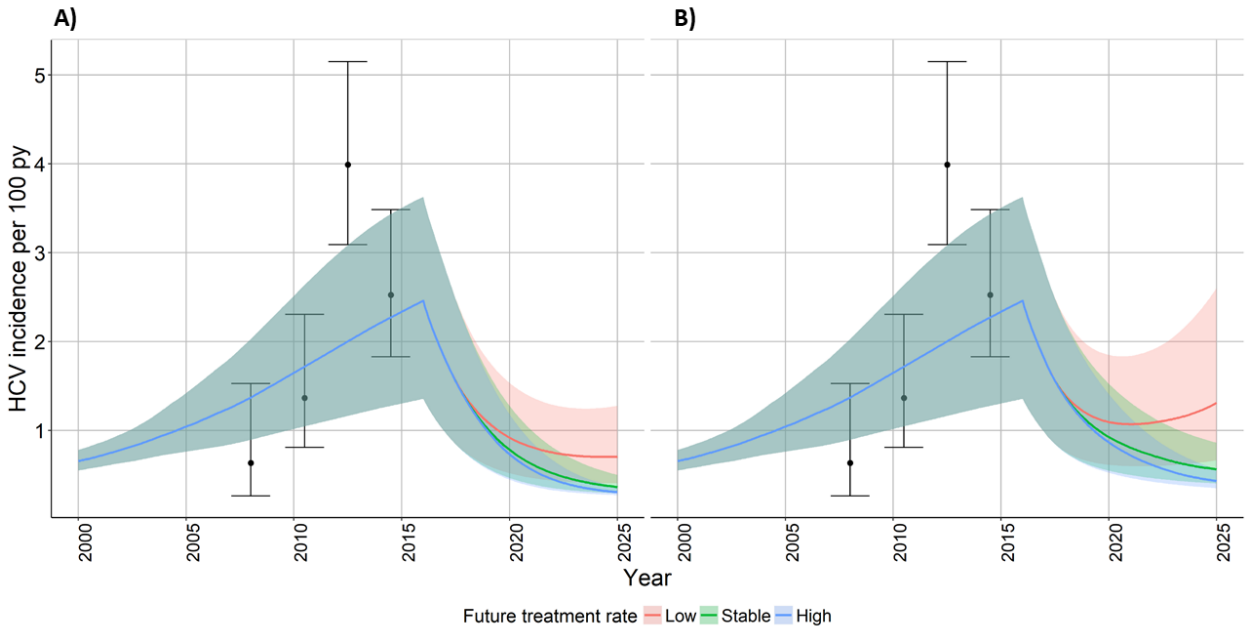

Figure 4

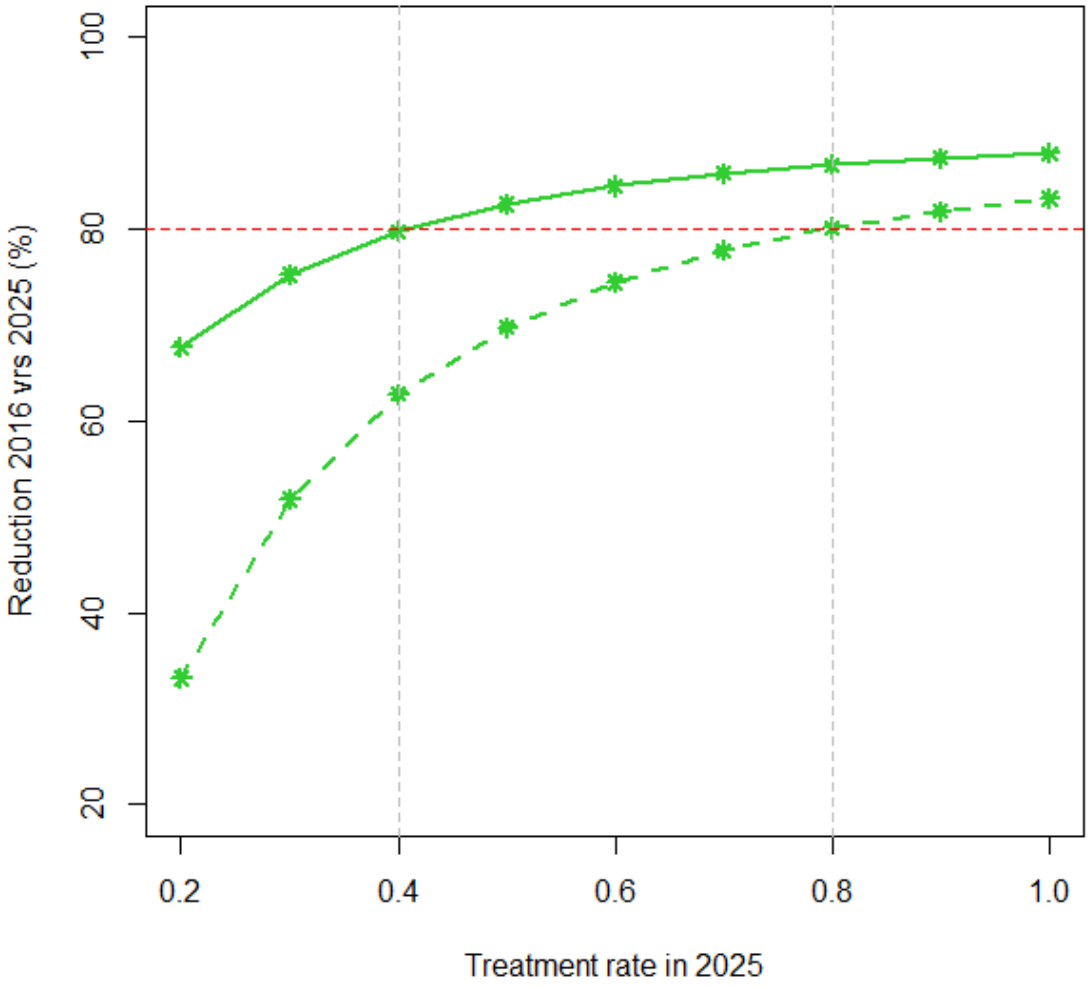

Figure 5

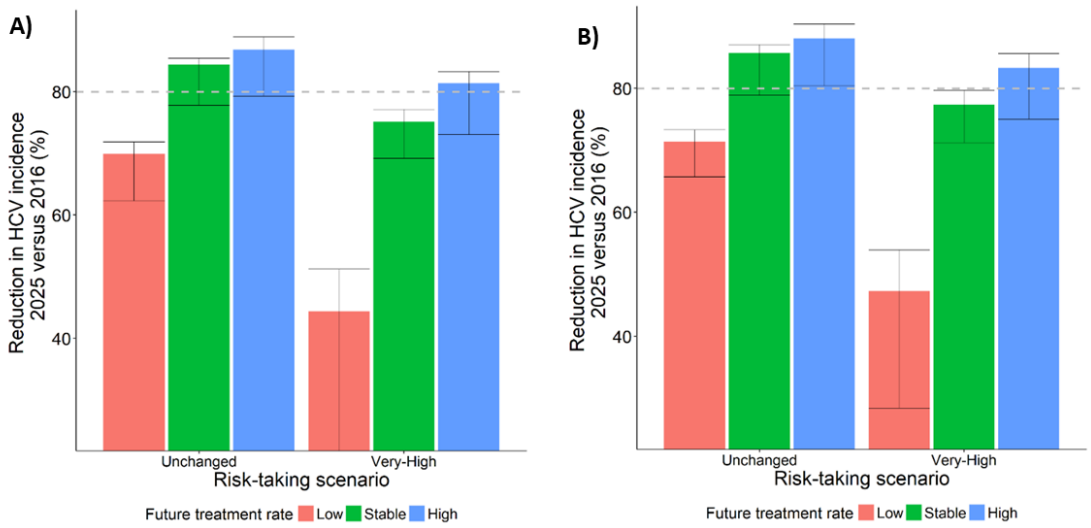

Figure 6