CSIRO PUBLISHING
Sexual Health, 2014, **11**, 146–154
http://dx.doi.org/10.1071/SH13069

Review

Predicting the population impact of increased HIV testing and treatment in Australia

James Jansson[A], *Cliff C. Kerr*[A] *and David P. Wilson*[A,B]

[A]The Kirby Institute, University of New South Wales, Sydney, NSW 2010, Australia.
[B]Corresponding author. Email: dwilson@kirby.unsw.edu.au

Abstract. ***Introduction*:** The treatment as prevention strategy has gained popularity as a way to reduce the incidence of HIV by suppressing viral load such that transmission risk is decreased. The effectiveness of the strategy also requires early diagnosis. ***Methods*:** Informed by data on the influence of diagnosis and treatment on reducing transmission risk, a model simulated the impact of increasing testing and treatment rates on the expected incidence of HIV in Australia under varying assumptions of treatment efficacy and risk compensation. The model utilises Australia's National HIV Registry data, and simulates disease progression, testing, treatment, transmission and mortality. ***Results*:** Decreasing the average time between infection and diagnosis by 30% is expected to reduce population incidence by 12% (~126 cases per year, 95% confidence interval (CI): 82–198). Treatment of all people living with HIV with CD4 counts <500 cells μL^{-1} is expected to reduce new infections by 30.9% (95% CI: 15.9–37.6%) at 96% efficacy if no risk compensation occurs. The number of infections could increase up to 12.9% (95% CI: 20.1–7.4%) at 26% efficacy if a return to prediagnosis risk levels occur. ***Conclusion*:** Treatment as prevention has the potential to prevent HIV infections but its effectiveness depends on the efficacy outside trial settings among men who have sex with men and the level of risk compensation. If antiretroviral therapy has high efficacy, risk compensation will not greatly change the number of infections. If the efficacy of antiretroviral therapy is low, risk compensation could lead to increased infections.

Additional keywords: efficacy, mathematical model, prevention, risk compensation, treatment as prevention, viral load.

Received 3 May 2013, accepted 30 October 2013, published online 7 February 2014

Introduction

Treatment as prevention (TasP) is an emergent public health strategy for reducing population HIV incidence.[1] Since HIV infectivity is associated with viral load,[2,3] treatment reduces infectivity among people living with HIV (PLHIV) by reducing viral load.[4] In this study, we investigate the population-level impacts of increased testing for HIV and treatment of PLHIV in Australia, a resource-rich setting with relatively high access to testing, treatment and care for HIV and related health conditions. The majority of PLHIV in Australia are men who have sex with men (MSM).

It has been shown that an increase in antiretroviral therapy (ART) use is associated with a reduced risk of transmission in serodiscordant heterosexual couples.[3,5] Increased ART use in the HIV-infected population is correlated with a decreased risk of acquiring HIV in the uninfected population in South Africa.[6] HIV-uninfected individuals were 38% less likely to be infected with HIV in areas with ART coverage at 30–40% compared with areas with coverage below 10%.[6]

Estimation of the per-person reduction in risk of onwards transmission following use of ART varies by setting and the study type used to investigate the effect. Although the Preventing Sexual Transmission of HIV with Anti-HIV Drugs (HPTN 052) clinical trial showed an annual reduction in linked transmission among serodiscordant heterosexual couples of 96% (95% confidence interval (CI): 74–99%),[4] lower levels of reduction are observed in population studies. In an observational study of heterosexual serodiscordant couples in China, there was a 26% relative reduction in HIV transmission associated with use of ART.[7] Although these studies represent very different populations, the difference between the clinical trial results and the observational study results may indicate the limitation of ART in preventing transmission in a nonclinical trial setting where counselling and follow-up rates are lower. Adherence and viral suppression should be investigated to determine the impact that they have on the transmission rate.

Ecological studies in resource-rich countries comparable to Australia have shown mixed impacts of increased diagnosis and treatment.[8] In almost all of these settings, there has been an increase in testing and initiation of treatment, but no change[9] or an increasing trend[10] in HIV incidence. There are two jurisdictions that have been widely heralded as being successful in TasP strategies. After an aggressive campaign to increase testing and early initiation of treatment in San

Francisco, where the epidemic is concentrated among MSM, there was a decreased trend in HIV incidence.[11] This was also associated with a decrease in community viral load.[11] In British Columbia, large scale-up of ART was associated with declines in HIV diagnoses.[12] However, this decline may be attributable to other prevention programs targeting priority populations (people who use drugs).[13] Evidence of changes in infectivity in the main population affected by HIV in British Columbia (i.e. MSM) remains unclear. There was no decline in diagnoses in this group; however, the size of the population of PLHIV has increased and thus per capita transmission may have decreased.

Following diagnosis, individuals tend to reduce risk behaviours that are associated with onwards transmission. Numerous studies have found that the number of unprotected anal and vaginal acts with people of unknown or HIV-negative status decrease following diagnosis. A study from the United States (US) comprised mainly of MSM found that following diagnosis, the number of partners of negative or unknown HIV status reduced by 75% compared with prediagnosis levels, and the number of unprotected vaginal and anal sex acts with HIV-negative or unknown partners reduced to almost zero.[14] In another US study, the number of reported risk behaviours decreased by 52% at 12 months following diagnosis and linkage to care.[15] Among MSM in the US, 76% of men stopped having unprotected intercourse with men who were HIV-negative or unknown, which could result in onward transmission following diagnosis.[16] A meta-analysis of several studies in the US showed that unprotected anal and vaginal intercourse with people believed to be HIV-uninfected reduced by 68% (95% CI: 59–76%) following diagnosis.[17] All of these studies show marked behaviour changes that reduce the likelihood of onward transmission of HIV.

To investigate the potential population-level impact of strategies of increased testing and treatment, mathematical models are used. Many models have been used to investigate TasP in a variety of resource-poor[18,19] and resource-rich settings.[20] In this study, we develop a mathematical model specific to the HIV epidemic in Australia to predict the potential population impact of TasP.

Methods

Model structure

We used an agent-based computer model to simulate disease progression, testing, treatment, transmission and mortality to determine the impact of increasing testing and treatment rates on the expected incidence of HIV in Australia. The structure of the model is shown in Fig. 1. The model was based on routinely collected Australian HIV surveillance data from a registry of all notified HIV diagnoses, of which the majority are MSM. These data include age, sex, diagnosis date and whether a previous HIV diagnosis has occurred overseas. To the end of 2011, there were a total of 31 651 people who were diagnosed with HIV in the Australian registry. CD4 count at diagnosis, diagnosis date and estimates of CD4 decline[21] were used to produce back-projected estimates of incidence and the total number of cases that remain undiagnosed (see Appendix S1, available online as supplementary material to this paper, for further detail).

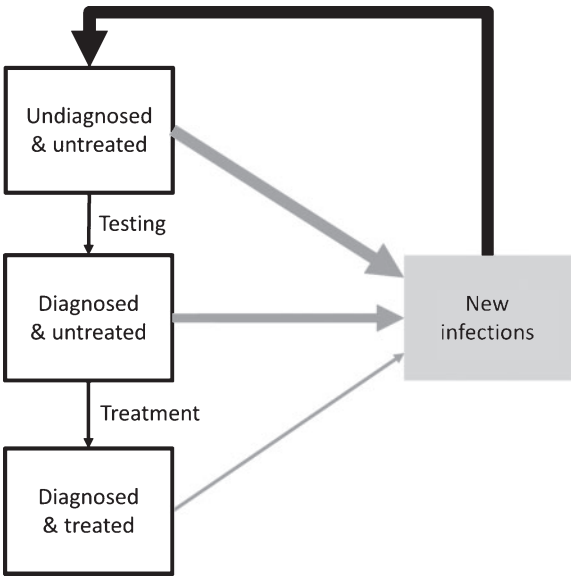

Fig. 1. Schematic diagram of the key processes in the model. The infectiousness of diagnosed individuals is somewhat lower than undiagnosed individuals (65% reduction) due to a reduction in risk behaviours; the infectiousness of those on treatment is lower (assumed to be either a 26% or 96% reduction) due to reduced viral load.

Mortality was calculated using estimates of the rate of AIDS development,[22] the general population mortality[23] and standardised mortality ratios of PLHIV in Australia.[24] The estimates for mortality were used to estimate the total number of PLHIV who have been diagnosed. PLHIV who were previously diagnosed overseas were assumed to contribute to transmissions in Australia following the date of notification in Australia. The number of people previously diagnosed overseas in 2011 was 160; we assume that this (constant) rate of entry of PLHIV will continue in the future.

Model simulations were run using custom software written in Matlab ver. 2012a (The Mathworks, Nantick, MA, USA). A detailed description of the model and the parameters used in the model can be found in the appendix.

Key model assumptions: impact of ART and diagnosis on infectivity

Given the large difference in transmission risk reduction between studies investigating the impact of ART, we chose to simulate the expected outcomes associated with optimistic and pessimistic assumptions separately. The HTPN 052 trial results[4] measured a 96% (95% CI: 74–99%) reduction in transmission due to ART. The ecological study of the impact of treatment on transmission rates in China by Jia *et al*.[7] showed a reduction of 26% (95% CI: 16–35%). Both of these studies have some similarities to and differences from the Australian population of PLHIV. The proportion of people with an undetectable viral load in the HTPN trial (89%) matches the proportion of PLHIV in Australia on ART who have an undetectable viral load (87–90%).[25] The relevance of the HPTN clinical trial to PLHIV in Australia under nonclinical trial conditions may be limited, as access to care, follow-up and

the differences in the nature of the infection risk behaviour (predominantly heterosexual monogamous contact in HTPN 052 *v.* predominantly MSM contact in Australia) may imply that the efficacy of TasP is different in Australia. The study by Jia *et al.*[7] reports transmission rates in a nonclinical trial setting, which makes it appropriate for simulating PLHIV in a nonclinical trial setting. However, Jia *et al.*'s study is also not ideal for simulating the available healthcare and treatments experienced by PLHIV in Australia. Jia *et al.* also do not report viral suppression levels, which are core to ART providing protection against transmission. A study that reports on the viral suppression rates of PLHIV in China shows that viral suppression occurs in 72% of cases,[26] which is somewhat lower than the rate in Australia. Both studies investigate transmission between heterosexual couples, which is a limitation when investigating the impact on a population of PLHIV who are predominantly MSM. In this study, we simulated the expected outcomes of treatment scale-up according to the ART efficacy assumptions aligned with these contrasting estimates.

The CIs of the studies were used to contribute to model uncertainty using a log-normal distribution.

Based on several studies, estimates for the reduction in the transmission-related risk behaviour following diagnosis were drawn from a uniform distribution between 0.5 and 0.8.[14–17,27] We investigated the impact of risk compensation. We chose two levels of risk compensation (no risk compensation and risk compensation returning to prediagnosis levels) in the model to indicate the range of possible risk compensation scenarios. We believe that risk behaviour returning to prediagnosis levels represents the upper limit of increases in risk behaviour for those involved in a TasP intervention. Given risk reduction to levels following diagnosis of 68%,[17] a return to prediagnosis levels of risk behaviour would represent a 3.1-fold increase in the risk behaviour following treatment initiation. A meta-analysis of beliefs about the protective nature of ART in preventing transmission showed that those who believed in the protective nature of ART had an odds ratio of 1.82 (95% CI: 1.52–2.17) of having unprotected sex.[28] Hence, a return to prediagnosis levels of risk behaviour seems to be a reasonable upper bound to the expected risk compensation.

Simulating interventions

Estimates of the testing rate for a given year were determined by matching the number of diagnoses (obtained via Australia's National HIV Registry) with the numbers of infections and undiagnosed PLHIV. The treatment rate was determined by matching the estimates of the size of the currently living HIV-infected population with the estimates of the total number of people in Australia on ART.[29] Rates of treatment and testing were then adjusted in the model to simulate a variety of intervention scenarios. The scale-up of increases in testing and treatment in the model occurred instantaneously at the beginning of 2013. The adherence of those who initiate treatment as a result of the interventions was assumed to be equal to that of those prescribed ART as a result of regular physician decisions.

Results

Baseline

The baseline scenario (where testing and treatment rates in the future remain the same as they are currently) is shown in Fig. 2. Fig. 2*a* shows incidence slowly increasing over time, from 983 (95% CI: 872–1138) new infections in 2012 to 1142 (95% CI: 991–1316) new infections in 2017. Similarly, diagnoses (Fig. 2*b*) are predicted to increase from 941 (95% CI: 898–994) in 2012 to 1049 (95% CI: 966–1157) in 2017, due to increases in the size of the population of PLHIV with the potential to transmit the virus to others.

The median CD4 count in 2011 of PLHIV in Australia who are diagnosed but not on treatment has previously been estimated to be 529 cells μL^{-1} (interquartile range: 409–681 cells μL^{-1}).[29] Using this information, we estimated that 43% of people who are not currently receiving treatment have CD4 counts below 500 cells μL^{-1}. The proportion of diagnosed PLHIV currently on treatment in the model at the

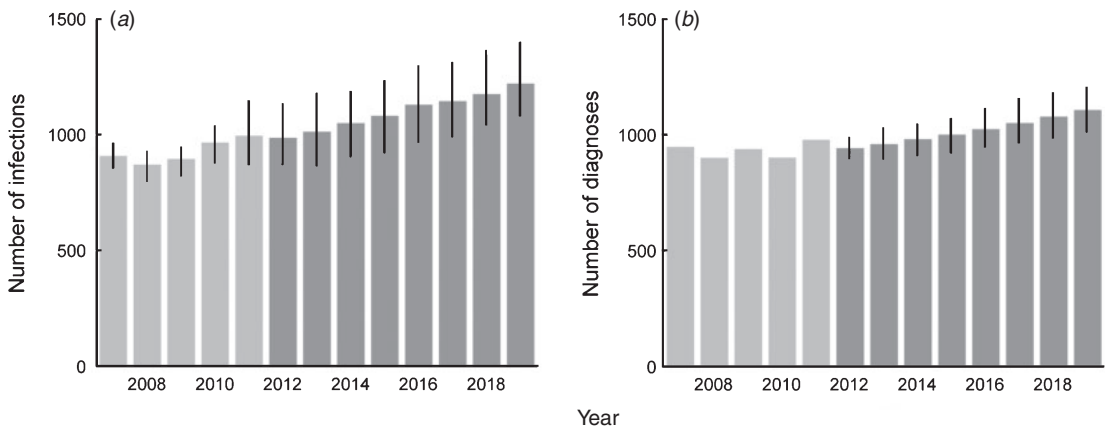

Fig. 2. Projection of current rates of testing and treatment. (*a*) Estimated new infections in each year, showing a rising trend. (*b*) New HIV diagnoses in each year. Values before 2012 are from surveillance data; values from 2012 onwards are simulated. Error bars show 95% confidence intervals.

beginning of 2012 is estimated to be 57%.[30] If all people with CD4 counts below 500 cells μL^{-1} were on treatment, the rate of treatment would rise to ~70% of the diagnosed population. We chose to report detailed results for this scenario and the scenario where testing rates were increased such that the average time between infection and diagnosis would reduce by 30%, since these represent what we consider to be conservatively attainable.

Increased testing only

To reduce the time between infection and diagnosis by 30% would require an increase in the mean testing rate among all PLHIV previously undiagnosed with their infection from 26.2% (95% CI: 24.0–28.0%) per year to 35% (95% CI: 32–37%) per year. This corresponds to a change in the mean duration between infection and diagnosis from 3.4 years to 2.6 years. The median time to diagnosis is estimated to be lower: 1.4 years currently, which is expected reduce to 1.0 years under this scenario. This increase in testing would be expected to prevent 126 (95% CI: 82–198) infections in the fifth year of the intervention (2017), an 8.7% (95% CI: 5.9–14.5%) reduction overall, as shown in Fig. 3*a*. An increased testing strategy would result in a marked increase in diagnoses during the first year of implementation, from 941 diagnoses in 2012 to 1290 (95% CI: 1206–1390) in 2013, as shown in Fig. 3*b*, but the number of diagnoses would decline thereafter.

Increased treatment only

If the treatment rate in diagnosed PLHIV were to increase from 50% to 70%, 243 (95% CI: 168–298) infections would be averted in 2017 (Fig. 3*c*). This corresponds to a 0.21 (95% CI: 0.15–0.25) reduction in infections compared with the baseline scenario. Implementing increased treatment only would not cause a short-term increase in diagnoses (Fig. 3*d*), unlike increased testing alone (Fig. 3*b*). Rather, diagnoses would decrease slowly with time, reflecting a reduction in infections, reducing to 905 (95% CI: 825–986) diagnoses per year in 2017.

Increased testing and treatment

A combination of both increased testing and treatment would have greater impact than increasing just one of these components. In Fig. 3*e*, we show that after 5 years of a TasP strategy, 370 (95% CI: 279–437) new HIV infections would be expected to be averted, with a 30% average reduction in the time from infection to diagnosis and an increase in treatment to 70% of diagnosed cases. This represents a 32% (95% CI: 24%–35%) reduction in infections compared with projections of current levels. Although a short-term spike in diagnoses would be observed in the first year of the intervention (as shown in Fig. 3*f*), it would be followed by a sharp decrease in the number of diagnoses, reaching 871 (95% CI: 801–990) diagnoses per year after 5 years. Since the effectiveness of treatment is assumed to be very high, risk compensation had a moderate impact on these results.

Impact of treatment efficacy

In the previous sections, we considered the impact of treatment where efficacy was assumed to be high (96%). However, treatment may not be as effective in field applications as in a clinical trial. The expected relative reductions in the population incidence in the fifth year of a TasP intervention under a range of testing and treatment levels are presented in Fig. 4. Fig. 4*a* shows the expected reductions in infections assuming treatment efficacy as estimated in Jia *et al*.[7] (26% (95% CI: 16–35%)); Fig. 4*b* shows treatment efficacy as estimated in the HTPN trial (96% (95% CI: 74–99%)).[4]

The baseline scenario is shown in the lower left corner (a default of 0% reduction in the time between infection and diagnosis compared with the current average duration, and 57% of diagnosed individuals on ART). If the testing rate were to increase such that the time between infection and diagnosis was reduced by half (50% on the horizontal axis), 21% of new HIV infections would be averted in the fifth year of the intervention at 96% efficacy versus 11% of infection prevented at 26% efficacy. If the fraction of diagnosed PLHIV on treatment increased from 57% to 90% (vertical axis), then 55% of new HIV infections would be averted in the fifth year of the intervention at 96% efficacy versus 9% of infections averted at 26% efficacy. These graphs can be used to estimate the required levels of testing and treatment required in order to attain a certain level of reduction in population incidence. For example, a 50% reduction in incidence could be attained solely by increasing the proportion of diagnosed PLHIV on ART to 86% at 96% efficacy. If the duration between infection and diagnosis decreased by 50%, then the proportion of diagnosed PLHIV required to be on ART to reduce incidence by 50% is 76% at 96% efficacy.

There appears to be very little interaction between increased testing and increased treatment. That is, the expected total number of infections prevented by strategies that increase testing and treatment is approximately the sum of the separate effects.

Treatment levels based on CD4 counts and the impact of risk compensation

We used the model to examine the impact of changing the CD4 thresholds for initiating ART. We also investigated the combined effect of risk compensation and the impact of different levels of efficacy. In Fig. 5, we show the proportion of infections averted in the fifth year of the intervention with increased treatment (without changes in testing) that are associated with treatment initiation below different CD4 thresholds. These results consider the impact on the epidemic if all people living with currently diagnosed and untreated HIV with a CD4 count below the specified threshold commence treatment. Treating all PLHIV who have a CD4 count below 500 cells μL^{-1} would result in an expected 30.9% (95% CI: 15.9–37.6%) decrease in infections at 96% efficacy with no risk compensation. If risk compensation caused risk behaviour to return to prediagnosis levels (100% risk compensation), then the reduction in infections would be lower at 27.0% (95% CI: 1.0–35.6%). If ART has high efficacy in preventing transmission, then significant reductions in transmissions would be seen even under high levels of risk compensation. However, if efficacy is lower (at 26%), then, at best, we would expect to see a 5.3% (95% CI: 3.1–7.4%) reduction in infections when targeting those with CD4 counts lower than 500 cells μL^{-1}.

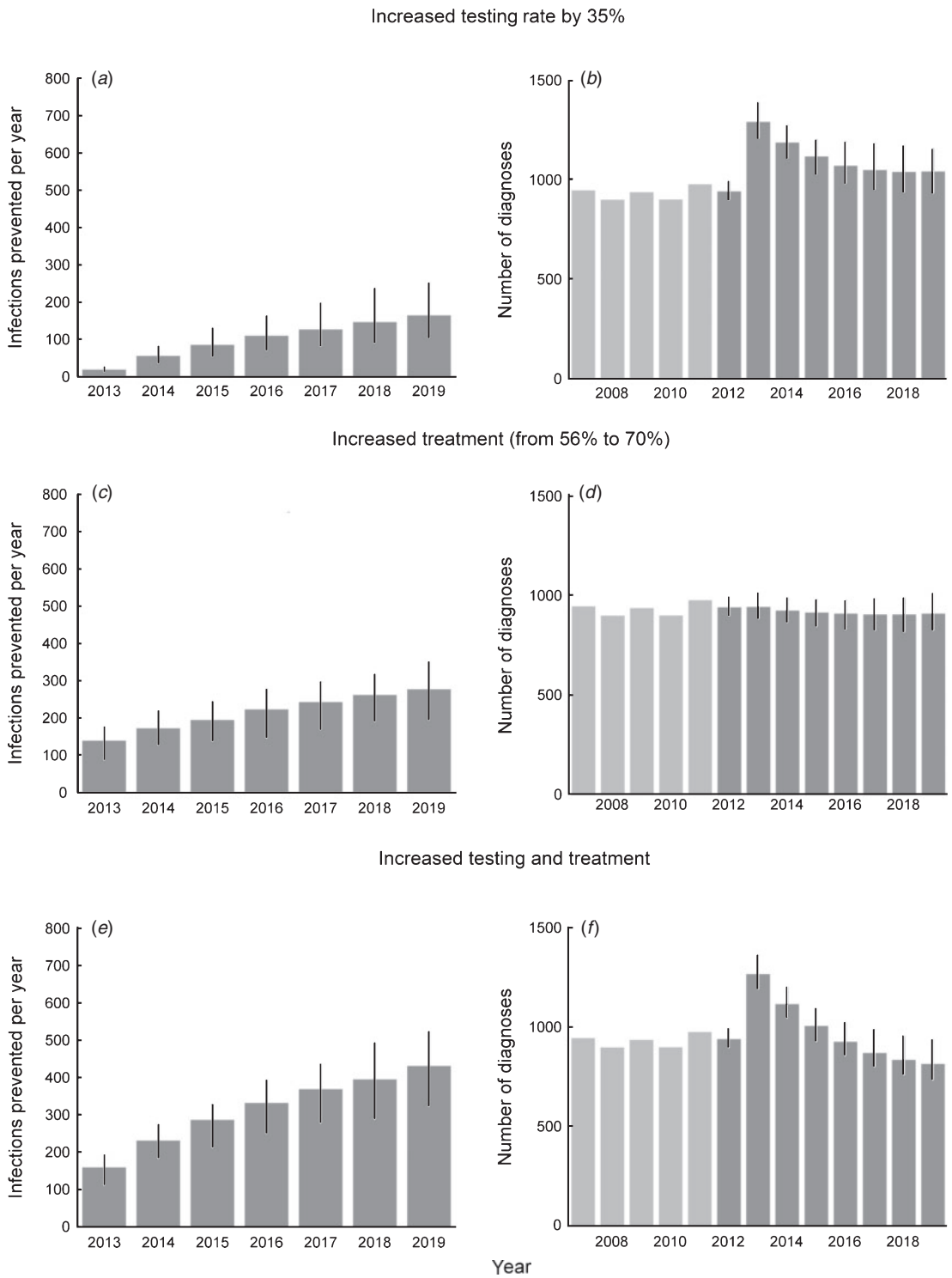

Fig. 3. (*a*, *c*, *e*) Infections prevented per year and (*b*, *d*, *f*) number of diagnoses per year in the scenarios of: (*a*, *b*) decreased time between infection and diagnosis of 30%, which corresponds to an increase in average annual testing rate from 30% to 40%; (*c*, *d*) increased treatment from 50% to 70%; and (*e*, *f*) the combination of both increased testing and increased treatment. Although infections are averted in all three scenarios, scenarios including increased treatment are far more effective than increased testing only.

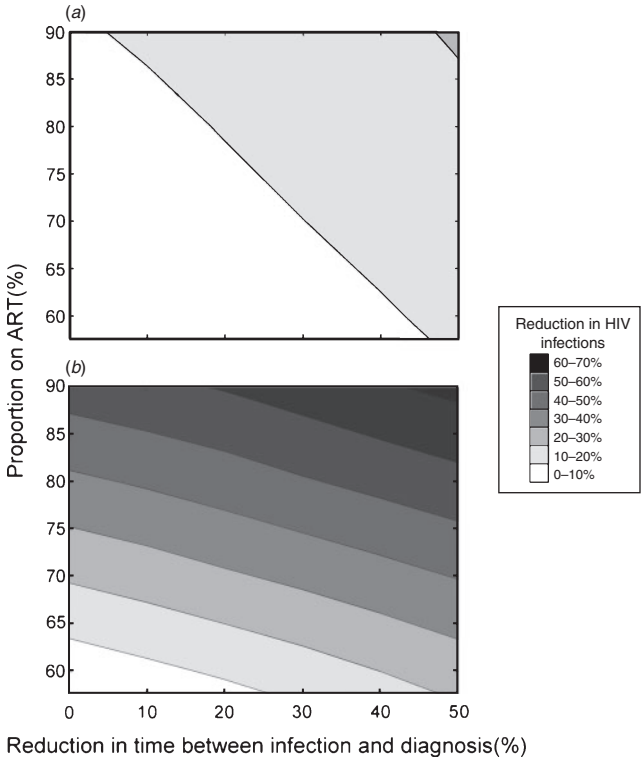

Fig. 4. The reduction in HIV infections in the fifth year of an intervention under varying levels of increased treatment among those diagnosed with HIV (vertical axis) and testing (horizontal axis). (*a*) Treatment at low efficacy (26% (95% confidence interval (CI): 16–35%)); (*b*) treatment at high efficacy (96% (95% CI: 74–99%)). ART, antiretroviral therapy.

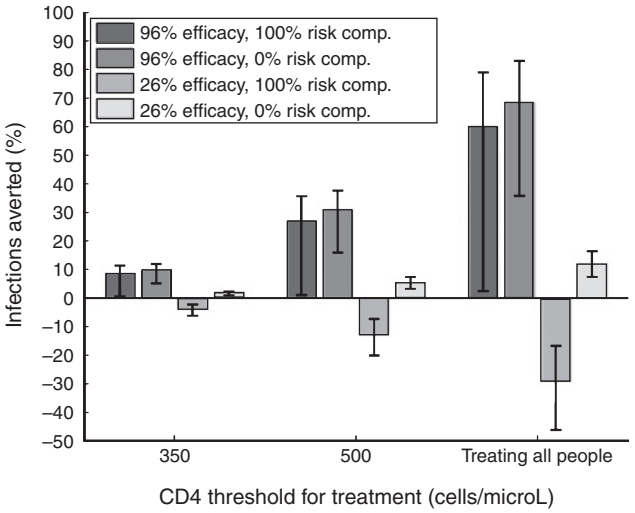

Fig. 5. Simulation of the number of infections averted in the fifth year of an intervention where 100% of people living with HIV with CD4 counts below the threshold are treated with antiretroviral therapy. A negative number of infections averted indicates an increase in infections.

If risk compensation were to return to prediagnosis levels, then the number of infections is actually expected to increase by 12.9% (95% CI: 7.4–20.1%).

Discussion

This study investigated the likely impact that increasing testing and treatment would have on Australia's HIV epidemic. Interventions that increase testing rates are expected to have net decreases in the number of incident infections. However, the number of diagnoses will initially increase, which may give the temporary appearance that the strategy is not working. To ensure a correct assessment of the effectiveness of such interventions, numerous years are required, along with monitoring indicators of testing rates and earlier diagnoses (such as newly acquired incident cases through laboratory evidence or testing history, through examination of the average CD4 count at diagnosis or both).

The results across all CD4 levels show two important results. First, at high efficacies, the expected number of infections averted is not sensitive to risk compensation. If treatment prevents 96% of infections, even tripling unsafe behaviour means that only 12% of the infections that happened previously would happen following treatment (i.e. risk compensation would lead to 88% of infections being averted per diagnosed individual instead of 96%, which is still a substantial improvement). Second, at lower efficacies, risk compensation may completely offset reductions in transmission and there is a risk of worsening the epidemic if efficacy is low and high levels of risk compensation occur. It is therefore important to specifically address two important but as yet unanswered questions: how likely risk compensation is to occur and to what extent in a group of people who are prescribed ART with the explicit purpose of preventing onward transmission, and how efficacious treatment is in preventing infection in MSM outside a trial setting.

Increasing treatment has a much greater impact on infection rates than increasing testing. Although diagnosis reduces a person's infectivity by 65% in our model, treatment reduces infectivity by 96%. Although increasing treatment is much more effective per person than testing in preventing further infection, the cost of increasing testing may be somewhat lower than the cost of increasing treatment. However, the incremental cost of finding undiagnosed cases will change according to the proportion of PLHIV who are undiagnosed. For example, finding the first 50% of undiagnosed cases will be easier and more cost-effective than finding the remaining 50% of cases. Increasing treatment would probably be more straightforward to implement than increasing testing, since those who are already diagnosed are easier to identify than a part of the population that has thus far failed to be identified as being infected.

Increasing treatment is also easily measurable, whereas decreasing the time between infection and diagnosis is harder to quantify, since the precise time between infection and diagnosis in the population is not well established. Although CD4 counts may be used to determine changes in the time between infection and diagnosis, they are highly irregular, particularly at the individual level.[31] This means a small change in the population CD4 count with a small sample size is unlikely to give meaningful information about the change in time between infection and diagnosis. Although an intervention may aim to reduce time between infection and diagnosis by a

certain amount, it would be hard for those implementing the intervention to know just how much testing rates have changed.

The model uses risk reduction parameters taken from studies that focussed on serodiscordant heterosexual couples, whereas the population simulated in the model is predominantly MSM. These MSM engage in anal intercourse, have uncertain (although likely to be very high) levels of condom use following diagnosis and often have multiple partners. Although there is some evidence for treatment-related risk reduction in MSM-dominated epidemics,[12] the effectiveness of treatment for reducing transmission in MSM communities is largely unknown. This is a limitation in any current predictive models of the impact of TasP among MSM and must be considered when interpreting our results. Two observational studies are currently recruiting serodiscordant MSM couples to collate evidence of the potential effectiveness of ART in reducing HIV transmission among MSM.

People on ART may have increased unprotected anal or vaginal intercourse if they believe that treatment alone provides sufficient protection from transmission. In a study of serodiscordant gay couples in Sydney, an undetectable viral load was associated with increased risk taking.[32] It has been found that a substantial proportion of transmissions in high-risk activities occur in situations where the viral load was believed to be undetectable.[33] Such risk compensation may be heightened further if patients are prescribed ART with the explicit purpose of reducing onward transmission. Although previous mathematical models have suggested that marginal increases in risk behaviours will result in a complete erosion of gains made by treatment,[34] such models assumed low levels of ART protection and low levels of knowledge about TasP. In contrast, we believe that knowledge about TasP is widespread among those currently on treatment. If treatment does indeed reduce infectivity by 96%, risk behaviour would have to increase by a factor of 25 to eliminate any benefit of increasing treatment in preventing infection; however, if treatment effectiveness is as low as 26%, as reported in Jia *et al.*,[7] then risk behaviours returning to prediagnosis levels will result in more infections. The degree of risk compensation should be assessed through observation following such an intervention.

Increased treatment rates also have an upper limit of effectiveness due to adherence. Although the rate of complete viral suppression is high in those treated in Australia, the number of people who report being currently on ART is higher (at around 57%)[30] than the equivalent full-time equivalent doses of antiretroviral regimens counted in Australia (at around 50%).[35] Although part of the discrepancy may be due to sampling bias in the surveys in which HIV-positive men report ART use, it is also possible that a person who is prescribed ART but is not taking all doses counts as only a fraction of a person taking doses as prescribed.

Our modelling study has shown that as an intervention strategy, increased treatment may result in a substantial reduction in the number of transmissions at the population-level if efficacy is at the higher end of reported results. However, if starting treatment early results in a net negative impact on the health of the individual in the long term, then early ART should not be initiated. Most medical practitioners in Australia focus on the course of action that is best for their patient and do not consider the impact of treatment on the broader population.[36] Hence, a justification of the introduction of TasP must show that the expected benefit to the individual of earlier initiation will also be positive to ensure that the doctor is always giving advice in the best interest of the patient to maintain the doctor–patient relationship. It has been noted that the implementation of a TasP strategy may have detrimental implications on those who are targeted for the intervention.[37] Since the side-effects, clinical benefit and protective qualities of ART will vary by individual, treatment decisions need to be made on an individual basis. Data from the Strategic Timing of Antiretroviral Treatment trial will assist in providing some of this information.[38]

HIV testing can facilitate reductions in onward transmission by informing individuals about their serostatus, which has been shown to result in changes in risk behaviour.[14–17,27] Some barriers such as inconvenience, cost and stigmatisation must be addressed if testing coverage and frequency is to increase.[39]

There are indications that the rate of morbidities and mortality in people who initiate treatment early is lower than in those who delay treatment.[40,41] Higher CD4 counts are associated with lower rates of both AIDS and non-AIDS defining illnesses that result in death, including non-AIDS infections,[42] malignancies,[42–44] liver disease[42] and renal events.[43] Cardiovascular events may also have an association with raised viral loads.[42] A substantial proportion of PLHIV who are not receiving treatment in Australia have CD4 counts below 500 cells μL^{-1}. Hence the early initiation of ART may confer benefits to the individual independent of prevention of HIV transmission.

Extremely early treatment may even result in a 'functional cure' where viral load is maintained at either very low or undetectable levels in some patients, even after stopping ART.[45] A program that encourages quick testing – and treatment if necessary – following an event with a high risk of transmission (in a manner similar to postexposure prophylaxis) may reduce the number of transmission and also reduce the long-term cost of treatment.

In contrast to these benefits, the implementation of increased treatment may also contribute to an increased rate of multiple drug resistance[46] and may result in PLHIV having limited drug options sooner than if treatment rates remained the same.[47] Treatment may need to be delayed even when CD4 counts are low in order to treat coinfections such as hepatitis C virus.[48] The decision to initiate a patient on ART must acknowledge that the individual should continue ART or risk a viral rebound and possibly the development of ART resistance.[49] Use of ART can result in a variety of short-term side-effects such as nausea, diarrhoea, fatigue and anaemia.[50] The use of specific types of ART may be associated with cardiovascular events.[51] Thus the impact of these side-effects on quality of life needs to be considered when initiating treatment.

The implementation of TasP, supported by regular testing of people at high risk of HIV who have not previously been diagnosed, will reduce the number of new infections in Australia substantially if efficacy is high. However, the epidemiological benefits of TasP need to be considered in the context of the benefits and detriments that increased treatment would have for the individuals who may be targeted by this intervention.

Conflicts of interest

None declared.

Acknowledgements

This study was funded by the National Health and Medical Research Council (1021790) with support from the National Association of People with HIV Australia and the Australian Research Council. The Kirby Institute is funded by the Australian government's Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian government. The Kirby Institute is affiliated with the University of New South Wales.

References

1 Granich R, Gupta S, Suthar AB, Smyth C, Hoos D, Vitoria M, *et al*. Antiretroviral therapy in prevention of HIV and TB: update on current research efforts. *Curr HIV Res* 2011; 9: 446–69. doi:10.2174/157016211798038597

2 Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis. *Lancet* 2008; 372: 314–20. doi:10.1016/S0140-6736(08)61115-0

3 Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen R, *et al*. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; 342: 921–9. doi:10.1056/NEJM200003303421303

4 Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; 365: 493–505. doi:10.1056/NEJMoa1105243

5 Castilla J, del Romero J, Hernando V, Marincovich B, García S, Rodríguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr* 2005; 40: 96–101. doi:10.1097/01.qai.0000157389.78374.45

6 Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science* 2013; 339: 966–71. doi:10.1126/science.1228160

7 Jia Z, Mao Y, Zhang F, Ruan Y, Ma Y, Li J, *et al*. Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study. *Lancet* 2013; 382: 1195–203.

8 Wilson DP. HIV treatment as prevention: natural experiments highlight limits of antiretroviral treatment as HIV prevention. *PLoS Med* 2012; 9: e1001231. doi:10.1371/journal.pmed.1001231

9 Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborne TR, *et al*. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. *Lancet Infect Dis* 2013; 13: 313–8. doi:10.1016/S1473-3099(12)70341-9

10 Sullivan PS, Hamouda O, Delpech V, Geduld JE, Prejean J, Semaille C, *et al*. Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia, 1996–2005. *Ann Epidemiol* 2009; 19: 423–31. doi:10.1016/j.annepidem.2009.03.004

11 Das M, Chu PL, Santos G-M, Scheer S, Vittinghoff E, McFarland W, *et al*. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS ONE* 2010; 5: e11068. doi:10.1371/journal.pone.0011068

12 Montaner JSG, Lima VD, Barrios R, Yip B, Wood E, Kerr T, *et al*. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010; 376: 532–9. doi:10.1016/S0140-6736(10)60936-1

13 Grulich AE, Wilson DP. Is antiretroviral therapy modifying the HIV epidemic? *Lancet* 2010; 376: 1824. doi:10.1016/S0140-6736(10)62162-9

14 Steward WT, Remien RH, Higgins JA, Dubrow R, Pinkerton SD, Sikkema KJ, *et al*. Behavior change following diagnosis with acute/early HIV infection – a move to serosorting with other HIV-infected individuals. The NIMH Multisite Acute HIV Infection Study: III. *AIDS Behav* 2009; 13: 1054–60. doi:10.1007/s10461-009-9582-6

15 Metsch LR, Pereyra M, Messinger S, del Rio C, Strathdee SA, Anderson-Mahoney P, *et al*. HIV transmission risk behaviors among HIV-infected persons who are successfully linked to care. *Clin Infect Dis* 2008; 47: 577–84. doi:10.1086/590153

16 Fox J, White PJ, Macdonald N, Weber J, McClure M, Fidler S, *et al*. Reductions in HIV transmission risk behaviour following diagnosis of primary HIV infection: a cohort of high-risk men who have sex with men. *HIV Med* 2009; 10: 432–8. doi:10.1111/j.1468-1293.2009.00708.x

17 Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. *J Acquir Immune Defic Syndr* 2005; 39: 446–53. doi:10.1097/01.qai.0000151079.33935.79

18 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; 373: 48–57. doi:10.1016/S0140-6736(08)61697-9

19 Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, *et al*. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med* 2012; 9: e1001245. doi:10.1371/journal.pmed.1001245

20 Phillips AN, Cambiano V, Nakagawa F, Brown AE, Lampe F, Rodger A, *et al*. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. *PLoS ONE* 2013; 8: e55312. doi:10.1371/journal.pone.0055312

21 Lodi S, Phillips A, Touloumi G, Pantazis N, Bucher HC, Babiker A, *et al*. CD4 decline in seroconverter and seroprevalent individuals in the precombination of antiretroviral therapy era. *AIDS* 2010; 24: 2697–704. doi:10.1097/QAD.0b013e32833ef6c4

22 Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, *et al*. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; 126: 946–54. doi:10.7326/0003-4819-126-12-199706150-00003

23 Australian Government Actuary (AGA). Australian life tables 2005–07. Canberra: AGA; 2009.

24 Nakhaee F, Black D, Wand H, McDonald A, Law M. Changes in mortality following HIV and AIDS and estimation of the number of people living with diagnosed HIV/AIDS in Australia, 1981–2003. *Sex Health* 2009; 6: 129–34. doi:10.1071/SH08007

25 Falster K, Gelgor L, Shaik A, Zablotska I, Prestage G, Grierson J, *et al*. Trends in antiretroviral treatment use and treatment response in three Australian states in the first decade of combination antiretroviral treatment. *Sex Health* 2008; 5: 141–54. doi:10.1071/SH07082

26 Ma Y, Zhao D, Yu L, Bulterys M, Robinson ML, Zhao Y, *et al*. Predictors of virologic failure in HIV-1-infected adults receiving first-line antiretroviral therapy in 8 provinces in China. *Clin Infect Dis* 2010; 50: 264–71. doi:10.1086/649215

27 Mao L, Kippax SC, Holt M, Prestage GP, Zablotska IB, , de Wit JBF. Rates of condom and non-condom-based anal intercourse practices among homosexually active men in Australia: deliberate HIV risk reduction? *Sex Transm Infect* 2011; 87: 489–93. doi:10.1136/sextrans-2011-050041

28 Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA* 2004; 292: 224–36. doi:10.1001/jama.292.2.224

29 The Kirby Institute. AHOD HIV observational database annual report 2012. Sydney: The Kirby Institute, The University of New South Wales; 2012.

30 Holt M, Mao L, Prestage G, Zablotska I, de Wit J. Gay community periodic surveys: national report 2010. Sydney: National Centre in HIV Social Research, The University of New South Wales; 2010.

31 Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. *J Acquir Immune Defic Syndr* 1990; 3: 144–51.

32 Van de Ven P, Mao L, Fogarty A, Rawstorne P, Crawford J, Prestage G, *et al*. Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney. *AIDS* 2005; 19: 179–84. doi:10.1097/00002030-200501280-00010

33 Jin F, Prestage GP, Ellard J, Kippax SC, Kaldor JM, Grulich A. How homosexual men believe they became infected with HIV: the role of risk-reduction behaviors. *J Acquir Immune Defic Syndr* 2007; 46: 245–7. doi:10.1097/QAI.0b013e3181565db5

34 Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. *Science* 2000; 287: 650–4. doi:10.1126/science.287.5453.650

35 The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia annual surveillance report 2012. Sydney: The Kirby Institute, the University of New South Wales; 2012.

36 Mao L, de Wit J, Adam P, Post JJ, Crooks L, Kidd MR, *et al*. Australian prescribers' perspectives on ART initiation in the era of "treatment as prevention". *AIDS Care* 2013; 25: 1375–9. doi:10.1080/09540121.2013.766304

37 Garnett GP, Baggaley RF. Treating our way out of the HIV pandemic: could we, would we, should we? *Lancet* 2009; 373: 9–11. doi:10.1016/S0140-6736(08)61698-0

38 Babiker AG, Emery S, Fätkenheuer G, Gordin FM, Grund B, Lundgren JD, *et al*. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clin Trials* 2013. 10(1): doi:10.1177/1740774512440342

39 Gray RT, Prestage GP, Down I, Ghaus MH, Hoare A, Bradley J, *et al*. Increased HIV testing will modestly reduce HIV incidence among gay men in NSW and would be acceptable if HIV testing becomes convenient. *PLoS ONE* 2013; 8: e55449. doi:10.1371/journal.pone.0055449

40 Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, *et al*. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009; 360: 1815–26. doi:10.1056/NEJMoa0807252

41 When to Start Consortium Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; 373: 1352–63. doi:10.1016/S0140-6736(09)60612-7

42 Marin B, Thiébaut R, Bucher HC, Rondeau V, Costagliola D, Dorrucci D, *et al*. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* 2009; 23: 1743–53. doi:10.1097/QAD.0b013e32832e9b78

43 Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, , MacArthur RD, *et al*. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* 2008; 22: 841–8. doi:10.1097/QAD.0b013e3282f7cb76

44 Guiguet M, Boué F, Cadranel J, Lang J-M, Rosenthal E, Costagliola D, *et al*. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol* 2009; 10: 1152–9. doi:10.1016/S1470-2045(09)70282-7

45 Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, *et al*. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog* 2013; 9: e1003211. doi:10.1371/journal.ppat.1003211

46 Sood N, Wagner Z, Jaycocks A, Drabo E, Vardavas R. Test-and-treat in Los Angeles: a mathematical model of the effects of test-and-treat for the population of men who have sex with men in Los Angeles county. *Clin Infect Dis* 2013; 56: 1789–96. doi:10.1093/cid/cit158

47 Jansson J, Wilson DP, Carr A, Petoumenos K, Boyd MA. Currently available medications in resource-rich settings may not be sufficient for lifelong treatment of HIV. *AIDS* 2012; 27(8): 1245–51. doi:10.097/QAD.0b013e32835e163d

48 Thompson MA, Aberg JA, Cahn P, Montaner JSG, Rizzardini G, Telenti A, *et al*. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society –USA panel. *JAMA* 2010; 304: 321–33. doi:10.1001/jama.2010.1004

49 Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, Kityo C, *et al*. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 2007; 21: 965–71. doi:10.1097/QAD.0b013e32802e6bfa

50 Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Res* 2010; 85: 201–9. doi:10.1016/j.antiviral.2009.10.016

51 DAD Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *The Lancet* 2008; 371: 1417–1426.