Supplemental Material

Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: A modelling study

This Supplemental Appendix includes additional information regarding model construction, calibration procedures, and the results of sensitivity analyses.

Revised: April 10th, 2018

Number of Tables/Figures: 6 (1 table, 5 figures)

Table of Contents

METHODS

Overview

An agent-based model (ABM) was developed to simulate HIV transmission in a virtual society representing the population of men who have sex with men (MSM) in Atlanta, Georgia, a setting with high HIV incidence and prevalence among MSM.[1] The model described in this supplemental file was adapted from an existing ABM of HIV transmission among people who inject drugs (PWID) in New York City.[2] The original development of this model has been described previously in detail.[3]

ABMs are an increasingly common approach for investigating the role of micro-level interactions (e.g., unprotected sexual activity) in producing macro-level patterns (e.g., HIV epidemic dynamics) of population health.[4–6] ABMs are individual-based models consisting of agents (also referred to as "nodes") who are linked to one another through ties (also referred to as "edges"), through which information, behaviors, and other social process can be transmitted. Standard protocols for ABM development, calibration, and validation were employed. These protocols have been described in detail elsewhere.[7] At each discrete time step, each agent's internal state (in this case, their HIV infection status and disease stage) is updated based on pre-programmed rules and interactions with other agents.[8] In this version of the model, links between agents represent male-to-male sexual behaviors through which HIV transmission can occur (i.e., receptive or insertive anal intercourse).

While we recognize that HIV transmission is possible through injection-related behaviors (e.g., needle-sharing) and through other sexual behaviors (e.g., oral sex), these are not explicitly

simulated in the ABM, given that likely contribute to few HIV infections within the modeled population. While syringe and needle sharing in the context of injection drug use has a higher per-act probability of HIV transmission than several sexual behaviors,[9] only 46 new HIV infections among adolescent and adult males in Georgia in 2015 were attributable to injection drug use (IDU).[10] As such, IDU represented only 2.1% of newly diagnosed infections among males in the state, compared to male-to-male sexual contact, to which new HIV infections were attributed (representing 83.7% of all newly diagnosed infections).[10]

The purpose of this model was to assess the potential impact of the use of cabotegravir (CAB) as long-acting injectable pre-exposure prophylaxis (LAI-PrEP) to prevent HIV infection among MSM on the cumulative HIV incidence in this population, compared to the use of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) as daily oral pre-exposure prophylaxis (PrEP). It was hypothesized that LAI-PrEP would outperform daily oral PrEP in reducing cumulative HIV incidence at all coverage levels as it provides a longer period of protection from HIV infection, independent of individual behavioral patterns (i.e., adherence).

Data Sources and Parameters

To derive parameter estimates for the model (provided in Supplemental Table 1), a hierarchical process in order of increasing geographic scope was executed. Estimates specific to the city of Atlanta were used wherever possible. If city-level estimates were not available, information at broader geographic areas (i.e., Fulton County, the Atlanta-Sandy-Springs-Roswell metropolitan statistical area [MSA], state of Georgia) were used. If more specific information was unavailable, national estimates were obtained.

Agent Characteristics

At the initiation of the model, there were 11,245 agents within the virtual population, representing the entire population of MSM in the City of Atlanta. Recent studies have estimated that MSM represent 5.4% of the adult male population in the wider Atlanta-Sandy Springs-Roswell MSA.[11] This proportion was applied to the overall population of adult males in the city of Atlanta (estimated at 208,240 in the American Community Survey in 2015)[12] to yield the number of agents to be included within the model.

Each agent is assigned an age, race, HIV status, and sexual position preference at model initialization. The distribution of ages among agents in the model was derived from the proportions recorded in the American Community Survey in 2015 for the overall adult male population of the city of Atlanta.[12] As the model progressed, agents aged out of the model at 60 years old. The racial distribution was also derived from the proportions recorded in the American Community Survey in 2015 for the overall adult male population of the city of Atlanta.[12] Several parameters are stratified by race, including HIV prevalence, AIDS prevalence, mortality rates, and all stages of the HIV treatment cascade, reflecting the elevated prevalence of HIV infection and likelihood of progressing to acquired AIDS among Black MSM, as well as the decreased likelihood of awareness of infection status, utilization of highly active antiretroviral therapy (HAART), and achievement of viral load suppression among Black MSM.[10,13–15] As such, agents were assigned an HIV status and, if HIV-infected, an awareness of their infection status, a HAART utilization status, and a viral load suppression status based on race-specific distributions for these parameters (see Supplemental Table 1).

All agents were also assigned a sexual position preference, with the distribution of sexual position preferences was derived from a national cross-sectional survey among MSM.[16] These position preferences determined partnering patterns (i.e., insertive agents partnering with receptive agents and vice versa, with versatile agents being able to partner with agents of any class) as well as the baseline per-act probability of HIV transmission with serodiscordant partnerships (see Supplemental Table 1).[9]

Network Structure and Sexual Partnership Formation

At model initialization, agents begin forming connections with other agents that represent sexual partnerships. The ABM progresses in discrete time-steps representing a month of elapsed time. During the transitions between time-steps, agents form, dissolve, or maintain their sexual partnerships. In constructing the sexual network, a value *r* is assigned to each index agent *i*, where *r* is defined as the target number of annual sexual partnerships with other agents. The value *r* is determined by a random sampling procedure given by a negative binomial distribution function (Formula 1), with mean given by Formula 2 for all agents per time-step. The mean and distribution of sexual partners per year were estimated from empirical data (see Supplemental Table S1).[17] This method of partnership formation ensures that partners are acquired with probability *p* until *r* suitable partners are found. Previous versions of this ABM have used negative binomial distributions to determine partnership formation patterns,[2,18] and the use of negative binomial distributions have been shown by other studies to provide reasonable approximations of real-world sexual networks,[19] in which the variance of the distribution is greater than would be expected assuming a constant-rate function (e.g., Poisson distribution).[20]

An *r* value is assigned to each agent at the beginning of each year (i.e., every 12 time-steps) along with a target number of sex acts per partner per year. At the beginning of each 12 time-step period, the target number of partners (*r*) is re-assigned and agents form new partnerships throughout that year based on this newly assigned target. Upon partnering with another agent (with their own unique target number of sex acts per partner per year), the number of sex acts per month for the dyad is determined from a Poisson distribution with a mean given by the average of the target number of sex acts per partner per month for each member of the dyad. The actual number of sex acts per month within the dyad is drawn randomly from this distribution for each month of the partnership. This process helps to ensure both stochasticity with respect to sexual behavior and prevent unrealistically high numbers of sex acts per month. The duration of the partnership is determined at dyad formation by drawing randomly from a distribution informed by empirical data (see Supplementary Table 1).

For example, assume an agent *i* is assigned a target of 1 partner and 156 sex acts per partner per year (equivalent to 13 sex acts per partner per month) and an agent *j* is assigned a target of 10 partners and 1 sex act per partner per year (equivalent to 0.083 sex acts per partner per month). If agent *i* and agent *j* were to partner, their target number of sex acts per month for the duration of their partnership is given by a Poisson distribution with a mean of 6.54 sex acts per month. The actual number of sex acts engaged in by the dyad is then randomly selected from this distribution and may be above or below this mean.

Formula 1:

$$K_{i,t} \sim NB(p,r) = \frac{(k_{i,t}+r-1)!}{(r-1)!\,k_{i,t}!} p^r (1-p)^{k_{i,t}}, \qquad k_{i,t} \in \aleph_0$$

Formula 2:

$$m = \frac{pr}{1-p}$$

Dynamic sexual networks are formed in the model through the formation, dissolution, and maintenance of these sexual partnerships. To illustrate this process, all agents whose cumulative partner number for a given year (defined as $k_{i,t}$) is less than their target annual partner number r can form a new sexual partnership with another agent at the next time-step. This agent can add a new concurrent partnership or dissolve a current partnership before forming a new one with one or more of the remaining eligible agents in the model. Agents who have met their target partner number may maintain all current sexual partners or dissolve a partnership or partnerships. In addition, partnerships were assortatively mixed based on race, where agents formed partnerships with other agents of the same race with a probability of 77.4%.[15]

HIV Transmission

Any pair of agents who are linked in the network can engage in anal intercourse. Events where condoms are used are assumed to carry no risk of HIV transmission or acquisition. The probability of condom use for each sexual act is estimated as a function of the number of previous contacts with a partner (see Supplemental Table 1), where condom use is most common among partners during their first contact and is increasingly less common with increasing number of contacts between partners.[21] Condomless acts between serodiscordant partnerships (i.e., those where one agent is HIV-infected and the other agent is HIV-uninfected) are assumed to carry some level of risk of transmission, based on existing estimates of per-act probabilities of HIV transmission,[9] and

scaled based on the following parameters within the dyad formed: the sexual position (i.e., receptive or insertive partner) occupied by each of the agents; whether or not the HIV-infected agent is aware of their HIV infection status; whether or not the HIV-infected agent is on antiretroviral viral and has attained viral load suppression; and whether or not the HIV-uninfected agent is using PrEP (either daily oral PrEP or LA-PrEP depending on the particular scenario). To increase the computational efficiency of the model, only condomless anal intercourse events occurring within serodiscordant partnerships are simulated explicitly.

The number of sexual acts engaged in by a given dyad at a given time-step is determined stochastically using an estimate derived from a Poisson distribution with a mean determined by each agent's target number of sex acts per partner per month. The overall risk of HIV transmission per partnership per time-step is given by a binomial process model (Formula 3), where β_α is the per-act probability of HIV transmission (specific to the behaviors engaged in between serodiscordant agents, such as condomless insertive anal intercourse and condomless receptive anal intercourse). The number of trials, *n*, is equal to the number of sex acts, determined by the Poisson distribution described earlier. The number of sex acts per time step per agent dyad is based on an average of the annual number of sex acts assigned to each agent within the dyad as provided by empirical data (Supplemental Table 1).

Formula 3:

$$\beta_p \sim Bin(n, \beta_a) = \frac{\beta_p!}{(\beta_p - n)!\, n!} {\beta_a}^{\beta_p} (1 - \beta_a)^{n - \beta_p}, \qquad \beta_p \epsilon \{1, \cdots, n\}$$

HIV Testing, Treatment, and Disease Progression

Agents sought testing for HIV with an annual probability of 69.0%, and at model initiation, 92.8% were considered to have ever been tested.[22] MSM aware of their infection posed a lower risk to their HIV-uninfected partners through the use of a scaling factor meant to reflect research suggesting that newly diagnosed MSM may decrease their sexual partnerships and attempt to avoid condomless anal intercourse with HIV-negative partners for a period of time following diagnosis.[23–25]

National data were used to estimate the proportion of HIV-infected MSM receiving highly active antiretroviral treatment (HAART) and achieving viral load suppression.[13] Separate proportions were used for Black and White MSM to reflect the proportions of HIV-infected MSM who were aware of their HIV infection status (74.7% and 84.4% respectively), receiving HAART (26.2% and 46.7% respectively), and achieving load viral suppression (21.0% and 40.5% respectively).[13] These estimates represent the proportions of all people living with HIV infection, regardless of diagnosis status. We note that viral load suppression is often presented as the percentage of individuals living with diagnosed HIV infection. Under our assumptions, these percentages become 28.1% and 48.8%, respectively. The per-act risk of HIV transmission with HIV-infected agents who achieved viral load suppression was subject to a 96% risk reduction, reflecting the decreased probability of HIV transmission among individuals with undetectable viral loads.[9]

Diagnosed HIV-positives agents were able to initiate HAART. At model initialization, the proportion of diagnosed agents on HAART was set to approximate national HIV care continuum surveillance estimates for each subclass of agent (i.e., Black MSM and White MSM)

(Supplemental Table 1). A monthly probability of HAART initiation among diagnosed HIV-positive agent in each class was interpolated such that the total population on HAART remained stable over the course of the simulation. In order to account for high rates of HIV treatment interruptions and discontinuations observed among some populations of people living with HIV/AIDS, it was assumed that some agents on HAART may discontinue therapy. The monthly probability of HAART discontinuation was estimated from previously published estimates.[26] Agents who discontinue HAART at time-step *j* may re-initiate care at any time at the same rate as those who are newly diagnosed. At model initiation, the proportion of diagnosed HIV-infected agents achieving optimal adherence (i.e., taking 90% or more of all doses) was set to match those values reported by HIV care continuum surveillance activities.

It was assumed that agents who achieve optimal adherence to HAART have an undetectable viral load at a threshold of less than 200 copies/mL, with a small but non-zero probability of transmission (see Supplemental Table S1). It was assumed that adherence is constant while an agent is on HAART. The current model does not account for the type of HAART regimen or the development of virologic resistance. As such, the effect of adherence on virologic suppression represents mean values observed in people living with HIV/AIDS who are engaged in treatment. The base probability of progression to AIDS assigned to all HIV-infected agents is based on published studies, where HIV-infected agents progressed to AIDS with a monthly probability of 0.51%.[27,28] An HIV-infected agent on HAART without full adherence had the same base probability of progression to AIDS as any other HIV-infected agent (regardless of whether or not they had been diagnosed with HIV infection), while an HIV-infected agent on HAART with full adherence was assigned a scalar reduction in this monthly probability of progression of AIDS by

a factor of 6.375, where an HIV-infected agent on HAART with full adherence progressed to AIDS with a monthly probability of 0.08%.[27,28]

Daily Oral Pre-Exposure Prophylaxis (PrEP) Use and Clinical Care

PrEP uptake in all scenarios was simulated using an "all comers" approach, where all HIV-uninfected agents who had engaged in condomless anal intercourse at any time in the past 12 time-steps (corresponding to a period of 1 year) were eligible and equally likely to begin daily oral PrEP. Data regarding retention in care and adherence to the daily pill-based regimen from real world settings were used to parameterize the behaviors of agents while on PrEP.[29] The probability of oral PrEP discontinuation is modeled using a cumulative binomial distribution function calibrated to existing data, agents who used daily oral PrEP were retained in related clinical care with probabilities of 72.5% after three months and 59.6% after six months.[29] The probability of discontinuation rapidly declines after six months, reflecting a short-term period of high discontinuation in the first 6 months of use. Agents who used daily oral PrEP and were retained in related clinical care were adherent (e.g., took four or more doses per week) with a probability of 92.3%.[29] The efficacy of daily oral PrEP in reducing risk for HIV infection was dependent on adherence, where optimal adherence (i.e., taking four or more doses per week) resulted in a 96.0% reduction in the per-act probability of HIV transmission and suboptimal adherence (i.e., taking two or three doses per week) resulted in a 76.0% reduction in the per-act probability of HIV transmission.[30] In addition, those who were retained in related clinical care received HIV testing every three months with 100% certainty.

Long-Acting Injectable Pre-Exposure Prophylaxis (LA-PrEP) Use and Clinical Care

The efficacy of CAB as LAI-PrEP is currently unknown in humans and is currently being assessed in a Phase IIb/III trial of at-risk HIV-uninfected MSM and transgender women.[31] However, data on the pharmacodynamic and pharmacokinetic properties of CAB are available in a macaque model.[32] The main analyses assume that LAI-PrEP will be as efficacious in humans as it is in the macaque model.

To estimate the efficacy for LAI-PrEP, we obtained raw data from a previously published macaque study.[33] Logistic regression was used on the primary dataset containing measured plasma CAB concentrations and observed seroconversions for a given intra-rectal SIV exposure in macaques. From these data, we derived a curve representing the probability of seroconversion for a given plasma concentration when compared to no plasma CAB concentration (see Figure 1A), and then estimated the reduction in per-act probability of transmission as a function of plasma CAB concentration based on the changes in probability of infection as concentration decreases (see Figure 1B). A biological half-life model was used to estimate the decay of plasma CAB concentration in humans as a function of time since last injection (see Figure 2A), using an estimated half-life of 40 days.[34] The resulting sigmoid curve between plasma CAB concentration and time since was injection was fit to determine the percent reduction in the per-act probability of HIV infection per act as a function of time since last injection (see Figure 2B).

The current dosing regimen being tested in humans involves an individual receiving a CAB injection once every eight weeks.[31] The safety and acceptability of this dosing regimen has been evaluated in humans in HPTN 077, a Phase IIa trial.[35] In this trial, participants began with an oral

CAB or placebo lead-in phase as a preliminary assessment of the safety and tolerability of CAB prior to the injection phase.[35] After the oral phase was complete, 88.9% received at least one CAB or placebo injection.[35] In total, 84.7% of those who began the injection phase completed all of their injections.[35] As such, agents are retained on LA-PrEP from injection to injection with a probability of 84.8%.[35] The probability of discontinuation is also modeled with a cumulative binomial distribution function, calibrated to a single time-point (2 months post-initiation).

Model Calibration

An iterative indirect approach based on published recommendations were used to calibrate the model.[36] The set of empirical behavioral and risk parameters were first applied to the model agents and then the preliminary outputs of these models (e.g., the incidence of HIV infection over the ten-year simulation period) were assessed. These outputs were then compared to available surveillance data from the Georgia Department of Public Health.[10]

Model refinement was then conducted by adjusting key parameters for which there were greater levels of uncertainty in their values (e.g., monthly probability of HIV testing, frequency of engagement in condomless anal intercourse) to minimize differences between the model output and available empirical data. We used an iterative stepwise sweep of "calibration parameters" in order to recreate observed empirical incidence rates and end of year prevalence of: diagnosed and undiagnosed HIV, diagnosed and undiagnosed AIDS, and HAART. This process does not guarantee the validity of the ABM, but it does, however, allow for the exclusion of parameter values that do not adequately reproduce the available empirical data.[7]

Prior to calibration procedures, an initial conditions test was performed to ensure that demographic distributions were adequately recreated in the model when compared to our input parameters. This test ensured that initial conditions of the model matched our input demographic parameters, where distributions for age and race were confirmed to be in accordance with empirical distributions. An iterative hyper-parameter grid search algorithm was implemented to fit model behavior to target empirical data using scalar modifiers as fitting parameter inputs. This method is executed by exhaustively searching through a selected range of parameters and their predefined space and evaluating model output performance at each input set by calculating R^2 as a measure of fit. The algorithm result chosen was based on the best fit of empirical data, as well as that result that required the least absolute Manhattan distance from the initial parameterized input variables (that is, the smallest linear combination of R^2 and absolute value of scaling parameter change from 1). This heuristic was implemented to minimize excessive scaling of parameters required to achieve proper empirical fitting to observed data. Each individual iteration of a single input parameter selection was run ten times and an average result of the target parameter for each grid point calculated.

The primary calibration targets were that of annual HIV incidence by race. We used annual HIV incidence estimates from a prospective cohort study of Black and White MSM in Atlanta (6.5 and 1.7 per 100 person-years, respectively).[15] We were able to reproduce these values as 6.37 (95% SI: 6.09, 6.58) and 1.61 (95% SI: 1.48, 1.72) per 100 person-years, respectively, for the no-PrEP base case, and assumed that, in the base case scenario with no PrEP, annual HIV incidence remains stable over the course of the simulation. These calibration targets were achieved by scaling parameters related to the number of sexual acts engaged in per-time step, race-based assortative

mixing in sexual partnerships, and condom use parameters. Once a satisfactory fit was achieved, these input parameters were fixed and held constant for the next iteration of calibration on the secondary set of targets.

We then evaluated trajectories of diagnosed HIV infections, AIDS prevalence, and HAART prevalence among those diagnosed, and adjusted scalars on the monthly probabilities of testing for HIV infection, progression to AIDS, and ART enrollment/discontinuation to ensure these values remained stable about the parameterized initial condition at the start of the model run. These parameters were then fixed at constant values as an additional tightly bound grid search for HIV incidence by race was run a second time to adjust for any performance loss due to changes in population dynamics with altered diagnosis rates, AIDS prevalence, and HAART utilization levels. Typically, these parameters required little tuning and, therefore, had only a minor impact on overall incidence curves. Lastly, we ensured that mortality measures were in line with maintaining a stable overall growth in prevalent HIV infections as observed in HIV surveillance data from the Georgia Department of Public Health by applying a fixed scalar value to the per-month mortality probability for each agent class. The performance of the calibrated model in comparison to empirical targets for the number of HIV-infected agents (Supplemental Figure 1) and the proportion of HIV-infected agents aware of their infection status (Supplemental Figure 2) are shown.

Sensitivity Analyses

As described in the manuscript, sensitivity analyses were performed on factors suspected to strongly influenced the main results, including the efficacy of LA-PrEP in preventing HIV

acquisition (decreasing from the efficacy assayed in macaques, >99%, to theoretical efficacies ranging from 80% to 95% in 5% increments), the half-life of CAB (decreasing from the mean half-life observed in humans of 40.0 days to minimum half-life observed in humans of 18.4 days), and the duration of protection afforded by CAB following a final injection (decreasing from 12 months to 0 months). In addition, we varied rates of retention in clinical care in LAI-PrEP (decreasing from 85% to 50% and increasing to 95%). These analyses were selected to challenge the sensitivity of the main analysis to assumptions made, such as inference of parameters from a macaque model when values for these parameters are currently unknown for humans.[32,37] The results regarding the cumulative number of new HIV infections over the simulation period for all sensitivity analyses are presented in Supplemental Figures S3 through S6.

Technical Details

Python™ (Version 2.7.13), an open-source programming language, was used for coding, testing, and calibrating the model. The simulation generated an agent matrix of 11,245 agents. Information on the current agent state and each agent's partners were recorded at each time step. Agents were assigned partners using the methods described in the "Network Structure" section of this supplemental file and then interacted along their network edges as described in the "HIV Transmission" section of this file.

The simulations were run on Oscar, Brown University's research computing cluster, which operates on the CentOS 6.7 Linux operating system and utilizes the SLURM workload manager. The simulations were processed using 2.53 GHz Intel Xeon E5540 processors operating with 8 cores at 14.84 Teraflops and 12GB of DDR3 memory. The model was run for a duration of 120

time-steps (10 years) and averaged over a total of 500 Monte Carlo runs per scenario, each with a stochastically generated population following the parameters provided in Supplemental Table 1. These 500 runs were run in parallel and aggregated from bundles of 100-run units, with each unit having an average runtime of 2.36 hours.

References

1. Rosenberg ES, Grey JA, Sanchez TH, Sullivan PS. Rates of prevalent HIV infection, prevalent diagnoses, and new diagnoses among men who have sex with men in US states, metropolitan statistical areas, and counties, 2012-2013. *JMIR Public Health Surveill*. 2016;2(1):e22.

2. Marshall BDL, Friedman SR, Monteiro JFG, et al. Prevention and treatment produced large decreases in HIV incidence in a model of people who inject drugs. *Health Aff* . 2014;33(3):401-409.

3. Marshall BDL, Paczkowski MM, Seemann L, et al. A complex systems approach to evaluate HIV prevention in metropolitan areas: preliminary implications for combination intervention strategies. *PLoS One*. 2012;7(9):e44833.

4. Galea S, Hall C, Kaplan GA. Social epidemiology and complex system dynamic modelling as applied to health behaviour and drug use research. *Int J Drug Policy*. 2009;20(3):209-216.

5. Maglio PP, Mabry PL. Agent-based models and systems science approaches to public health. *Am J Prev Med*. 2011;40(3):392-394.

6. Auchincloss AH, Diez Roux AV. A new tool for epidemiology: the usefulness of dynamic-agent models in understanding place effects on health. *Am J Epidemiol*. 2008;168(1):1-8.

7. Grimm V, Berger U, Bastiansen F, et al. A standard protocol for describing individual-based and agent-based models. *Ecol Modell*. 2006;198(1):115-126.

8. Marshall BDL, Galea S. Formalizing the role of agent-based modeling in causal inference and epidemiology. *Am J Epidemiol*. 2015;181(2):92-99.

9. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: A systematic review. *AIDS*. 2014;28(10):1509-1519.

10. Georgia Department of Public Health. Adult (Core) HIV/AIDS Surveillance. https://dph.georgia.gov/adult-core-hivaids-surveillance. Published April 17, 2017.

11. Grey JA, Bernstein KT, Sullivan PS, et al. Estimating the population sizes of men who have sex with men in US states and counties using data from the American Community Survey. *JMIR Public Health and Surveillance*. 2016;2(1).

12. United States Census Bureau. Community Facts - City of Atlanta, Georgia. American FactFinder. https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=CF. Published October 5, 2010. Accessed November 13, 2017.

13. Rosenberg ES, Millett GA, Sullivan PS, del Rio C, Curran JW. Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: A modelling study. *Lancet HIV*. 2014;1(3):e112-e118.

14. Sullivan PS, Peterson J, Rosenberg ES, et al. Understanding racial HIV/STI disparities in

black and white men who have sex with men: A multilevel approach. *PLoS One*. 2014;9(3):e90514.

15. Sullivan PS, Rosenberg ES, Sanchez TH, et al. Explaining racial disparities in HIV incidence in black and white men who have sex with men in Atlanta, GA: a prospective observational cohort study. *Ann Epidemiol*. 2015;25(6):445-454.

16. Wall KM, Stephenson R, Sullivan PS. Frequency of sexual activity with most recent male partner among young, Internet-using men who have sex with men in the United States. *J Homosex*. 2013;60(10):1520-1538.

17. Chan PA, Rose J, Maher J, et al. A Latent Class Analysis of Risk Factors for Acquiring HIV Among Men Who Have Sex with Men: Implications for Implementing Pre-Exposure Prophylaxis Programs. *AIDS Patient Care STDS*. 2015;29(11):597-605.

18. Escudero DJ, Lurie MN, Mayer KH, et al. The risk of HIV transmission at each step of the HIV care continuum among people who inject drugs: a modeling study. *BMC Public Health*. 2017;17(1):614.

19. Hamilton DT, Handcock MS, Morris M. Degree distributions in sexual networks: a framework for evaluating evidence. *Sex Transm Dis*. 2008;35(1):30-40.

20. Handcock MS, Jones JH. Likelihood-based inference for stochastic models of sexual network formation. *Theor Popul Biol*. 2004;65(4):413-422.

21. Rosenberger JG, Reece M, Schick V, et al. Condom use during most recent anal intercourse event among a US sample of men who have sex with men. *J Sex Med*. 2012;9(4):1037-1047.

22. Centers for Disease Control and Prevention. *HIV Infection Risk, Prevention, and Testing Behaviors among Men Who Have Sex with Men - National HIV Behavioral Surveillance, 20 U.S. Cities, 2014*. Atlanta, Georgia: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention; 2016.

23. Gorbach PM, Weiss RE, Jeffries R, et al. Behaviors of recently HIV-infected men who have sex with men in the year postdiagnosis: effects of drug use and partner types. *J Acquir Immune Defic Syndr*. 2011;56(2):176-182.

24. Gorbach PM, Drumright LN, Daar ES, Little SJ. Transmission behaviors of recently HIV-infected men who have sex with men. *J Acquir Immune Defic Syndr*. 2006;42(1):80-85.

25. Colfax GN, Buchbinder SP, Cornelisse PGA, Vittinghoff E, Mayer K, Celum C. Sexual risk behaviors and implications for secondary HIV transmission during and after HIV seroconversion. *AIDS*. 2002;16(11):1529-1535.

26. Robison LS, Westfall AO, Mugavero MJ, et al. Short-term discontinuation of HAART regimens more common in vulnerable patient populations. *AIDS Res Hum Retroviruses*. 2008;24(11):1347-1355.

27. Egger M, May M, Chêne G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*.

2002;360(9327):119-129.

28. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS*. 2001;15(9):1181-1183.

29. Chan PA, Mena L, Patel R, et al. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities. *J Int AIDS Soc*. 2016;19(1):20903.

30. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med*. 2012;4(151):151ra125.

31. HIV Prevention Trials Network. A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men. https://www.hptn.org/research/studies/hptn083. Published 2016.

32. Andrews CD, Bernard LS, Poon AY, et al. Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251. *AIDS*. 2017;31(4):461-467.

33. Andrews CD, Spreen WR, Mohri H, et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. *Science*. 2014;343(6175):1151-1154.

34. Markowitz M, Frank I, Grant RM, et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): A multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. *Lancet HIV*. 2017;4(8):e331-e340.

35. Landovitz R, Li S, Grinsztejn B, et al. Safety, tolerability and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected women and men: HPTN 077. In: *9th IAS Conference on HIV Science*. ; 2017.

36. Windrum P, Fagiolo G, Moneta A. Empirical validation of agent-based models: Alternatives and prospects. *Journal of Artificial Societies and Social Simulation*. 2007;10(2):8.

37. Spreen WR, Margolis DA, Pottage JC Jr. Long-acting injectable antiretrovirals for HIV treatment and prevention. *Curr Opin HIV AIDS*. 2013;8(6):565-571.

38. Centers for Disease Control and Prevention. CDC Wonder Database. Centers for Disease Control and Prevention. https://wonder.cdc.gov/. Accessed November 13, 2017.

Supplemental Tables and Figures

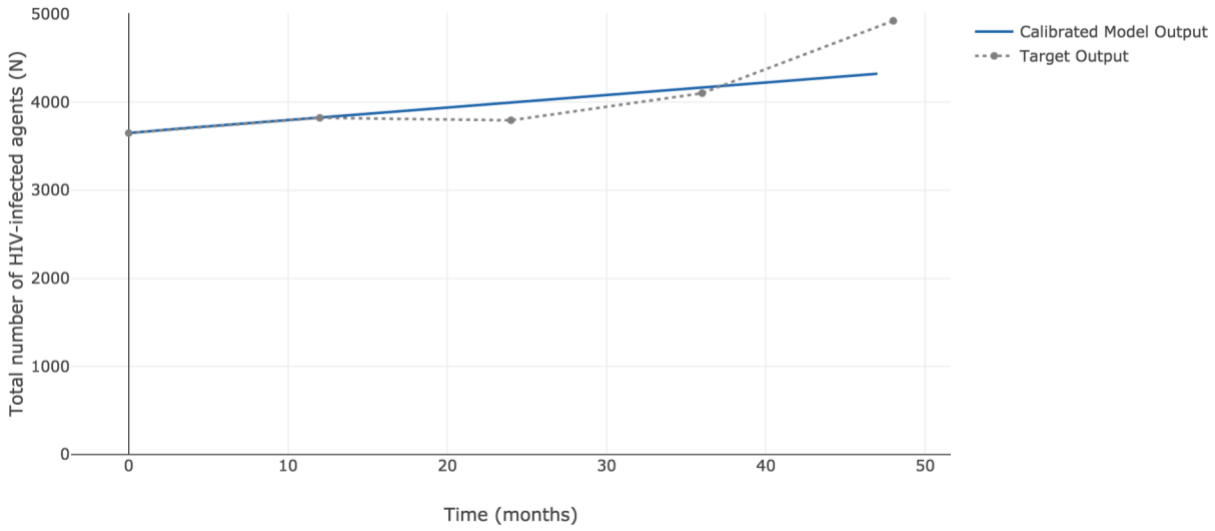
Supplemental Table S1. Initial Model Parameters

Domain	Description
Demographics	
Population size[11]	*n* = 11,245
Age[12]	18 to 19 years old: 4.9% 20 to 29 years old: 23.2% 30 to 39 years old: 24.7% 40 to 49 years old: 26.1% 50 to 59 years old: 21.0%
Race/ethnicity[12]	White, non-Hispanic: 43.5% Black, non-Hispanic: 56.5%
Mortality rates[38]	White MSM - No HIV Infection: 8.6 per 1000 person-years - HIV-infected, HAART: 8.6 per 1000 person-years - HIV-infected, No HAART: 17.2 per 1000 person-years - AIDS diagnosis: 34.4 per 1000 person-years Black MSM - No HIV Infection: 10.4 per 1000 person-years - HIV-infected, HAART: 10.4 per 1000 person-years - HIV-infected, No HAART: 20.8 per 1000 person-years - AIDS diagnosis: 41.6 per 1000 person-years
HIV Risk Behaviors	
Number of sex acts per year[16]	1 act: 1.8% 2 to 5 acts: 8.2% 6 to 11 acts: 6.3% 12 to 23 acts: 7.2 24 to 35 acts: 29.9% 36 to 51 acts: 20.0% 52 to 155 acts: 12.4% ≥156 acts: 14.1%
Sexual role in anal intercourse[21]	Receptive: 39.5% Insertive: 42.1% Versatile: 18.4%
Per-act probability of condomless anal intercourse[21]	0 prior encounters with partner: 46.6% 1 prior encounters with partner: 50.3% 2 to 9 prior encounters with partner: 53.9%

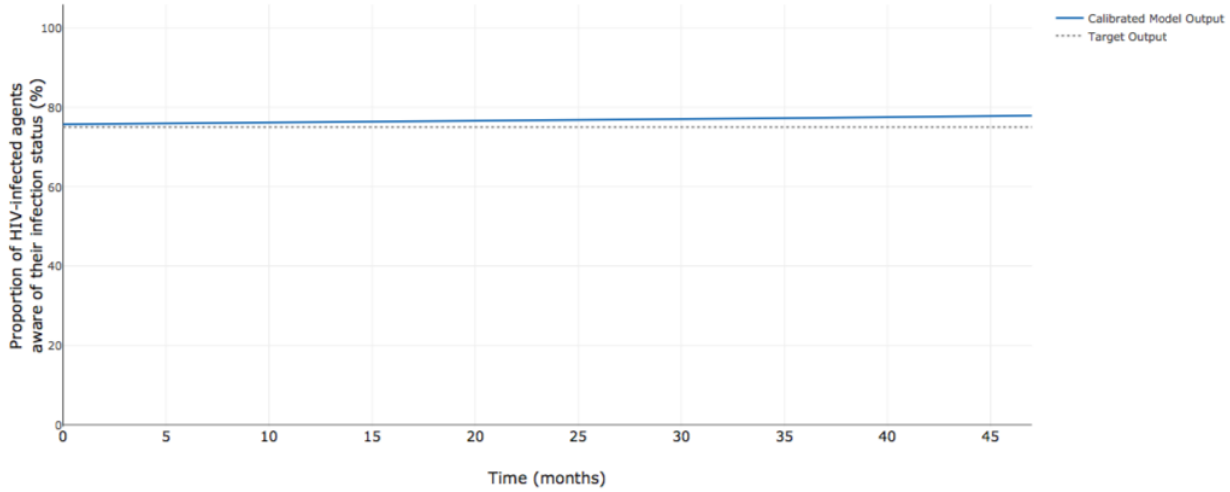
	≥10 prior encounters with partner: 77.0%
Per-act transmission risk (Condomless Anal Intercourse)[9]	Receptive partner base risk: 1.38% per-act Insertive partner base risk: 0.11% per-act
Sexual Networks	
Number of sex partners per year[17]	0 partners: 8.4% 1 partner: 24.4% 2 partners: 16.3% 3 to 4 partners: 17.6% 5 to 9 partners: 25.3% ≥10 partners: 7.9%
Duration of relationships[16]	Less than 1 month: 32.3% 1 to 6 months: 26.2% 7 to 12 months: 11.6% 13 to 24 months: 12.1% 25 to 36 months: 6.0% ≥37 months: 11.8%
Daily Oral Pre-Exposure Prophylaxis	
Population-level coverage	5% to 35%, in 5% increments
Probability of retention in clinical care[29]	3 months post-initiation: 72.5% 6 months post-initiation: 59.6%
Probability of full adherence (≥4 pills per week)[29]	92.3%
Percent reduction in per-act transmission risk[30]	96.0% (≥4 pills), 76.0% (2–3 pills)
Long-Acting Injectable Pre-Exposure Prophylaxis	
Population-level coverage	5% to 35%, in 5% increments
Probability of retention in clinical care[35]	2 months post-initiation: 84.8% Varies as a function of time since last injection
Percent reduction in per-act transmission risk[32]	
HIV Testing	
Probability of having ever tested[22]	92.8%

Annual probability of obtaining HIV testing[22]	69.0%
HIV Treatment	
Proportion of PLWH aware of their HIV infection status[13]	84.4% (White MSM), 74.7% (Black MSM)
Proportion of PLWH on HAART[13]	46.7% (White MSM), 26.2% (Black MSM)
Proportion of PLWH with viral load suppression[13]	40.5% (White MSM), 21.0% (Black MSM)
Percent Reduction in Per-Act Transmission with HAART[9]	96.0%, among PLWH with viral load suppression

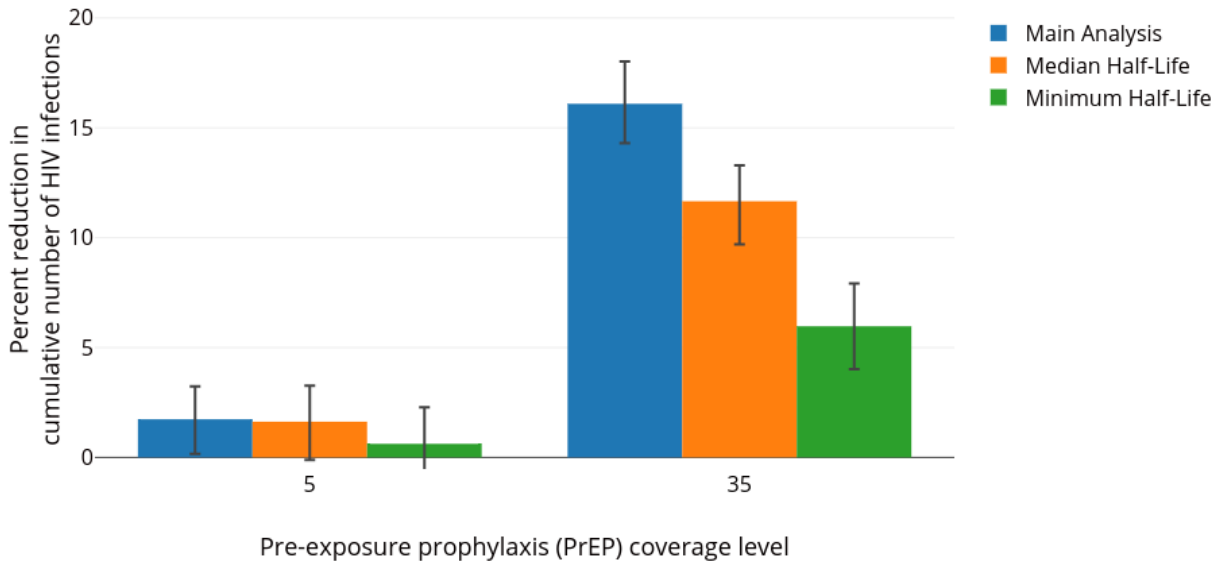
Note: Men who have sex with men (MSM); Highly active antiretroviral therapy (HAART); People living with HIV (PLWH)



Supplemental Figure S1. Model output after calibration compared to empirical targets for the cumulative number of HIV-infected agents among MSM in Atlanta, Georgia (2011-2015).[10]

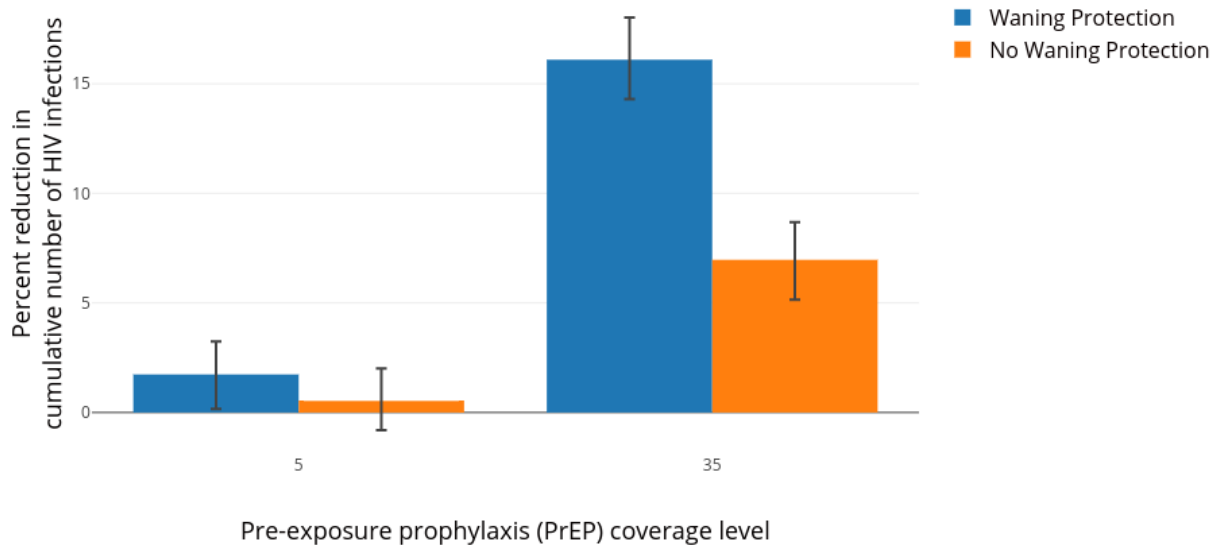


Supplemental Figure S2. Model output after calibration compared to empirical targets for the proportion of HIV-positive agents with diagnosed HIV infection among MSM in Atlanta, Georgia (2011-2015).[13]

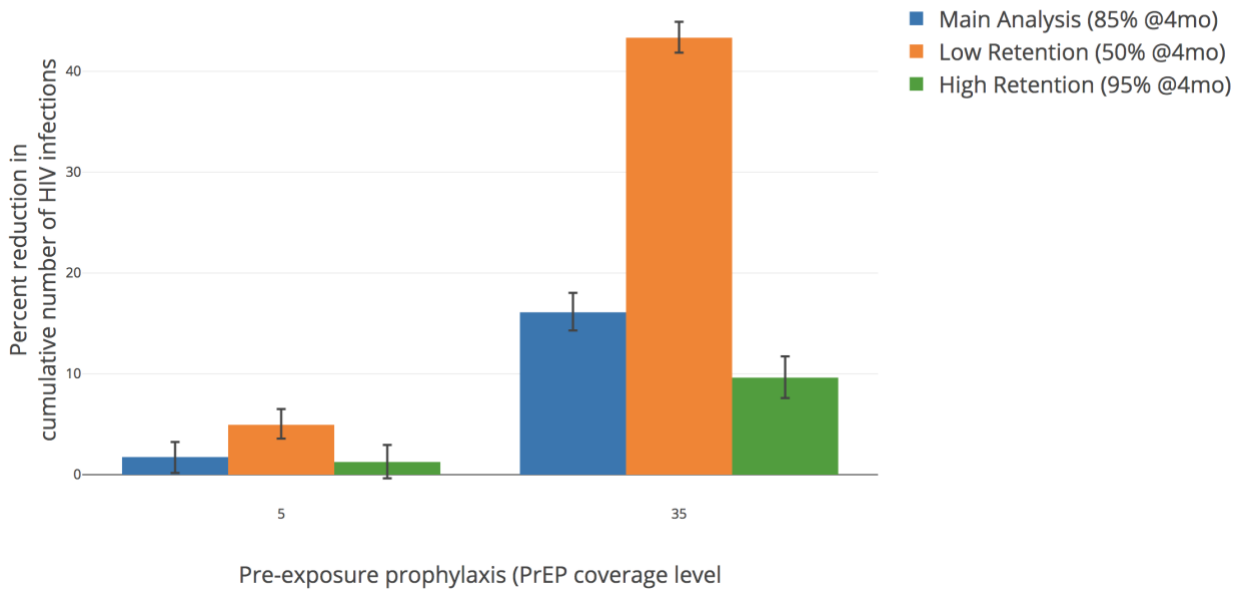


Supplemental Figure 3. Percent reduction in cumulative number of new HIV infections with LAI-PrEP among MSM in Atlanta, Georgia (2015–2024) relative to equivalent coverage of daily oral PrEP, with varying length of CAB half-life

Note: The half-life used in the main analysis was 40.0 days. The median half-life is 29.2 days and the minimum half-life is 18.4 days. These values are derived from Phase II trial data in humans.[34]



Supplemental Figure S4. Percent reduction in cumulative number of new HIV infections with LAI-PrEP among MSM in Atlanta, Georgia (2015–2024) relative to equivalent coverage of daily oral PrEP, with varying waning period of protection.



Supplemental Figure S5. Percent reduction in cumulative number of new HIV infections with LAI-PrEP among MSM in Atlanta, Georgia (2015–2024) relative to equivalent coverage of daily oral PrEP, with varying retention on LAI-PrEP.

Note: These analyses assume constant population-level coverage (i.e., that those who are not retained in care are immediately replaced by a steady state of potential users). This assumption of constant coverage is needed to isolate the effects of retention in care from other factors (e.g., initiation rates, efficacy) on the benefits of LAI-PrEP relative to oral PrEP.