**Online technical supplement**

**HIV Population-Level Adaptation Can Rapidly Diminish the Impact of a Partially Effective Vaccine**

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# Model overview

Simulations were conducted on two stochastic, agent-based simulation models. The first, reflective of a South African heterosexual population, has been described in detail elsewhere (*1*). The second, *EvoNetHIV*, is described in detail below.

*EvoNetHIV* is a stochastic, agent-based simulation model that incorporates sexual network structure, behavior, and HIV evolution. Each simulation first estimates a statistical model that governs sexual network structure, and then proceeds through a burn-in period and epidemic simulation. At each time step of both the burn-in period and epidemic simulation, (1) partnerships form and dissolve; (2) sexual acts take place within a subset of existing partnerships; (3) HIV transmission occurs probabilistically within a subset of sexual acts; (4) viral dynamics and disease progression are updated for each infected agent; and (5) vital dynamics, such as aging, are updated. In addition, HIV treatment and preventive interventions are implemented at user-specified intervals. Each of the afore-mentioned processes is described in further detail below.

*EvoNetHIV* is programmed in the R software language (*2*). Model code is accessible at https://github.com/EvoNetHIV/Herbeck-et-al-Vaccine-201x. *EvoNetHIV* is written as a series of modules, with multiple options for each module and the option to write additional modules. It also includes over 100 parameters that users can alter, while providing default values for all of those parameters. Here we describe the *EvoNetHIV* components and parameters used in this paper; for more details, see https://github.com/EvoNetHIV/EvoNetHIV-Overview.

Simulations were conducted on the Hyak supercomputer system at University of Washington, an

advanced computational, storage, and networking infrastructure provided by funding through the Student Technology Fee and the Center for Studies in Demography and Ecology.

# Sexual network

## 2.1 Empirical data

Parameters governing sexual network structure, sexual behaviors, and agent attributes are obtained primarily from two modeling studies of the HIV epidemic among United Statues men who have sex with men (MSM) (*3, 4*). Parameter values in the present study are obtained from weighted means of race- and ethnicity-specific values in Goodreau, et al., (under review) (*4*) or directly from Jenness, et al., 2016 (*3*). Empirical data for parameter values in Jenness, et al., 2016 and Goodreau, et al. are from two studies of black and non-Hispanic white MSM conducted in the Atlanta area in 2010-2014 (*5, 6*). Additional details regarding study design and analysis are available in Jenness, et al., 2016 (*3*) and the forthcoming Goodreau, et al. (*4*).

We initiate each simulation with a 12-year burn-in period in order to fit a stable prevalence of approximately 26%, consistent with prevalence in the Atlanta area (*3*). Prevalence is 20% at model initialization, and antiretroviral treatment (ART) coverage of 40% is introduced at year 7. All agents initiate ART with CD4 < 350 cells/mm3 during the burn-in period.

## 2.2 Network structure

The sexual network consists of a population of MSM. Our network model is relatively simple: all actor pairs are equally likely to form a relationship, with the exception of those with incompatible sexual role (i.e., two exclusively insertive men or two exclusively receptive men). All existing relationships have a constant and equal daily probability of dissolution. Parameters include mean momentary degree (0.70, i.e., average number of relationships a man is in at a cross-section of time) and mean relational duration (50 days).

We estimate the network using separable temporal exponential random graph models (ERGMs) (*7*), as implemented in the statnet (*8*) and EpiModel (*9*) software suites. These algorithms also allow us to simulate a dynamic network that maintains our desired network features stochastically, even as the number of men in the network changes, as do their attributes. In the case of a model such as the one used here, in which all terms are dyadic-independent, the mathematics of the ERGM estimation are equivalent to those of logistic regression.

**Table 2.1**. Model parameters utilized in network estimation

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Momentary mean degree | 0.70 | Jenness, et al., 2016. (*3*) Calculated as the weighted mean of the momentary mean degree of the main, casual, and one-time sexual networks. |
| Sexual role proportions | Exclusively insertive: 24%  Exclusively receptive: 27%  Versatile: 49% | Goodreau et al., under review (*4*); based on data from the InvolveMENt (*5*) and MAN Project (*6*) studies |
| Relationship duration | 50 days | Jenness, et al., 2016. (*3*) Calculated as the weighted mean of the mean relationship durations of the main, casual, and one-time sexual networks. |

The parameter estimates obtained at model initialization are then used in each subsequent time step of the simulation to update the network configuration. We use the offset method of Krivitsky, et al. (2011) (*10*) to account for the changing size of the network as the simulation progresses.

# Sexual behaviors and agent attributes

Sexual acts are determined among agents in a serodiscordant relationship at each time step. Among these partnerships, the number of sexual acts per partnership at a given time step is assigned according to a Poisson draw with mean . Condom use is determined for each sexual act with probability of 50%. Circumcision status is assigned to agents at model entry with 85% probability.

**Table 3.1**. Model parameters specifying sexual behaviors and agent attributes

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Mean sex acts per day | 0.20 | Reanalysis of parameters in Goodreau et al., (under review) (*4*) for a single relational type; based on data from the InvolveMENt (*5*) and MAN Project (*6*) studies |
| Condom probability | 0.50 | Jenness, et al., 2016 (*3*) |
| Circumcision probability | 0.85 | Mean from two previous modeling studies among MSM. Jenness, et al., 2016 (*3*); Goodreau, et al., 2012 (*11*) |

# HIV transmission

The risk of HIV transmission to the uninfected agent is determined for each sex act according to characteristics of the sexual act and characteristics of the agents engaged in the sexual act. We begin with the model from Hughes, et al., 2012 (*12*), which provides a function form that includes numerous covariates, and relative risk estimates for those covariates. However, the published results did not include an estimate for the base value of the function (, which we obtained directly from the authors. Moreover, that model was specified for penile-vaginal sex, whereas our model considers penile-anal sex. To identify relative risks for these two act types by role, we turned to Patel, et al., 2014 (*13*), which provides risk estimates from a meta-analysis for vaginal receptive (8 per 10,000 exposures), vaginal insertive (4 per 10,000 exposures), anal receptive (138 per 10,000 exposures), and anal insertive intercourse (11 per 10,000 exposures). However, each of these risks was irrespective of circumcision status of the insertive partner. Because our model explicitly accounts for reduced risk among circumcised males, we performed back-calculations accounting for prevalence of circumcision in United States males to estimate the risk for an uncircumcised male of vaginal insertive (8 per 10,000 exposures) and anal insertive intercourse (23 per 10,000 exposures). From these values, we calculated the risk of insertive and receptive anal intercourse relative to vaginal intercourse.

Combing these pieces, the probability of transmission is calculated for each sexual act that occurs in a serodiscordant relationship, as:

where

**Table 4.1**. Model parameters determining HIV transmission probability per serodiscordant sexual act

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Per-act infectivity (λ) | 0.000247 | J. Hughes, personal communication, November 14, 2014 |
| Viral load base | 4.0 | J. Hughes, personal communication, November 14, 2014 |
| Relative risk of log10 increase in viral load | 2.89 | Hughes, et al., 2012 (*12*) |
| Relative risk of condom use | 0.22 | Hughes, et al., 2012 (*12*) |
| Relative risk of circumcision | 0.53 | Hughes, et al., 2012 (*12*) |
| Relative risk of insertive anal intercourse | 2.9 | Derived from Patel, et al., 2014 (see text) (*13*) |
| Relative risk of receptive anal intercourse | 17.3 | Derived from Patel, et al., 2014 (see text) (*13*) |

# Set point viral load

Set point viral load (SPVL) in infected agents at model initialization is generated as a combination of viral and environmental factors. The viral contribution to SPVL is drawn from a normal distribution with mean 4.5 log10 copies/mL and standard deviation of . The environmental contribution is drawn from a normal distribution with mean of 0 and standard deviation of . SPVL is then the sum of the viral and environmental contributions, constrained to a minimum value of 2 log10 copies/mL and a maximum value of 7 log10 copies/mL.

Upon transmission, the SPVL of a newly infected agent is determined by the SPVL of the donor virus, viral mutational variance, and an environmental contribution. The viral mutational variance is drawn from a normal distribution with mean 0 and standard deviation 0.01. The environmental contribution to the SPVL of newly infected agents is drawn from the same distribution as that of infected agents at model initialization. The SPVL of newly infected agents is then the sum of the inherited SPVL of the donor agent, mutational variance, and an environmental contribution.

**Table 5.1**. Model parameters utilized in the assignment of set point viral load

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Mean log10 SPVL at model initialization | 4.5 | Fraser, 2007 (*14*); Korenromp, 2009 (*15*) |
| Heritability of SPVL across transmissions (h2) | 0.36 | Fraser, 2014 (*16*) |
| Variance of log10 SPVL | 0.8 | Herbeck, 2012 (*17*) |
| Mutational variance | 0.01 | There are no published estimates of mutational variance. We have therefore programmed a low value to be conservative and to maintain approximately 0.36 heritability output measure. |

# Viral dynamics

Upon infection, viral load, *V*, grows exponentially at rate *r*0 for the first 21 days according to the formula

where *V*0 is the initial value (set to 0.0001 copies/mL) and *t* indicates the number of days since initial infection. Robb, et al., 2016 (*18*) have shown that viral loads during primary infection correlate with SPVL. Thus, we allowed the peak viral load to depend on the agent’s SPVL as follows

where the values of 4.639 and 0.495 are based on regression data given in Robb (*18*). We set *r*0 = *ln*(*V*peak/*V*0)/21 in order to obtain peak viral load on day 21. After reaching peak viral load, viral load decays biphasically. The first phase has a duration of 11 days, in which viral load decays linearly according to the following formula:

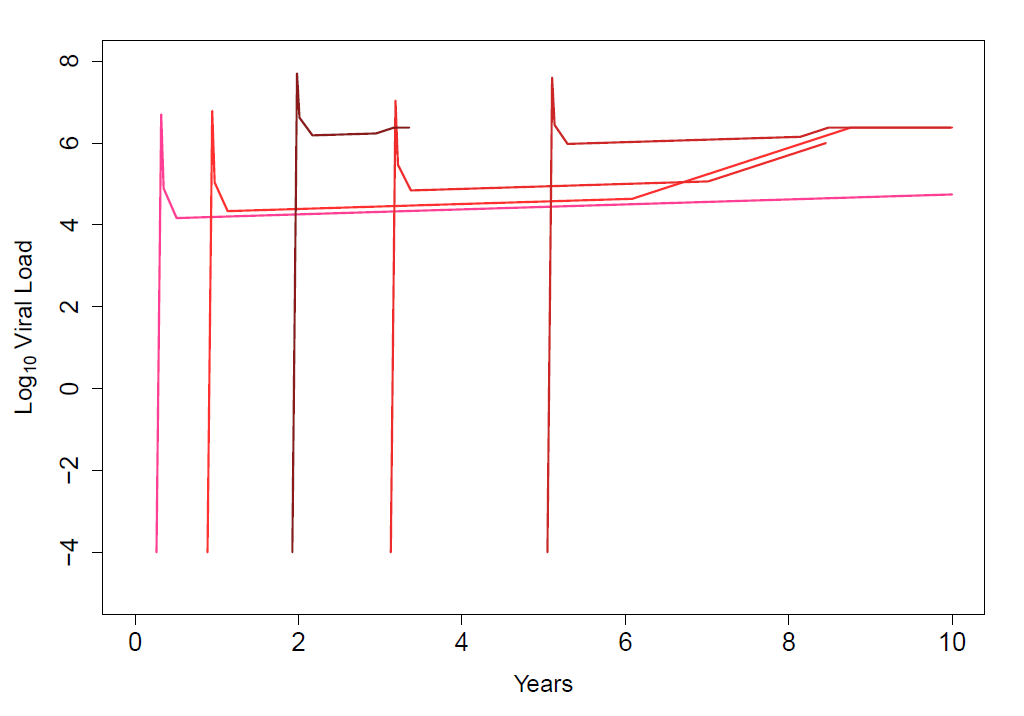
where viral load at t=32 is a weighted geometric mean of Vadj\_peak and SPVL:

For the remainder of the duration of acute infection, viral load declines linearly until reaching the agent’s SPVL at day 90 of infection. Viral load decay in this phase is calculated by

In the chronic phase of HIV infection, an agent’s viral load increases at a constant annual rate of 0.14 loge copies/mL, calculated as follows

This trajectory continues until an agent initiates antiretroviral treatment or enters the AIDS stage, defined by CD4 less than 200 cells/mm3. During the AIDS stage, the agent’s viral load increases linearly by 1.004112-fold per day:

Viral load in AIDS increases up to a maximum viral load of 2,400,000 copies/mL.



**Figure 6.1**. Viral load dynamics in five agents in an example simulation of ten years.

**Table 6.1**. Model parameters utilized in viral load dynamics

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Viral load at day 0 of infection | 0.0001 | Model-calibrated to replicate viral dynamics in Lindback, 2000 (*19*) |
| r0 | 1.19367006 | Model-calibrated to replicate viral dynamics in Lindback, 2000 (*19*) |
| Duration of exponential viral growth | 21 days | Lindback, 2000 (*19*) |
| Duration of phase 1 decay | 11 days | Lindback, 2000 (*19*) |
| Duration of phase 2 decay | 58 days | Lindback, 2000 (*19*) |
| Duration of acute infection | 90 days | Fiebig, 2003 (*20*) |
| Viral load progression rate, natural log | 0.14 | Geskus, 2007 (*21*) |
| Maximum viral load in AIDS (CD4<200) | 2.4x106 copies/mL | Piatak, 1993 (*22*) |

# Disease progression

CD4 values determine the additional risk of death among infected agents. Values are categorized as CD4 ≥ 500 cells/mm3, 500 < CD4 ≤ 350, 350 < CD4 ≤ 200, and CD4 < 200. Agents are assigned a CD4 category probabilistically according to their set point viral load (Cori, et al., 2015 (*23*); Table 7.1). No agents are assigned a CD4 category of less than 200 cells/mm3 upon initial infection.

**Table 7.1**. Probability of assignment to CD4 category stratified by set point viral load

|  |  |  |  |
| --- | --- | --- | --- |
| Set point viral load (log10 copies/mL) | CD4 level (cells/mm3) | | |
| ≥ 500 | 350 – 500 | 200 – 350 |
| [2.0, 3.0] | 0.88 | 0.12 | 0.00 |
| (3.0, 3.5] | 0.87 | 0.12 | 0.01 |
| (3.5, 4.0] | 0.85 | 0.12 | 0.03 |
| (4.0, 4.5] | 0.78 | 0.19 | 0.03 |
| (4.5, 5.0] | 0.73 | 0.21 | 0.05 |
| (5.0, 5.5] | 0.71 | 0.25 | 0.04 |
| (5.5, 6.0] | 0.64 | 0.27 | 0.09 |
| (6.0, 6.5] | 0.00 | 0.00 | 1.00 |
| (6.5, 7.0] | 0.00 | 0.00 | 1.00 |

In the absence of antiretroviral treatment, infected agents progress through CD4 categories probabilistically according to a geometric distribution with mean *p*-1, where *p* is the inverse of the mean amount of time that an individual remains in a specified CD4 category. The mean duration of time in each CD4 category is determined by SPVL (Cori, et al., 2015 (*23*) and personal communication; Table 7.2).

**Table 7.2**. Mean time (in years) spent in each CD4 category stratified by set point viral load

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Set point viral load (log10 copies/mL) | CD4 level (cells/mm3) | | | |
| ≥ 500 | 350 – 500 | 200 – 350 | < 200 |
| [2.0, 3.0] | 6.08 | 5.01 | 3.60 | 4.67 |
| (3.0, 3.5] | 4.69 | 2.52 | 3.68 | 4.11 |
| (3.5, 4.0] | 3.94 | 4.07 | 2.38 | 3.54 |
| (4.0, 4.5] | 2.96 | 3.09 | 3.81 | 2.98 |
| (4.5, 5.0] | 2.25 | 2.32 | 3.21 | 2.42 |
| (5.0, 5.5] | 1.47 | 1.55 | 2.27 | 1.86 |
| (5.5, 6.0] | 0.95 | 1.19 | 1.00 | 1.29 |
| (6.0, 6.5] | 0.32 | 0.59 | 0.68 | 0.73 |
| (6.5, 7.0] | 0.30 | 0.46 | 0.37 | 0.17 |

# Vital dynamics

## 8.1 Model initialization

The epidemic model is initialized with a population size of 10,000 agents. The initial age distribution of model agents is obtained for United States males ages 18-85 from Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) data for the years 1999-2003 (*24*). This age distribution was used in a model without treatment, reflecting the high AIDS mortality rate observed in the first two decades of the AIDS epidemic, until reaching an equilibrium with respect to age. This equilibrium age distribution is scaled to the age range of 18-55, such that the sum of proportions of agents in each age category is equal to 1. The age of each agent is then randomly assigned with probability of a given age equal to the proportion of the scaled equilibrium U.S. male population of that age.

## 8.2 Entries

The number of entries (births) into the model at each time step is determined by a Poisson draw from a distribution with mean 1.37. This distribution results in approximately 1% annual population growth when all of the default Evonet parameters are used. Each new agent enters the model uninfected with age 18.

## 8.3 Exits

Age-specific annual mortality rates for US males ages 18-55 were obtained from the CDC WONDER database for the years 1999-2003 (*24*). We converted these annual mortality rates to daily probabilities.

Natural deaths occur according to each agent’s age-specific probability of death, and are determined probabilistically by a random draw from a uniform distribution on [0, 1]. HIV-infected agents with CD4 greater than 200 cells/mm3 have an increased probability of death that is dependent on their CD4 category.

Deaths due to AIDS occur when an agent’s time in CD4 category 4 (CD4 < 200 cells/mm3) is completed according to disease progression described in Section 7.

## 8.4 Aging

Each agent’s age is incremented by 1/365 at each time step.

**Table 8.1**. Model parameters governing vital dynamics

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Initial population size | 10,000 | NA |
| λ for model entries (births) | 1.37 | Model-calibrated to produce 1% annual growth |
| Minimum age | 18 | NA |
| Maximum age | 55 | NA |
| Age distribution | 0.0450, 0.0440, 0.0430, 0.0420, 0.0410, 0.0400, 0.0390, 0.0380, 0.0370, 0.0360, 0.0350, 0.0340,  0.0330, 0.0320, 0.0310, 0.0300, 0.0290, 0.0280, 0.0270, 0.0260, 0.0250, 0.0240, 0.0230, 0.0220, 0.0210, 0.0200, 0.0190, 0.0180, 0.0170, 0.0160, 0.0150, 0.0140, 0.0130, 0.0120, 0.0110, 0.0100,  0.0090 | Modified from CDC WONDER (*24*) |
| Age-specific annual mortality rates | 0.0011, 0.0012, 0.0013, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0015, 0.0015, 0.0016, 0.0016, 0.0017, 0.0018, 0.0019, 0.0021, 0.0022, 0.0024, 0.0026, 0.0028, 0.0030, 0.0033, 0.0036, 0.0039, 0.0043, 0.0046, 0.0050, 0.0055, 0.0059, 0.0064, 0.0069, 0.0074 | CDC WONDER (*24*) |
| Additional probability of death with CD4 > 500 cells/mm3 | 0.0000112 per day | The values in CASCADE, 2011 (*25*) are for men with mean age 30. Rates presented here therefore subtract 0.0014, the natural mortality rate for North American males aged 30 (*24*), to estimate an excess death rate associated with this CD4 category. |
| Additional probability of death with CD4 350-500 cells/mm3 | 0.0000148 per day | See note above |
| Additional probability of death with CD4 200-350 cells/mm3 | 0.0000333 per day | See note above |

# Antiretroviral treatment

Antiretroviral treatment (ART) becomes available in the model at a user-specified time point. In these simulations, ART is introduced during the burn-in period, and is available at all time points during the experimental portion of the simulations. A user-specified proportion of the population is randomly selected as eligible for receipt of ART; this proportion corresponds to ART coverage. Each individual who initiates ART does so after he is diagnosed as HIV-positive and after a user-specified treatment initiation delay has passed. The treatment delay is assigned from a random draw of a normal distribution with user-specified mean and standard deviation. Each agent who initiates ART is completely adherent and continues to receive ART until death or model exit due to aging.

## 9.1 Effect of ART on viral dynamics

Following initiation of ART, viral load decays exponentially according to the following formula

until reaching a value that is less than or equal to 13 copies/mL, at which point viral load does not change.

## 9.2 Effect of ART on disease progression

Following ART initiation, each agent’s CD4 category improves in a memoryless process until reaching CD4 greater than 500 cells/mm3. At each time step, a given agent receiving treatment has a 3% probability of improving by one CD4 category. Individuals who initiate treatment while in AIDS stage of infection have an increased daily probability of death (*25, 26*).

**Table 9.1**. Model parameters determining antiretroviral treatment and effects

|  |  |  |
| --- | --- | --- |
| **Model parameter** | **Value** | **Source(s) and notes** |
| Mean HIV test interval | 365 | Several of our previous models are based on data showing a mean test interval for MSM of approximately one year. These include Jenness, et al., 2016 (*3*) and Goodreau, et al., 2012 (*11*) |
| CD4 threshold for treatment eligibility | No CD4 threshold | NA |
| ART coverage | Varies: 0.40; 0.70 | Experimental parameter; see main text for additional details |
| Mean treatment initiation delay | 3 years | NA |
| Relative risk of ART | 0.96 | Cohen, et al., 2011 (*27*) |
| Rate of exponential decay of viral load | -0.6 per day | Ho, 1995 (*28*); Wei, et al., 1995 (*29*); Perelson, et al., 1996 (*30*); Perelson, et al., 1997 (*31*) |
| Viral load at suppression | 13 copies/mL | Palmer, et al., 2003 (*32*) |
| Daily probability of improving by one CD4 category when on ART | 0.03 | Pakker et al., 1998 (*33*) |
| Daily probability of death among treated individuals with AIDS | 0.0000760 | CASCADE, 2011 (*25*); Lifson, et al., 2012 (*26*) |

# Vaccination

Vaccine rollout occurs after a twelve-year burn-in period. Each susceptible agent has a daily probability of vaccination that is a function of the user-specified vaccine population coverage and mean vaccine efficacy duration, equal to

Vaccine population coverage is achieve within three years and maintains a steady coverage throughout the remainder of the simulation. Upon receipt of the vaccine, vaccinated individuals experience a reduction in HIV infection risk that is constant and has mean duration of three years, following the RV144 results (*34*). The protective effect of the vaccine applies only to viral variants that are sensitive to the vaccine. A user-specified proportion of HIV-positive individuals are infected with virus that is sensitive to the vaccine, while the remainder of HIV-positive individuals are infected with virus that is resistant to it. Vaccination does not confer a reduction in infection risk for contact between a vaccinated susceptible agent and an agent infected by resistant virus.

**Table 10.1.** Vaccination parameters

|  |  |  |
| --- | --- | --- |
| Relative risk of vaccination | Varies: 0.25, 0.90 | Experimental parameter; see main text for additional details |
| Vaccine efficacy duration | 3 years | RV144 (*34*) |
| Vaccine coverage | Varies: 0.50; 0.70; 0.90 | Experimental parameter; see main text for additional details |
| Proportion of HIV sensitive to vaccine | Varies: 0.75, 0.50 | Experimental parameter; see main text for additional details |

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