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Modeling HIV disease progression and transmission at population-level: The potential impact of modifying disease progression in HIV treatment programs

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Abstract

Introduction—Mathematical models that incorporate HIV disease progression dynamics can estimate the potential impact of strategies that delay HIV disease progression and reduce infectiousness for persons not on antiretroviral therapy (ART). Suppressive treatment of HIV-positive persons co-infected with herpes simplex virus-2 (HSV-2) with valacyclovir, an HSV-2 antiviral, can lower HIV viral load, but the impact of partially-suppressive valacyclovir relative to fully-suppressive ART on population HIV transmission has not been estimated.

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Methods—We modeled HIV disease progression as a function of changes in viral load and CD4 count over time among ART naïve persons. The disease progression Markov model was nested within a dynamic model of HIV transmission at population level. We assumed that valacyclovir reduced HIV viral load by log copies/μL, and that persons treated with valacyclovir initiated ART more rapidly when their CD4 fell below 500 due to retention in HIV care. We estimated the potential impact of valacyclovir on onward transmission of HIV in three scenarios of different ART and valacyclovir population coverage.

Results—The average duration of HIV infection was 9.5 years. The duration of disease before reaching CD4 200 cells/μL was 2.53 years longer for females than males. Relative to a baseline of ART initiation at CD4 <=500 cells/μL, the valacyclovir scenario resulted in 167,000 fewer HIV infections over ten years, with an incremental cost-effectiveness ratio (ICER) of $5,276 per HIV infection averted. A Test and Treat scenario with 70% ART coverage and no valacyclovir resulted in 350,000 fewer HIV infections at an ICER of $2,822 and $812 per HIV infection averted and QALY gained, respectively.

Conclusion—Even when compared with valacyclovir suppression, a drug that reduces HIV viral load, universal treatment for HIV is the optimal strategy for averting new infections and increasing public health benefit. Universal HIV treatment would most effectively and efficiently reduce the HIV burden.

Keywords

HIV; valacyclovir; herpes simplex virus; disease progression; mathematical modeling; ART; HIV prevention

Introduction[1]

Dynamic HIV transmission models are used to guide implementation of HIV prevention and treatment interventions, estimate the cost and cost-effectiveness, and explore the potential impact of new strategies [1–3]. In principle, HIV models incorporate prevention interventions, such as behavioral changes, medications, or vaccines, based on known mechanisms of action or assumptions about how each intervention achieves its preventive effect. However, HIV viral load, despite being the primary predictor of HIV transmission, [4] is rarely modeled with a detailed description of its dynamics along stages of HIV disease progression [5, 6]. A potential modeling approach is nesting stochastic algorithms using Markov chain for HIV disease progression (i.e., changes in viral load and CD4 count over time) into HIV transmission models [7]. These estimates of changes in HIV viral load and CD4 count are particularly applicable when modeling interventions that exert a preventive effect by reducing HIV viral load.

While universal treatment with antiretroviral therapy (ART) is the most effective strategy for reducing HIV viral load and onward transmission [8, 9], 72% of HIV-positive people in western and central Africa and 46% of HIV-positive people in eastern and southern Africa

[1]Abbreviations – HSV-2, Herpes simplex virus type two; MSM, men who have sex with men; ART, antiretroviral therapy; VL, viral load; HTC, HIV testing and counseling; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; WHO, World Health Organization

lack access to ART [10], suggesting that adjunctive strategies to slow disease progression and prevent HIV transmission may be beneficial in these settings. Suppression of herpes simplex virus type two (HSV-2) in persons co-infected with HIV who are not yet on ART has been explored as an adjunctive tool for HIV prevention because HIV-HSV-2 co-infected individuals have faster CD4 count decline, increased HIV viral load and increased risk of onward transmission of HIV compared to HIV-infected individuals who are HSV-2 uninfected [11, 12]. Drugs used for HSV suppression, acyclovir and valacyclovir, may be more widely available for persons who don't meet eligibility criteria for initiating ART in settings that have not adopted universal eligibility. Additionally, they may be acceptable to persons who are not ready to initiate ART, as they do not require laboratory monitoring and can be discontinued with few clinical consequences apart from HSV clinical recurrence [13]. A previous study of HSV-2 suppression on HIV transmission and disease progression in co-infected individuals (the Partners in Prevention HSV/HIV Transmission Study) found that acyclovir 400mg, taken twice daily, did not reduce HIV transmission between HIV serodiscordant heterosexual couples, despite lowering viral load by a median 0.25 $\log_{10}$ copies/mL and reducing the occurrence of HSV-2 positive genital ulcers by 73% [12]. However, administration of twice daily high-dose (1.5g) valacyclovir, an acyclovir pro-drug, to HIV-HSV-2 co-infected individuals achieved a 1.2 $\log_{10}$ reduction in HIV viral load compared with treatment with acyclovir [14]. This finding raises the possibility that valacylovir could also impact HIV progression and transmission differently than acyclovir. Dynamic transmission modeling allows for estimation of how the additional reduction of HIV viral load achieved with valacyclovir could impact HIV progression, transmission, and at what programmatic cost.

Here, we report on a three step modeling investigation into the impact of co-infection treatment on HIV disease progression and transmission. First, we calibrate a discrete-time Markov model of HIV disease progression using data from the Partners in Prevention HSV/HIV Transmission Study [12] and the Partners PrEP Study [9] to assess CD4 and viral load changes over time in ART-naïve HIV-infected persons. Then, we validate our disease progression estimates using data on the distribution of CD4 counts and viral load from a trial of home-based HIV counseling and testing in KwaZulu-Natal, South Africa. Finally, we combine our disease progression model with a dynamic transmission model to compare strategies of valacyclovir HSV-2 suppression versus enhanced ART access to reduce onward transmission of HIV.

Methods

Study population

Data to inform the model of HIV disease progression came from two studies of HIV prevention in serodiscordant heterosexual partnerships in sub-Saharan Africa—the Partners in Prevention HSV/HIV Transmission Study [12] and the Partners PrEP Study [9]. Briefly, the Partners HSV/HIV Transmission Study, a prospective placebo-controlled randomized study, enrolled 3,408 serodiscordant couples from eastern and southern Africa, in which the HIV-positive partner was ART-naïve and co-infected with HSV-2. The study evaluated the impact of HSV-2 suppression with acyclovir for the HIV-positive partner on HIV

transmission, in which there was no reduction in HIV transmission in spite of a median 0.25 $\log_{10}$ reduction in plasma HIV levels[12] and a 16% reduction in HIV disease progression [15]. The Partners PrEP Study, a prospective placebo-controlled randomized study, enrolled 4,758 serodiscordant couples from East Africa in which the HIV-infected partner was ART-naïve. In the Partners PrEP Study, CD4 and viral load were measured quarterly for individuals who acquired HIV infection. Nearly 56% of the HIV-negative partners were seropositive for HSV-2 at enrollment [9]. We included all CD4 and HIV viral load follow-up data for both studies from partners who were HIV-negative at enrollment and seroconverted during the study period.

Data

CD4 count and viral load were measured immediately following identification of seroconversion, and every six months thereafter. For intervals that ended with ART initiation, the CD4 count and VL were estimated by the aggregate distribution of CD4 and viral load measurements ≤3 months prior to ART initiation. There were 151 HIV seroconverters in the Partners in Prevention HSV/HIV Transmission Study and 138 HIV seroconverters in the Partners PrEP Study [9, 12].

Analysis of disease progression

To estimate disease progression among HIV-infected individuals, we organized individuals into discrete CD4 and viral load categories. The amount of time spent in each CD4 and viral load category was then estimated by applying discrete-time Markov models for CD4 and viral load, and calculating the time to absorption (Fig. 1). Only observations with simultaneous CD4 and viral load measurements were included in the analysis. The proportions of individuals progressing from one CD4 and viral load category to another were assumed to form the transition matrix for progression from one category to another. For CD4 cell progression, we calculated the average time from CD4>500 cells/μL to absorption in each of the subsequent CD4 categories. The duration in each category was estimated to be the difference between times to absorption for adjacent absorption scenarios. A similar process was used for viral load progression, but with starting viral load of <1,000 copies/mL.

Model validation

We validated the disease progression model by comparing the annual cross-sectional distribution of CD4 counts and HIV viral load during the epidemic between our model and as observed values in KwaZulu-Natal from a previous study of home-based HIV testing and counseling (HTC) in KwaZulu-Natal, South Africa [16].

HIV transmission model

We developed a dynamic, compartmental model of HIV transmission at population level in KwaZulu-Natal in which the disease progression model was embedded. The transmission model is parameterized from our observational home-based HTC study, which was conducted in Vulindlela, KwaZulu-Natal from September 2011 to May 2013 (Table 1). The model is stratified by age, gender, sexual risk, and HSV-2 status, with HIV-infected persons

progressing through CD4 and viral load categories as defined for the Markov model. An individual's HSV-2 status could be HSV-2 uninfected, HSV-2 infected, or HSV-2 suppressed with valacyclovir prophylaxis. At baseline, we assume no valacyclovir prophylaxis is used and that 60% of HIV infected men are co-infected with HSV-2, and 80% of HIV-infected women are co-infected with HSV-2 [22]. Prevalence of HSV-2 co-infection remains constant throughout the simulation, and HSV-2 transmission is not separately modeled. HSV-2 infection is assumed to increase HIV transmission and HIV acquisition as estimated in a previous trial and meta-analysis [15, 22] (Table 1). The age-specific HIV incidence and prevalence were validated with independent South African national survey data [27].

Valacyclovir intervention scenarios

We assessed the impact of valacyclovir prophylaxis on HIV progression and HIV transmission in three scenarios (Table 2). All scenarios assume that home-based HTC is a platform for reaching individuals, which results in a greater proportion of individuals accessing ART than strictly facility based programs [28]. The baseline scenario (Scenario 1) assumes that persons become eligible for ART when their CD4 count falls below 500, that 48% of individuals with CD4≤500 cells/μL initiate ART[29], and that valacyclovir suppressive therapy is not provided. The valacyclovir scenario (Scenario 2) also assumes that 48% of individuals with CD4≤500 cells/μL are on ART, but that the initiation of valacyclovir suppressive therapy by participants not on ART leads to a 25% increase in ART coverage (60%), due to retention in pre-ART care and more rapid initiation of ART when an individual's CD4 count falls below 500 cells/μL. The final scenario (Scenario 3) assumes a Test and Treat program where 70% of all HIV-positive individuals are on ART [30], and no one is taking valacyclovir prophylaxis. We assumed that for HSV-2-HIV co-infected persons, valacyclovir prophylaxis reduces viral load by 1.23 log copies/mL, as observed previously, thus slowing CD4 progression and reducing the risk of onward HIV transmission by 67% [4, 14]. In the valacyclovir scenario (Scenario 2), persons using valacyclovir were assumed to be on valacyclovir for five years, or until ART initiation.

Cost analysis

Costs for this program were determined by estimates in the literature. The costs of ART and valacyclovir (1.5g) were estimated to be $102 [24] and $615[25] per person per year. Home-based HTC was assumed to cost $28.06 per HIV-positive person tested and $8.22 per HIV-negative person tested [23]. Finally, the costs of care for HIV-positive persons with and without ART were assumed to be as estimated by Meyer-Rath and colleagues[26].

For each scenario, the incremental cost-effectiveness ratio (ICER) was estimated relative to ART uptake projections. The ICER was estimated per HIV infection averted and QALY gained over a ten-year time horizon. One-way sensitivity analyses were conducted for the ICERs by varying the annual cost of ART ($51 to $204), the annual cost of 1.5g valacyclovir ($308 to $1230), the impact of HSV-2 co-infection on HIV progression (no increase to 50% increase in progression), the background ART scale-up (20% decrease to 20% increase), and the amount of additional linkage to ART conferred by valacyclovir treatment (no increase to 50% increase).

Results

Sample characteristics

The final sample included 5,388 6-month transitions and 10,706 12-month transitions, which were drawn from 289 unique individuals. Transitions are overlapping intervals of time that include movement of an individual from one CD4 and viral load compartment to another in the Markov model. The median length of follow-up following seroconversion was 15 months (range, 3 to 27 months) for the Partners HSV cohort and 31 months (range, 4 to 56 months) for the Partners PrEP cohort. The age distribution of seroconverters was similar between the two datasets, with 23% and 20% of individuals being less than 25 years of age in the Partners HSV and Partners PrEP cohorts, respectively, and 65% and 66% being less than 35 years, respectively.

Estimated duration of disease stage by CD4 and viral load

The overall durations of each disease stage by CD4 and viral load are shown in Table 3. Excluding acute infection, the average times spent with CD4>500 cells/μL, CD4 350–500 cells/μL, and CD4 200–350 cells/μL are 1.88 years, 1.22 years, and 5.90 years, respectively. The duration of disease after acute infection and before reaching CD4 200 cells/μL is 2.53 years longer for females than males. After assuming a three-month duration for acute infection and including estimates for mortality at each stage and for CD4≤200 cells/μL, overall life expectancy is estimated to be 11.58 years for HIV-positive females and 9.23 years for HIV-positive males.

Excluding acute infection, the average times spent with viral load ≤1,000 copies/mL, 1,000–10,000 copies/mL, and 10,000–50,000 copies/mL are 3.13 years, 1.99 years, and 4.40 years, respectively. The duration of disease after acute infection and before reaching viral load >50,000 copies/mL is 2.85 years longer for females than for males.

Validation of disease progression estimates

With the disease progression estimates input as parameters in a mathematical model of heterosexual HIV transmission in KwaZulu-Natal, we determined the cross-sectional distribution of CD4 count and HIV viral load. We estimated that in 2012, the proportion of HIV-positive persons with CD4 counts <200, 200–350, 350–500, and >500 cells/μL were 12%, 38%, 19%, and 31%, which we compared to estimates from KwaZulu-Natal, South Africa, of 11% (95% CI 7%–15%), 22% (95% CI 17% –28%), 25% (95% CI 20% –31%), and 42% (95% CI 36% –49%). The model also estimated the proportion of HIV-positive persons with viral load >50000, 10000–50000, 1000–10000, and <1000 copies/mL to be 22%, 23%, 12%, and 38%, which we compared to estimates of 24% (95% CI 18% –30%), 22% (95% CI 17% –28%), 29% (95% CI 23% –35%), and 25% (95% CI 20% –31%)(Fig. 2).

Estimated impact and cost-effectiveness of valacyclovir on HIV outcomes

Relative to a baseline of community HTC, valacyclovir with increased linkage to care results in 167,000 fewer HIV infections over ten years, with an incremental cost-effectiveness ratio (ICER) of $5,276 per HIV infection averted (Table 4). The Test and Treat scenario of 70%

ART coverage and no valacyclovir results in 350,000 fewer HIV infections at an ICER of $2,822, which is less than three times the per capita gross domestic product of South Africa and considered cost-effective.

Although valacyclovir is expected to prevent infections, it results in a reduction in quality-adjusted life-years (QALY) relative to baseline, due to slowing of CD4 decline and thus delaying ART eligibility in settings without universal eligibility for ART. The Test and Treat scenario, however, increases QALYs at an ICER of $812 per QALY gained relative to baseline.

Sensitivity analyses

In sensitivity analyses, the ICER per HIV infection averted (Fig. 3a) of the valacyclovir suppression strategy (Strategy 2) remains cost-effective (less than three times the per capita GDP of South Africa) across a wide range of parameters, except for with high annual valacyclovir cost ($1,230). Suppressing HSV-2 is not cost-saving within our range of estimated parameters. The ICER per QALY gained remained more costly and less effective than the third scenario of expanded ART coverage for most parameters. HSV-2 suppression is only cost-effective at high background ART coverage and when HSV minimally impacts HIV progression, suggesting that most QALY effects are due to expanded ART.

Discussion

In this multi-part study, we first estimated HIV disease progression using data from two previous clinical trials fit to a discrete-time Markov model. Then, we validated and applied our disease progression findings to estimate the impact of valacyclovir prophylaxis taken by HIV-HSV-2 co-infected persons on HIV disease progression and transmission in a dynamic transmission model. In estimating disease progression, we found that women progress through the course of HIV disease more slowly than men, resulting in a longer life expectancy following seroconversion than men. Most of the additional time spent living with HIV for women is spent in the later stage of HIV infection (CD4 200 to 350 cells/μL and viral load 10,000 to 50,000 copies/mL). Estimating these HIV viral load values allowed us to further estimate the impact of providing valacyclovir to HIV-HSV-2 co-infected patients on onward transmission of HIV. Using our model of HIV transmission, we found that valacyclovir prophylaxis was a cost-effective strategy for averting HIV transmission and subsequent new infections. However, unintuitively the valacyclovir strategy reduced QALYs due to the slower CD4 decline and delay in ART eligibility among persons who were taking it. A test and treat scenario of 70% ART coverage without CD4 eligibility criteria was found to be the most cost-effective strategy. These results were robust in one-way sensitivity analyses, with valacyclovir suppression only becoming cost-effective per QALY gained when HSV-2 impact on HIV disease progression was minimized and ART coverage was increased.

Disease progression modeling in context

Our modeled estimates of HIV disease progression are similar to those found in observational studies. In HIV-infected adults in Cote d'Ivoire and Uganda, the median time

from seroconversion to CD4<350 cells/μL was 3.2 years, and from CD4<350 cells/μL to death was 7.6 years, which were similar to our estimates of 3.35 years and 7.86 years, respectively [31]. Two studies of European cohorts also found similar estimates. In the CASCADE Collaboration of primarily European individuals, estimates of 3.80 years from seroconversion to CD4<350 cells/μL and 7.10 years to CD4<200 cells/μL were similar to our estimates of 3.35 and 9.25 years, respectively [32]. The time from seroconversion to CD4<350 cells/μL was estimated to be shorter for Dutch MSM who acquired HIV infection in 2003–2007 versus in 1984–1995, with the estimate for 2003–2007 varying between 2.2 and 3.0 years between three different methods of calculation [33].

Previous studies have also found that women have slower disease progression than men. A recent Markov model of HIV disease progression by CD4 cell decline, which included seroconverter cohorts on four continents, reported slower CD4 decline in women than men (Hazard Ratio 0.92, 95% CI 0.86–0.99), but no gender difference in overall mortality [34]. An analysis of the CASCADE Collaboration found that women have a relative risk of 0.76 of progressing to AIDS and a 0.68 relative risk of progressing to death compared to men [35]. Viral load has also been estimated to be lower in females than males at all CD4 levels in a cohort of intravenous drug users in the USA [36], as well as to increase at a slower rate in women than in men in an African cohort [37]. However, other studies have found no difference in CD4 count and progression between men and women [38]. Differences in results may be due to variable progression by HIV subtype [39, 40], co-infection status [22], or geographic region [34].

Valacyclovir prophylaxis in context

Despite prior published estimates of CD4 and viral load progression, few models have incorporated such estimates of disease progression into their assessments of the impact of valacyclovir therapy for HIV-HSV-2 co-infected persons. A previous study by Vickerman and colleagues estimated that acyclovir use in HIV-HSV-2 co-infected women, assuming increased retention in care for women prior to initiating ART, would cost $1130 per life-year gained [41], whereas the model used here found that valacyclovir prophylaxis would worsen health outcomes due to delayed ART initiation. The difference between our results can be attributed to different model structures. Whereas the model used by Vickerman and colleagues followed the life-time trajectory for 300 HIV-negative women, the model used here is population-level and measures outcomes on a ten-year time horizon. Furthermore, Vickerman and colleagues modeled the use of acyclovir rather than valacyclovir, with the former having been demonstrated to be less effective at reducing HIV viral load. Another model investigating the HIV-HSV-2 synergy was developed by Feng and colleagues, who estimated the contribution of HSV-2 infection to the HIV epidemic, finding that nearly 10% of all HIV cases can be attributed to HSV-2 infection [42].

Strengths and limitations of this study

A primary contribution of this study is developing a novel Markov model of HIV disease progression through CD4 and VL categories and comparing modeled estimates with observed data. While the estimates were generally similar, the model did estimate that a larger proportion of the HIV-positive population would fall within the VL<1,000 category,

relative to the observed data from KwaZulu-Natal (38% versus 25%), and a smaller proportion of the population to fall within the VL 1,000 – 10,000 category (12% versus 29%). The model also estimated that a greater proportion of the population would fall within the CD4 category of 200–350 (38% versus 22%), and a smaller proportion with CD4>500 (31% versus 42%). These differences may be due to the structure of the model, where all individuals entered the VL <1000 category after acute infection, or due to differences in the cohorts used to derive the parameters (stable serodiscordant couples) versus the general population cohort used for validation. However, adjusting the modeled population viral load distribution to more closely match the KwaZulu-Natal data could be expected to further increase the benefit of the universal test and treat scenario, due to the efficacy of ART in reducing viral load and averting additional HIV transmissions. Additionally, although the data used to fit the Markov model were limited to recent HIV seroconverters rather than the general population of HIV positive persons, estimates of disease progression from seroconverters have been previously extrapolated to the general seroprevalent population [43].

Another strength of this analysis is that the datasets used to estimate the disease progression came from cohorts with high prevalence on HSV-2 seropositivity. These estimates would be generalizable to the many populations with high rates of HIV-HSV-2 co-infection [22], but may not apply as well to populations with low prevalence of HSV-2 infection. Individual variations in patterns of HSV-2 viral replication activity and shedding may impact HIV disease progression differently between individuals. Finally, a major driver of our cost estimates was medication. Although our values were rigorously researched estimates, exact costs frequently change - even for generic medications - and can be related to purchase volumes. For example, ART cost has decreased in recent years, corresponding to major advocacy efforts to increase ART access [44, 45].

Future directions

As more national health programs adopt the WHO recommendation for universal ART eligibility, there will be additional opportunities to use models of disease progression to predict how expansion of ART in different care models will impact the epidemic. Understanding differences in disease progression by sex and by co-infection status will be important to include in these estimates. Models that explicitly include disease progression can be used to estimate the impact of therapeutic vaccines which aim to decrease the progression of HIV.

Conclusion

Our finding that universal ART access achieves the greatest QALY gains supports current WHO goals of extending ART to all HIV-infected persons. Using validated estimates of disease progression in this model allowed us to estimate the population-level impact of a drug that slows disease progression. Even when compared with initiation of a safe drug (valacyclovir) that could potentially reduce HIV transmission in a setting of high HSV-2 prevalence, universal treatment for HIV is the optimal strategy for increasing QALYs and

public health benefit. Universal HIV treatment should be pursued by all countries to most effectively and efficiently reduce the HIV burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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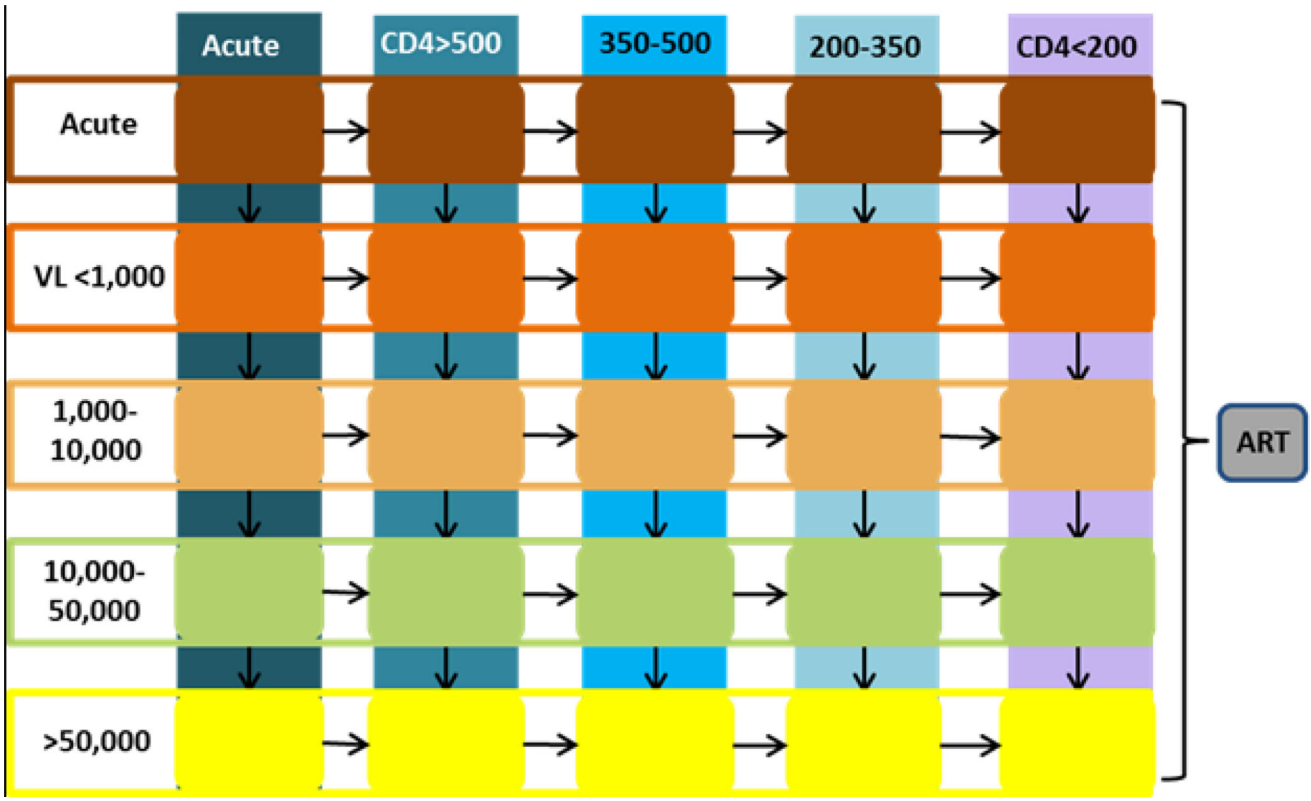

Figure 1. Model transition diagram

A diagram of the natural history of HIV infection. All movement is in one direction except for enrollment in and dropout from interventions from ART. Acute infection is modeled as a transient period immediately following HIV infection with high probability of onward HIV transmission, and is independent of CD4 count and viral load.

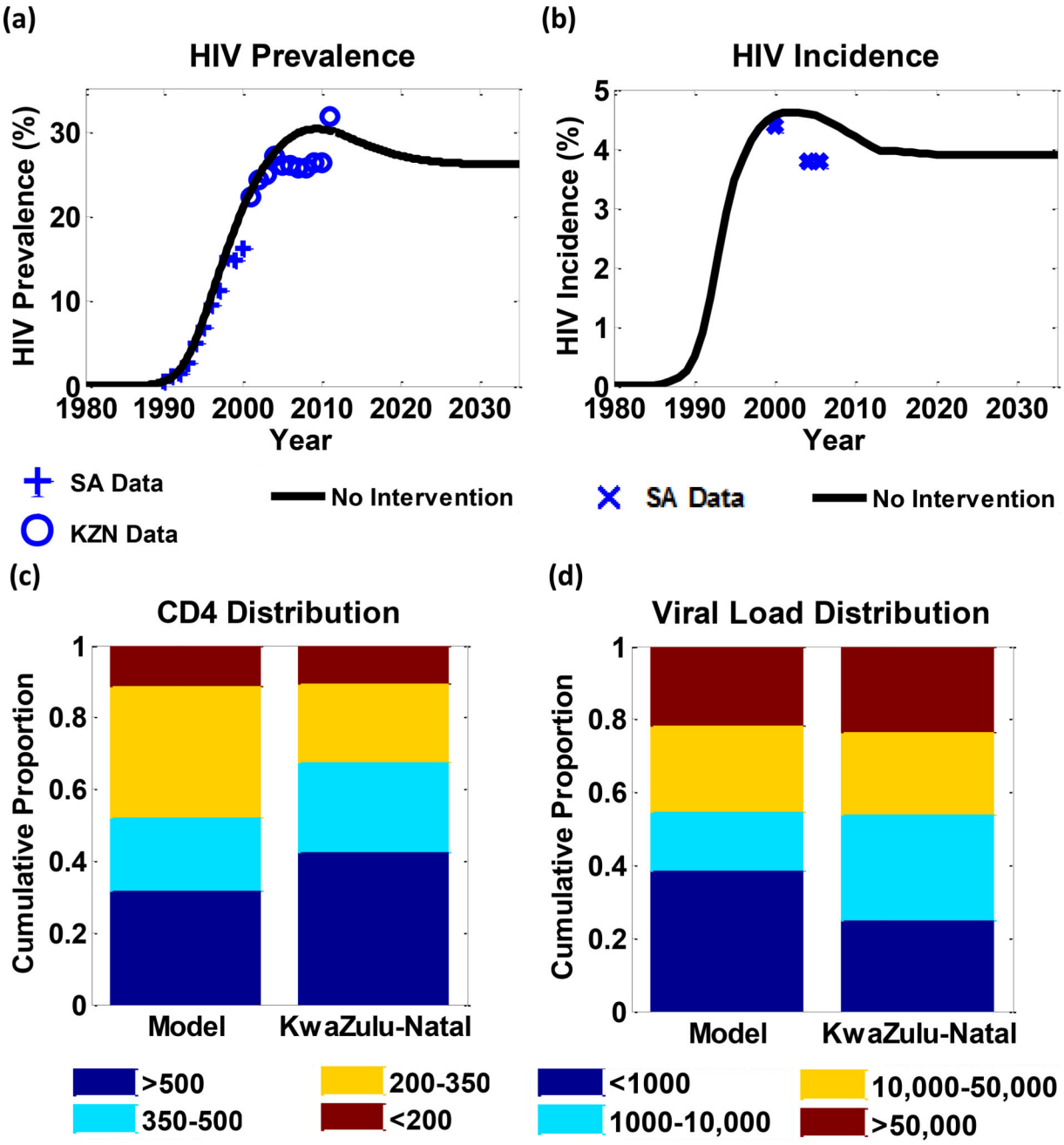

Figure 2. Model output for HIV prevalence and incidence

Model HIV prevalence (a) is similar to observed prevalence in KZN, and model HIV incidence (b) is similar to the average HIV incidence observed in KZN. Model output for the distribution of CD4 counts (c) and viral load (d) in HIV positive persons compared to the distribution seen in a study of Home HIV Testing and KwaZulu-Natal

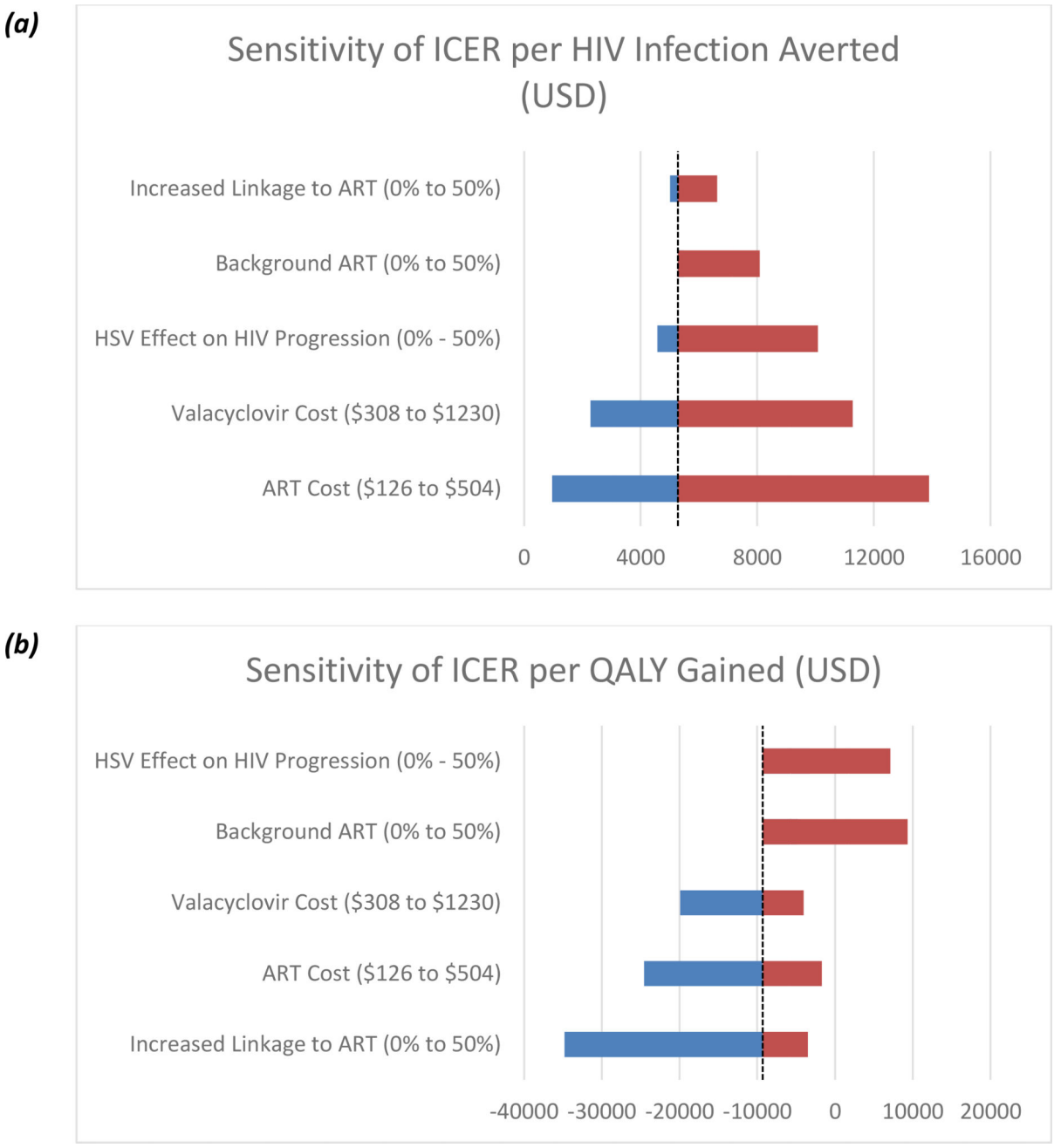

Figure 3. Sensitivity of ICER per HIV infection averted (a) and QALY gained (b)

The dashed line represents the parameter value modeled, and horizontal bars represent the parameter bounds of the sensitivity analysis. The base case ICER per HIV infection averted is $5276 per HIV infection averted and Dominated (−$9324) per QALY gained.

Table 1

Key parameters used in model

The parameters were based on the HBHCT study and other literature. For parameters with varying estimates, we used a value that best fit our model.

Model Parameter	Value [Range]	Reference
Transmission Probability[a]		
Baseline Probability	0.00048	Boily *et al.*, Powers *et al.* [17, 18]
Acute	26 × Baseline [0.0082, 0.015]	Hollingsworth *et al.* [19]
VL≤1,000 copies/mL	1 × Baseline	Quinn *et al.* [4]
VL 1,000–10,000 copies/mL	5.8 × Baseline [2.26, 17.80]	Quinn *et al.* [4]
VL 10,000–50,000 copies/mL	6.9 × Baseline [2.96, 20.15]	Quinn *et al.* [4]
VL>50,000 copies/mL	11.9 × Baseline [5.02, 34.88]	Quinn *et al.* [4]
ART Effectiveness for Reducing HIV Transmission[b]	90% [c]	Donnell *et al.*, Cohen *et al.* [8, 20]
Baseline ART Coverage	36% of all HIV-infected persons	Barnabas *et al.* [21]
HSV-2 Prevalence		
Males	60%	Barnabas *et al.* [22]
Females	80%	Barnabas *et al.* [22]
HSV-2 Impact on HIV		
HIV acquisition in males	RR 2.8	Barnabas *et al.* [22]
HIV acquisition in females	RR 3.4	Barnabas *et al.* [22]
Increased risk of CD4 and viral load progression	20%[d]	Lingappa *et al.* [15]
Costs		
HBHCT with Community Care Workers[e]	Per HIV-positive person: $28.06 Per HIV-negative person: $8.22	Ying et al. [23]
ART	$252 per person per year	CHAI [24]
Valacyclovir	$615 per person per year	MSH[25]
Hospitalization: pre-ART CD4≤200 cells/μL	$121 per HIV-infected person per year	Meyer-Rath *et al.* [26]
Hospitalization: pre-ART CD4 200–350 cells/μL	$58 per HIV-infected person per year	Meyer-Rath *et al.* [26]
Hospitalization: pre-ART CD4>350 cells/μL	$39 per HIV-infected person per year	Meyer-Rath *et al.* [26]
Hospitalization: post-ART CD4 200–350 cells/μL	$111 per HIV-infected person per year	Meyer-Rath *et al.* [26]

Model Parameter	Value [Range]	Reference
Hospitalization: post-ART CD4>350 cells/μL	$45 per HIV-infected person per year	Meyer-Rath *et al.* [26]

[a] Probability of HIV transmission per coital act assumes that HIV transmission is a Bernoulli process.

[b] Proportion of transmissions from or to a specific demographic averted due to intervention.

[c] Value includes 96% reduction in HIV transmission due to ART with 6% annual loss to follow-up.

[d] Individuals with HSV co-infection are 20% more likely to progress to the next viral load stage, making them more likely to transmit HIV.

[e] Community Care Workers (public-sector salary)

Table 2

Intervention programmatic assumptions

The scenarios used in model to evaluate home-based HTC are based on an observational study of home-based HTC in KwaZulu-Natal from March 2011 to March 2013.

Scenario	Drug Coverage by CD4 Category (cells/μL)				Drug
	>500 after acute stage	500 to 350	350 to 200	≤200	
1.Baseline ART[a]	0%	20%	60%	90%	ART
	0%	0%	0%	0%	Valacyclovir
2.Valacyclovir[b]	0%	60%	60%	90%	ART
	40%	16%	16%	4%	Valacyclovir
3.Test and Treat[c]	70%	70%	70%	70%	ART
	0%	0%	0%	0%	Valacyclovir

[a]Baseline represents ART coverage with Home HTC.

[b]40% of HIV-positive persons not on ART use valacyclovir.

[c]Persons are eligible for ART at any disease stage, but only 70% of persons access ART.

Table 3

Estimated duration of time in each CD4 (a) and Viral Load (b) category in ART-naïve persons, by gender

Estimates are based on average time to absorbing state in Markov model. Life expectancy estimate is the summation of time in each stage adjusted for CD4-specific mortality.

(a) Gender	Time (years) CD4 Stage					Life Expectancy[a]
	Acute	>500	500 to 350	350 to 200	≤200	
Female	0.25	1.94	1.35	6.71	1.96	11.58
Male	0.25	1.71	1.05	4.71	1.96	9.23
Both	0.25	1.88	1.22	5.90	1.96	10.66

(b) Gender	Time (years) Viral Load Stage					Life Expectancy[a]
	Acute	≤1,000	1,000 – 10,000	10,000 – 50,000	>50,000 (est)	
Female	0.25	3.06	2.27	5.45	1.18	11.58
Male	0.25	3.44	1.45	3.04	1.50	9.23
Both	0.25	3.13	1.99	4.40	1.44	10.66

[a] Life expectancy estimates include mortality based on CD4.

Table 4

Effectiveness and cost-effectiveness of expanded ART coverage with and without valacyclovir prophylaxis

The baseline scenario assumes that 48% of HIV positive persons are virally suppressed. The outcomes reflect 3% annual discounting of health outcomes for a ten-year time horizon.

Outcome	Scenario	Effectiveness	Cost (Millions, 2014 USD)	ICER
HIV Infections Averted	**1. Baseline: Community HTC**	0	$0	0
	2. Valacyclovir	167,000	$880	$5,2764
	3. Test and Treat	350,000	$987	$2,822
QALYs Gained	**1. Baseline: Community HTC**	0	$0	0
	2. Valacyclovir	−940,000	$880	Strongly Dominated
	3. Test and Treat	1,215,000	$987	$812