The Impacts of Sexual Role, HIV Treatment, and Pre-Exposure Prophylaxis Use on HIV Set Point Viral Load: A Network Modeling Study

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Abstract

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The analyses in this dissertation investigate how sexual role, treatment increases, and pre-exposure prophylaxis (PrEP) increases impact HIV virulence. All analyses used set point viral load (SPVL), the viral load (VL) found shortly after the period of acute HIV infection, as a proxy for virulence. This is a good proxy because higher SPVLs are associated with faster progression to AIDS and higher probability of transmission. The aims of this dissertation were: 1) to understand the effects of different sexual roles in MSM (exclusively insertive, exclusively receptive, or versatile) on the virulence of the viruses men acquired; 2) to understand the effects of increasing treatment on HIV virulence evolution; and 3) to understand the effects of increasing PrEP on HIV virulence evolution.

All chapters used a stochastic, dynamic network model (EvoNetHIV) to partially or fully complete their analyses. EvoNetHIV is based in temporal exponential random graph models (ERGMs) and uses the *statnet* suite of R packages and the EpiModel package API.

The findings in these studies help to overturn the previously modeled trade-offs in which higher treatment or PrEP coverage resulted in higher HIV virulence. Instead, increasing treatment or PrEP coverage can lead to lower virulence levels becoming evolutionarily advantageous, allowing their influences to positively affect the entire population. They also show that, because different sexual roles are associated with different HIV acquisition probabilities, there are significant differences in the virulence of the viruses men with different sexual roles acquire. These studies also show how virulence evolves differently when contrasting pressures are present: infected individuals going on treatment creates a different evolutionary environment than do susceptible individuals going on PrEP. Finally, these studies emphasize the impacts of model assumptions on all outputs. Careful consideration of and transparency about model assumptions are important for realistic and replicable models.

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Introduction

HIV & Set Point Viral Load

Human immunodeficiency virus (HIV) infection occurs in three phases: acute, chronic, and AIDS phase. There are distinct transmission probabilities, governed by viral load (VL), at each phase. In the acute phase, VL increases rapidly as the virus multiplies, then decreases as the immune system regains control (Figure 1, (Nelson, 2007)). This phase lasts approximately three months and has very high transmission potential, as there is high VL here. While the acute phase may be asymptomatic, flu-like symptoms are common here and severity of symptoms is correlated with VL (Kelley et al., 2007). In addition to high VL driving high transmission probability, there may be as much as a five-fold increase in transmission risk during this phase once VL is controlled for (Wawer et al., 2005), because the recently acquired virus is optimized for transmission. In the chronic phase, VL increases slowly over many years. In men who have sex with men (MSM) in Europe, North American and Australia, this phase has a median duration of 9.4 years (95% CI 8.7,10.0) without treatment (Babiker et al., 2000). Without treatment, there is a large amount of variation in both length of infection and probability of transmission based on SPVL here (Mellors et al., 1997; Modjarrad et al., 2008). Finally, in the AIDS phase, VL (and transmission risk) increases dramatically as the immune system can no longer control the virus. One hallmark of the AIDS phase is the development of opportunistic infections, such as *Pneumocystis carinii* pneumonia or HIV wasting syndrome, due to the infected individual's immunocompromised state (Nelson, 2007).

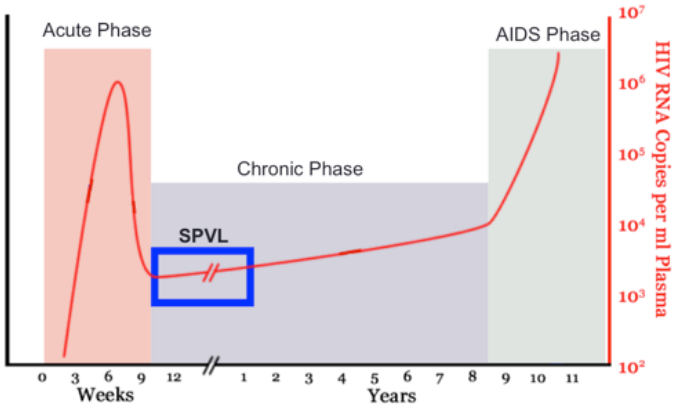

Figure 1: HIV viral load progression and SPVL measurement in an individual (http://www.healthhype.com/wp-content/uploads/Hiv-timecourse.png, modified)

HIV set point viral load (SPVL) is the VL established at the beginning of the chronic phase. It is also a good proxy for viral virulence (the severity of disease) as it influences both disease progression and thus mortality. It also impacts the probability of transmission. Without treatment, higher SPVLs result in higher VLs throughout the course of infection, which cause faster progression to AIDS-defining illnesses (Modjarrad et al., 2008) and higher transmission probabilities (Fraser et al., 2007b; Hughes et al., 2012a). There are high levels of heterogeneity in SPVL between individuals (Figure 2). Individual SPVLs can vary between 10^2—10^6 $\log_{10}$ copies/mL of blood (Fraser et al., 2007b) and are therefore usually referenced on the log scale.

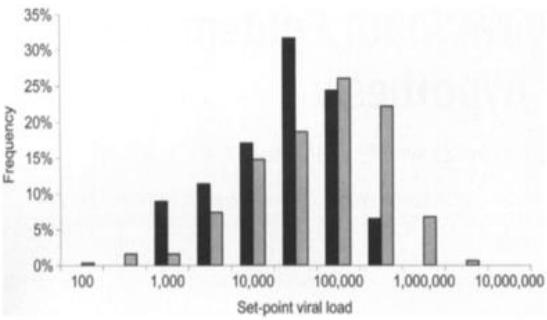

Figure 2: Range of variation in individual SPVLs in two populations. Gray bars show SPVL values from the Zambian Transmission Study while black bars show values from the Amsterdam Seroconverters Cohort (from Fraser et al. (2007b))

Many factors within an individual can influence SPVL. SPVLs for females are usually lower than for males (Gandhi et al., 2002). Genital tract inflammation from sexually transmitted infections (STIs) can increase HIV SPVL as the inflammation causes immune cells to be concentrated at the genital tract, where they can quickly become infected with HIV (Roberts et al., 2012). CCR5Δ32 is a genetic mutation that causes, in the homozygotic form, the carrier to be protected from most forms of HIV infection (Sabeti et al., 2005). Heterozygotes with this mutation are less susceptible to HIV and those who become infected generally have progression to AIDS delayed by two to three years (Blanpain et al., 2002).

SPVL is partially heritable from the infecting partner (Bonhoeffer et al., 2015). One meta-analysis estimated that 33% (95% CI 20-46%) of the variation in SPVL between individuals is due to heritability (Fraser et al., 2014). This estimate comes from three studies comparing SPVLs between partners in couples where transmission is likely to have occurred, with a total of 433 couples (Hollingsworth et al., 2010b; Lingappa et al., 2013; Yue et al., 2013).

Alizon et al. (2010) estimated that the viral genotype could explain up to 59% of the variance in SPVL by reconstructing a phylogeny of infections with viral sequence data. While other estimates of heritability range from 2% to 50%, the wide range in these estimates may arise as studies estimate heritability with factors only indirectly related to the actual measure (Fraser et al., 2014).

Because SPVL has high levels of heterogeneity between infected individuals, is partially inherited from the infecting partner, and different genetic strains of HIV (with different associated SPVLs) compete for survival and transmission, SPVL can evolve via natural selection. We can therefore consider the optimal level it can evolve to under different conditions.

Virulence Evolution

Virulence evolution in HIV and other infectious diseases is constrained by a trade-off curve (Figure 3, (Alizon et al., 2009; Bull and Lauring, 2014)). The theoretical literature suggests that transmission potential is tied to duration of infection (comprising both mortality and recovery rates). While a pathogen may begin under the curve, evolution will favor pathogen strains that move toward the boundary of the curve to maximize transmission. Once it reaches the boundary, however, transmission rate can only increase if mortality or recovery rates change as well. Models with some simplifying assumptions find that a line tangent to the curve and passing through the origin gives the most evolutionarily optimal level of virulence. In HIV, the duration of infection is determined solely thorough mortality as there is no recovery. HIV follows the trade-off curve constraint, as time to AIDS-defining illness and probability of transmission are linked: both depend on SPVL level (Fraser et al., 2007b; Hughes et al., 2012a; Modjarrad et al., 2008). Viruses with lower SPVL allow for longer duration of asymptomatic infection so that there can be more potential transmission events, though each event will have a lower probability of transmission. In contrast, higher SPVL viruses will have fewer potential transmission events with a higher chance of transmission at each one.

Figure 3: The trade-off curve (solid line) is the boundary of potential combinations of a pathogen's transmission rate and mortality rate. The tangent of the curve passing through the origin (dotted line) gives the evolutionarily optimal level of virulence (from Goodreau et al. (2018b), modified).

One of the oldest theories about how virulence evolution occurs was the avirulence hypothesis, which suggested that new infectious diseases tended to be more virulent, and subsequent evolution towards less virulent forms would be favored (Alizon et al., 2009). This hypothesis is not supported by many infectious diseases that have been present in humans for a great deal of time but remain highly virulent, such as tuberculosis. Other theories on the evolution of virulence consider the pathogen's transmission mechanism. Ewald (2011a); (1983b) argues that pathogens that require their hosts make direct contact with susceptible individuals in order to spread, such as sexually transmitted infections (STIs), should allow the host to remain mobile longer than other pathogens. He hypothesizes that this is why STIs such as HIV are generally benign in the early stages of infection but may be fatal in later years. Ewald (2011a) further suggests that, if there is high potential for sexual transmission, sexually transmitted pathogens will become more virulent.

HIV Virulence Evolution

Recent modeling work has shown that individual-level behavior can influence HIV virulence evolution, consistent with Ewald's (2011a) hypothesis. Factors such as sexual role,

relationship duration, and coital frequency can affect the virulence of a strain one person acquires, and on a population level, influence the evolution of HIV virulence over time in a group. Concurrency, which occurs when individuals have multiple ongoing and overlapping sexual relationships, affects HIV incidence (Goodreau et al., 2012b; Morris and Kretzschmar, 1997) and SPVL evolution (Goodreau et al., 2018b). If there are high levels of concurrency in a population, more infections are likely to occur early in the course of infection. This occurs as a newly positive person is not exclusively with the partner who infected them during the highly infectious acute phase. If many transmissions can occur early in the course of infection, the drawback of a shorter time to AIDS-defining illness is less influential, and higher mean SPVLs can evolve in a population (Goodreau et al., 2018b). Shorter relationship durations can influence SPVL evolution in a similar way if individuals are likely to end one relationship and begin another while still in the acute phase (Goodreau et al., 2018b).

In mathematical models with no treatment, Fraser et al. (2007b) found that SPVL evolved to intermediate levels (mean 4.52 $\log_{10}$ copies/mL) to maximize transmission potential in a population where most individuals were not infected and partner change rates were high enough not to limit transmission. The intermediate SPVLs balanced length of infection with probability of transmission at each serodiscordant act to generate more new infections than in individuals with higher or lower SPVLs. This model estimate was supported by data from the Amsterdam Seroconverters Cohort (de Wolf et al., 1997) and the Zambian Transmission study (Fideli et al., 2001a); these were both studies of populations before treatment became available and in which intermediate VLs were the most common (Fraser et al., 2007b).

Whether worldwide HIV virulence is changing through time has been examined in cohorts of HIV positive individuals, but results have been contradictory: some studied found that virulence increased (Dorrucci et al., 2005; Dorrucci et al., 2007), some found virulence decreased (Keet et al., 1996; Payne et al., 2014), and some found no change (Herbeck et al., 2008; Muller et al., 2006).

HIV Treatment and Prevention Efforts

Large-scale innovations in HIV care and prevention dramatically change the environment in which HIV exists and so have enormous potential implications for HIV virulence evolution. Treatment increases around the world are one example of this. Current antiretroviral therapy

(ART) guidelines are to initiate treatment as soon as HIV is diagnosed, in order to prevent disease progression and onward transmission (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016). This recommendation was initiated in 2015 by the World Health Organization (World Health Organization, 2015a). Individuals who achieve durable HIV suppression with ART reduce risk of transmission to their partners by over 96% (Cohen et al., 2011; Quinn et al., 2000b) and those who are fully adherent to ART, with undetectable VLs, are extremely unlikely (perhaps entirely so) to transmit to their sexual partners, known in public health messaging as U=U (Undetectable = Untransmittable) (Rodger et al., 2016)). Despite treatment guidelines, ART use is far from universal for multiple reasons. The HIV treatment cascade includes diagnosis, linkage to care, retention in care, ART adherence, and viral suppression (Kay et al., 2016). At a population level, the proportion of people living with HIV (PLWH) falls at each step of the cascade. While approximately 86% of PLWH in the United States are diagnosed, the percent of PLWH who are durably virally suppressed is only estimated at 30% (Kay et al., 2016). ART use has continually increased since its introduction, although initiation guidelines have changed over time. Earlier antiretroviral drugs had more potent side effects, which made treatment delay recommended for individuals whose immune system function had not yet begun to deteriorate past certain thresholds. For example, before 2015, individuals with HIV whose CD4 counts were over 500 cells/μL did not have a clear indication to begin ART (Coffey and Agins, 2011).

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy in which HIV-negative individuals take ART to reduce their HIV acquisition risk. Daily oral PrEP was approved by the US Food and Drug Administration in 2012 (US Food and Drug Administration, 2012). This regimen consists of a tablet including tenofovir disoproxil fumarate and emtricitabine. It has been shown to reduce the probability of HIV acquisition by 95% or more when taken as directed (Grant et al., 2014; Molina et al., 2017). PrEP use has continued to increase since its introduction: in 2014, the proportion of MSM reporting PrEP use in the Centers for Disease Control's (CDC) National HIV Behavioral Surveillance (NHBS) was 6% while in 2017 it was 35% (Finlayson et al., 2019). These increases have important racial differences, as 2017 PrEP use was 42% in white men and 26% in black men, despite persistently higher risk of HIV acquisition in the latter group. PrEP use is also concentrated in the US, which accounts for 71%

of all users worldwide (Fitch et al., 2018), followed by Sub-Saharan Africa, accounting for 15% of users.

Population

In the United States, men who have sex with men (MSM) have the highest proportion of new infections each year, accounting for 67% of new HIV infections in 2016 (CDC Fact Sheet 2018). US MSM also have high levels of HIV testing and treatment, as 71.1% of US MSM reported testing in the previous year in the 2014 National HIV Behavioral Surveillance data (Hall et al. 2017) and 52% of HIV-positive US MSM were virally suppressed in 2015 (CDC Fact Sheet, 2018). HIV is likely to face different evolutionary pressures in an MSM population than in a heterosexual population: anal intercourse has a higher probability of transmission than vaginal intercourse (Patel et al., 2014) and relationship patterns are different between MSM and heterosexuals (Glick et al., 2012).

This dissertation was inspired by three questions surrounding human behavior and human-pathogen coevolution. The studies here examine factors inherent in HIV acquisition and virulence evolution over time in a US MSM population. Because current ART recommendations are to treat all HIV cases immediately, SPVL can no longer be measured, leaving simulation the only way to estimate these effects on viral evolution.

Question 1:

Is HIV virulence different in men with different sexual roles?

The first aim in this dissertation was to investigate, in both mathematical models and in actual data, whether sexual role in US MSM can influence the virulence of the viruses acquired. There is a large difference in acquisition risk between insertive and receptive anal intercourse (Patel et al., 2014), with receptive anal intercourse having an estimated 12.5-fold higher probability of acquisition. Men who are exclusively insertive thus experience lower acquisition risk than do men who are exclusively receptive or role versatile. This project used a one-generation Bernoulli model, a stochastic dynamic network model, and data from the Multicenter AIDS Cohort Study (MACS) to examine whether this difference in risk of acquisition translated into a difference in the virulence of the virus men with different sexual roles acquired.

Question 2:

Is HIV virulence changing as more people go on treatment in the test-and-treat era?

The second aim of this dissertation was to investigate the consequences of increasing treatment coverage on HIV virulence evolution in an MSM population. Modeling work suggested that increasing treatment coverage can impact virulence evolution (Herbeck et al., 2016; Roberts et al., 2015a), but thus far, to my knowledge, has not considered virulence evolution in an MSM population. Initial results had the opposite direction of effect than what was found in previous models, so the impact of model assumptions on virulence evolution was also examined. This project used a stochastic dynamic network model to estimate virulence changes in an MSM population with increasing treatment coverage under different modeling assumptions.

Question 3:

Is HIV virulence changing as more people go on PrEP?

The third aim of this dissertation was to investigate the consequences of increasing PrEP coverage on HIV virulence evolution in an MSM population. PrEP coverage is increasing, but should impact the HIV evolutionary environment differently than treatment because it removes uninfected individuals from the pool of people susceptible to the disease. This project used a stochastic dynamic network model to examine virulence changes with increasing PrEP coverage in an MSM population with two mean relationship duration groups and heterogeneity in PrEP adherence. Modeling differences in mean relationship duration was important, as individual-level risk behaviors are key in targeting PrEP to those at higher risk of HIV acquisition. This project also included several sensitivity analyses to investigate whether these findings were robust to assumptions about HIV transmission function, risk compensation, PrEP adherence in relation to risk group, and assortative mixing within groups (when the majority of relationships are between individuals in the same group).

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Chapter 1: Sexual role and HIV-1 set point viral load among men who have sex with men

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Running Head: MSM Sexual Role and Set Point Viral Load

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Abstract

Background. HIV-1 set point viral load (SPVL) is a highly variable trait that influences disease progression and transmission risk. Men who are exclusively insertive (EI) during anal intercourse require more sexual contacts to become infected than exclusively receptive (ER) men. Thus, we hypothesize that EIs are more likely to acquire their viruses from highly infectious partners (i.e., with high SPVLs) and to have higher SPVLs than infected ERs.

Methods. We used a one-generation Bernoulli model, a dynamic network model, and data from the Multicenter AIDS Cohort Study (MACS) to examine whether and under what circumstances MSM differ in SPVL by sexual role.

Results. Both models predicted higher SPVLs in EIs than role versatile (RV) or ER men, but only in scenarios where longer-term relationships predominated. ER and RV men displayed similar SPVLs. EI men remained far less likely than ER men to become infected, however. When the MACS data were limited by some estimates of lower sex partner counts (a proxy for longer relationships), EI men had higher SPVLs; these differences were clinically relevant (>0.3 $\log_{10}$ copies/mL) and statistically significant ($p<0.05$).

Conclusions. Mode of acquisition may be an important aspect of SPVL evolution in MSM, with clinical implications.

Keywords

HIV-1, network modeling, mathematical modeling, men who have sex with men (MSM), sexual role, MACS study, set point viral load

Introduction

Viral load (VL)—the density of HIV-1 particles in an infected person's peripheral blood plasma—varies over time and across individuals. Set point viral load (SPVL)—the average viral load during the period shortly after acute HIV-1 infection—also varies. Individuals with higher SPVLs average faster disease progression in the absence of treatment (Modjarrad et al., 2008), while higher plasma VL is associated with higher rates of transmitting HIV-1 (Fideli et al., 2001b; Quinn et al., 2000a). This viral evolutionary trade-off spawned the hypothesis that, after introduction of the virus into a treatment-naïve population, HIV-1 evolves to intermediate SPVL values; one model found that, for their proposed relationship between VL and transmission, SPVL evolved to a value (4.52) close to the mean observed within some empirical populations (Fraser et al., 2007b).[1]

Nonetheless, SPVL varies greatly among infected individuals, as influenced by host HLA and CCR5 genotypes (Blanpain et al., 2002; McLaren et al., 2015; Sabeti et al., 2005), age (Hollingsworth et al., 2010b), sex (Gandhi et al., 2002), repeated exposure (Hasselrot et al., 2010; Pala et al., 2013), concurrent STI infection (Roberts et al., 2012), and viral genotype (Fraser et al., 2014; Touloumi et al., 2013). Intra-host meta-population dynamics may also play a role (Lythgoe et al., 2016). Heritability in SPVL between HIV-1 donor and recipient—that is, the proportion of the variation in SPVL among individuals that is attributable to variation in the viral genotype—is maintained despite the wide range of host responses (Bonhoeffer et al., 2015; Hollingsworth et al., 2010b; Lingappa et al., 2013; Yue et al., 2013). Although individual genome studies have presented widely varying estimates of heritability, one meta-analysis

[1] List of main abbreviations: VL = Viral load; SPVL = Set point viral load; MSPVL = Mean set point viral load; MSM = Men who have sex with men; EI = Exclusively insertive; ER = Exclusively receptive; RV = Role versatile; MACS = Multicenter AIDS Cohort Study; AI = Anal intercourse; VI = Vaginal intercourse; PWID = Persons who inject drugs; STERGM = Separable temporal exponential random graph models.

(Fraser et al., 2014) demonstrated that much of this apparent discrepancy is explained by differences in reported metrics; a re-analysis of heritability estimates using a common definition for the classic h^2 measure of heritability across serodiscordant couples studies obtained a pooled estimate of 33% (95% confidence interval, 20 to 46%)

One additional potential source of variation in individual SPVL is the route of HIV-1 acquisition—e.g. insertive vs. receptive role during anal intercourse (AI). These routes entail different *mean* acquisition probabilities (receptive much higher), while the probability for any individual act depends on the transmitting partner's current viral load (VL) (Baggaley et al., 2010; Patel et al., 2014). Although the exact functional form linking VL to transmission probability is debated, there is consensus that transmission risks increase monotonically with VL (Fraser et al., 2007b; Hughes et al., 2012b). Following on a concept introduced in Carlson et al. (2014), we hypothesize that someone who is at high risk of HIV-1 acquisition (e.g., an exclusively receptive male) is more likely to get infected during one of their earliest exposures, and thus to acquire a subset of circulating viruses that is relatively unbiased with respect to fitness. A person engaging in sexual acts with lower transmission risk may require more contacts on average before getting infected, or be disproportionately infected during scenarios with higher transmission probability, i.e. during acute infection or from partners with very high SPVL (Ma et al., 2009; Wawer et al., 2005). The latter effect could theoretically cause sub-populations infected by different routes to have different mean SPVLs (MSPVL).

Indirect evidence for this hypothesis may come from heterosexual transmission. Analyses have found women to have higher per-act risk of acquisition than men during penile-vaginal sex (Patel et al., 2014), and average lower SPVL (Gandhi et al., 2002). One study found that viruses transmitted female-to-male contain amino acid variants reflecting higher mean fitness than those

transmitted male-to-female (Carlson et al., 2014), demonstrating the transmission bottleneck's evolutionary impact and suggesting the potential for SPVL in transmitted strains to differ by sex through similar mechanisms. However, alternative explanations for SPVL sex differences exist. These include higher estrogen concentrations in women, which may reduce TNFα concentration (Shanker et al., 1994) and thus viral expression (Folks et al., 1989; Mellors et al., 1991), and higher progesterone concentration, which could inhibit CCR5 expression (Portales et al., 2001), lowering VL (Jackson, 2015). Some studies of persons who inject drugs (PWIDs) show lower SPVL for women (Farzadegan et al., 1998), supporting endocrine-mediated mechanisms over transmission bottleneck selection. However, other studies found no significant sex differences in PWID's SPVL (Moroni, 1999), and those found could be due to sex-specific cocaine and opiate usage, which upregulates HIV-1 replication (Peterson et al., 1991; Peterson et al., 1990).

To our knowledge, the question of acquisition mode and SPVL has not been explored among men who have sex with men (MSM), even though the effects may be larger among MSM than heterosexuals, as the acquisition probability differential via receptive vs. insertive AI is greater than the same differential (receptive vs. insertive) for vaginal intercourse (Patel et al., 2014). Moreover, MSM are less constrained than heterosexuals in terms of transmission chains alternating by sexual role (Goodreau and Golden, 2007). For heterosexuals, males and females represent each other's source viral pool, and evolution in one group should change the substrate for evolution in the other, holding divergence in check. For MSM, however, an individual man could be infected through receptive AI, allowing transmission of a viral genotype that maintains a relatively low SPVL, and then transmit through insertive AI, allowing his receptive partner to acquire the same low-SPVL genotype. The resulting dynamics are thus less intuitive than for heterosexual transmission. Teasing them apart may provide theoretical insight into SPVL

dynamics, as well as provide an additional explanation for unexplained but clinically relevant SPVL variation. It might also help disentangle hypotheses about SPVL differences by sex for heterosexuals.

In this paper, we use a combination of mathematical modeling and empirical data analysis to explore differences in HIV-1 SPVL among exclusively insertive (EI), exclusively receptive (ER), and role versatile (RV) MSM.

Methods

Our methods comprise three parts: a basic one-generation model to gain insight about expectations under different assumptions; a more complex, data-driven dynamic network simulation to understand SPVL evolution in a linked system between groups; and an empirical analysis of SPVL measures in an HIV-1 incidence cohort, by self-reported sexual role.

One-generation model

Our first model was purposely simple in order to gain theoretical insight, and was not based on empirical data. It is a stochastic agent-based pair-formation Bernoulli model of one generation of HIV-1 transmission from a founder population. Code was written in R and is available at github/EvoNetHIV/RoleSPVL/OneGenModel.

We seeded an initially-infected population of 100,000 men with SPVLs ($\log_{10}$ copies/mL) distributed at random using a beta function with mean 4.5 and range 2-7. We then simulated an equally sized pool of HIV-1-negative men engaging in condomless AI acts with the HIV-1-positive men, comparing runs where the negative men were EI vs. ER. We varied the number of acts per negative man between 1 and 10^4, the order of magnitude we considered a reasonable

upper limit. Values for numbers of acts were concentrated at the lower end of the scale to provide more insight into mean population SPVL where it was changing most quickly. We considered one scenario in which all acts for an HIV-1-negative man were with the same partner, and another in which the HIV-1-negative men randomly select a new partner for each act. Transmission probability depended on each partner's sexual role, the number of acts in the relationship, and the HIV-1-positive partner's SPVL using a modified version of the function in Fraser et al. (2007b). Their function focused on vaginal intercourse (VI) and assumed equal risk for insertive (male) and receptive (female) VI. To convert this to AI, we added two relative risks from Patel et al. (2014), which estimated receptive and insertive AI to have 23.0 and 1.8 times higher acquisition risks per serodiscordant act than VI, when the latter is averaged by role. Fraser's model was also per-time-period, and we back-calculated approximate per-act estimates following our earlier models (see Supplementary section S4). The population had no mortality, arrivals, or departures. As the population was large and the events independent, we did not repeat simulation runs.

Dynamic Network Model

The one-generation model fostered development of basic insight about the relationship between role and SPVL. However, it assumed 100% heritability and complete role segregation, i.e. it did not include RV men. It also ignored the stages of HIV-1 infection that are marked by changes in VL and transmission probability. Moreover, it could not account for the fact that transmissions are a linked system: changes in VL in one generation of transmission changes the source VLs for the next. To explicitly address these points in a more realistic and empirically-parameterized context, we extended a stochastic, dynamic, network-based model described

previously (Herbeck et al., 2018). This code builds upon the *EpiModel* (Jenness et al., 2016a) and *statnet* (Handcock M, 2008, 2016) R packages and is available at github/EvoNetHIV/RoleSPVL. Full methods for this model are found in Supplement Sections S1-S8.

Model parameters governing sexual network structure, sexual role categories and other behavioral parameters, and agent attributes were obtained primarily from two modeling studies of HIV among US MSM, either directly from Jenness et al. (2016c) or by obtaining weighted means of race-specific values in Goodreau et al. (2017). Empirical data for these parameters came from two studies of Atlanta-area non-Hispanic Black and White MSM conducted 2010-2014 (Hernandez-Romieu et al., 2015; Sullivan et al., 2015).

Agents were defined by a variety of attributes (e.g. age, CD4+ cell count); key ones included sexual role (EI, ER, RV), SPVL, and current VL. Sexual network structure was modeled with separable temporal exponential random graph models (STERGM) (Krivitsky and Handcock, 2014a), as implemented in *statnet*. We simulate a dynamic model that maintains the desired network features stochastically. Partnership formation occurred to preserve mean momentary degree (0.70, the average number of relationships a man is in at a cross-section of time), with partnerships between two EI men or two ER men forbidden. Coital acts occurred stochastically within partnerships with probability 0.4/day, but terminated at late-stage AIDS. The number of arrivals followed a Poisson distribution with mean set to give 1% population growth, while departures occurred through AIDS mortality, background mortality, and aging out. Relational dissolution occurred with a constant hazard, leading to geometrically distributed relationship durations. We explored mean relationship durations between 50 and 3,000 days (corresponding roughly to 20-1200 coital acts/relationship given coital frequency). The

transmission function matched that used in our one-generation model. Recipient SPVL had both inherited and non-inherited components, with heritability = 0.36 based on one study (Hollingsworth et al., 2010b); we note this is very similar to the subsequent meta-analysis value of 0.33 described above (Fraser et al., 2014). We did not explicitly model host HLA or other host genetic factors, as we have no expectation that these would systematically differ between EI and ER men. However, we note that non-viral-genetic factors influencing SPVL are implicitly modeled within the non-inherited component of SPVL variation. MSPVL in the initial population was 4.5.

VL varied continuously through time, following a set of parameters described in the Supplement (section S6) and in Herbeck et al. (2018). We modeled four CD4+ cell categories, with transition times dependent on SPVL; CD4+ cell category governed progression and mortality. The model excluded treatment, as our goal was to understand the basic evolutionary dynamics more clearly. Not including treatment also allowed us to compare results to the MACS data, where infections in men in our analysis mainly predate the onset of treatment. The population had 1,000 individuals aged 18-50, with 20% initial HIV-1 prevalence; population size was smaller than for the one-generation model given much higher computational burden. Simulations were run in one-day timesteps, with results compiled from years 2-5 of the simulation; we ran 50 simulations for each relationship duration value. All other parameters were fixed at the point estimates derived from our literature review.

MACS Analysis

Finally, we conducted an empirical analysis of data from the Multicenter AIDS Cohort Study (MACS) (Kaslow et al., 1987), an ongoing prospective cohort study begun in 1984 among

MSM in four US cities. Participants are asked to return every 6 months for HIV-1 testing (including VL measurement) and a behavioral survey. Our initial dataset had 712 individuals, comprising men who entered the study HIV-1-negative and who have seroconverted during the course of the study (Table 1).

Table 1: Derivation of sample

	Variable	N	%
Conditions required for all analyses (nested)	MACS Cohort total	7,087	
	Entered seronegative	4,124 / 7,084	58.2%
	Seroconverted	712 / 4,124	17.3%
	Seroconversion interval <1 year	535 / 712	75.1%
	Had SPVL information	435 / 535	81.3%
	Had seroconversion interval role information	374 / 435	86.0%
Role distribution of sample	Exclusively insertive (EI)	46 / 374	12.3%
	Role versatile (RV)	278 / 374	74.3%
	Exclusively receptive (ER)	50 / 374	13.4%

We defined the interval between last negative visit and first positive visit as the seroconversion interval. While the size of this interval is designed to be 6 months, it varies in practice, sometimes widely. We thus restricted our sample to men for whom a last HIV-1-negative and first HIV-1-positive visit were strictly less than 1 year apart (i.e. maximum 364 days), in order to limit the uncertainty in seroconversion timing; this reduced our sample size to 535. The distribution of the seroconversion interval size is shown in Figure 1; this concentrates around 6 months given the study design, and maxes out at <1 year given our inclusion criterion. Seroconversion could occur anywhere within the interval. We estimated SPVL by using VL measures for study visits between 6 and 18 months after the midpoint of the seroconversion interval (Herbeck et al., 2008). If two visits fell in the interval, their $\log_{10}$ measures were

averaged. For men following the 6-month visit schedule perfectly, our method ensures that the VL measures fall approximately 9 and 15 months post seroconversion, since actual seroconversion could have occurred anywhere in the seroconversion interval. For men with more variable follow-up schedules, our SPVL could in theory fall quite early after seroconversion. We thus separately checked durations of the time between the first HIV-1-positive visit and first VL measure included in our SPVL calculation for each man in the analysis, and determined that only one of these was <90 days (our estimate of acute phase infection duration). This man's interval was 87 days, and his first viral load reading (5.02) was slightly less than his subsequent one (5.17), so we retained him in the analysis. Figure 1 also shows a lack of clear relationship between seroconversion interval length and estimated SPVL (linear regression p=0.559), further suggesting that our method is not systematically capturing VLs that are poor representations of SPVL for men with either short or long seroconversion intervals. We had at least one SPVL measure and information about role during seroconversion interval for 374 men; Table 2 shows demographic characteristics for this sub-sample.

Figure 1: Seroconversion window and SPVL distributions, MACS sample.
Size of the seroconversion window reflects the duration in months between the last visit with HIV-1-negative test results and first visit with HIV-1-positive test results for men in our sample. SPVL is measured at the subsequent one or two visits, as described in the text.

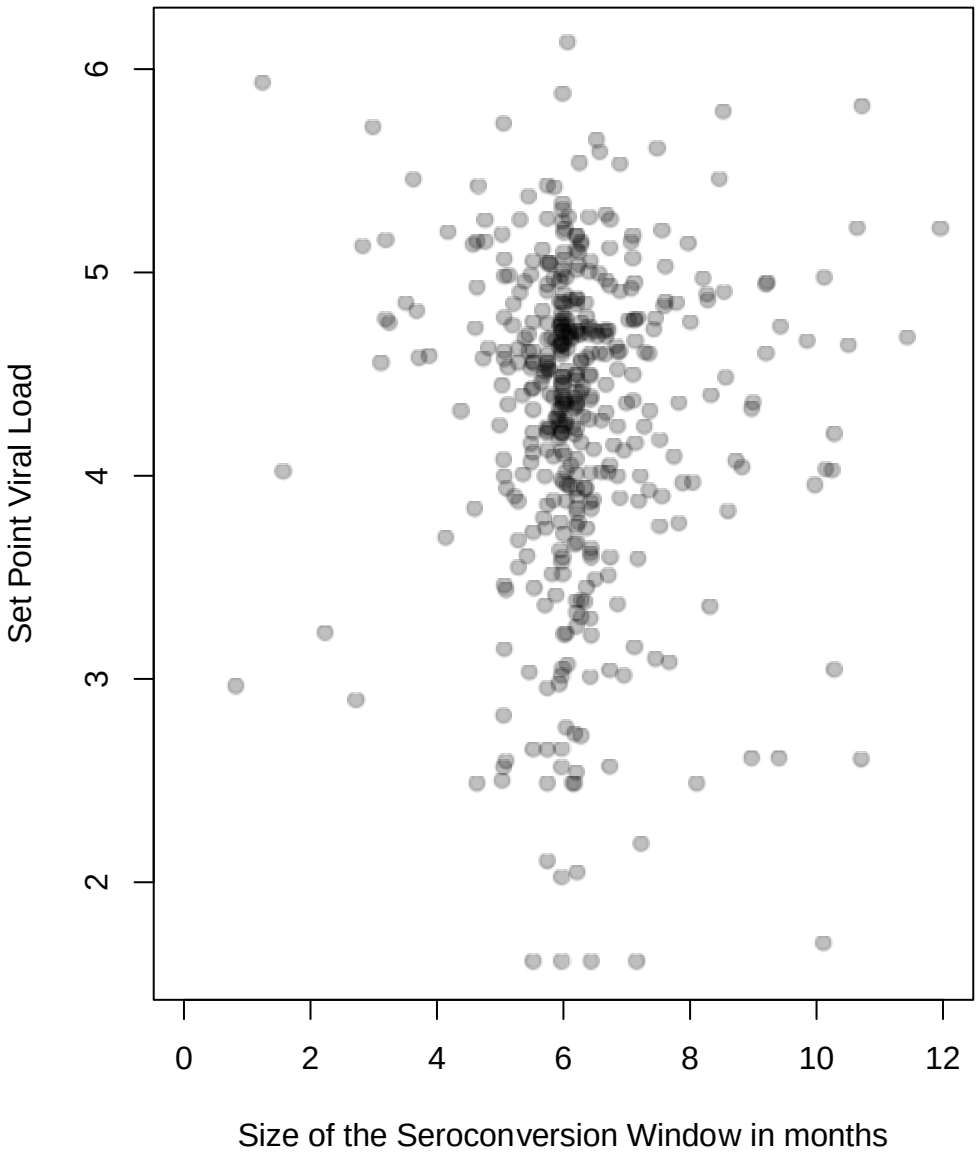


Table 2: Demographic characteristics of the MACS sample, individuals with set point viral load data and seroconversion role data available

Categorical Variables	**Category**	**n**	**%**		
Age at Seroconversion	<30	106	28.3		
	30-39.9	174	46.5		
	40-49.9	73	19.5		
	≥50	21	5.6		
Cohort (enrollment years)	1984 (1984-1985)	344	92.0		
	1987 (1987-1991)	11	2.9		
	2001 (2002-2003)	19	5.1		
Race/ethnicity	Black, non-Hispanic	32	8.6		
	Hispanic	25	6.7		
	Asian or Pacific Islander	2	0.5		
	White, non-Hispanic	315	84.2		
City	Baltimore	101	27.0		
	Chicago	87	23.3		
	Los Angeles	105	28.0		
	Pittsburgh	81	21.7		
Continuous Variables	**Measurement Time**	**n**	**Mean**	**Median**	**IQR**
Est. age at seroconversion	Seroconversion interval midpoint	374	35.3	34.0	29.4 40.1
Plasma $\log_{10}$ viral load	Visit 1	334	4.30	4.49	3.95 4.83
	Visit 2	304	4.28	4.40	3.90 4.76
	2-visit mean	264	4.31	4.47	3.94 4.75
	Overall	374	4.29	4.45	3.92 4.76

Seroconversion sexual role was estimated from reported numbers of insertive or receptive partners at the first HIV-1-positive visit. We classified individuals reporting receptive AI with ≥1 partner and no insertive AI partners as ER, individuals reporting the reverse as EI, and individuals reporting each with ≥1 partner as RV. We use role behaviors in the seroconversion interval only since these are most directly related to virus acquisition, and, had we included role throughout the entire study, few men would have been anything other than role versatile.

Methods for obtaining and quantifying VL have been published previously (Mellors et al., 1996). Statistical comparisons of MSPVL by subgroup were completed in Stata 13.1 using both Mann-Whitney and *t*-tests for the empirical analyses. Based on our model findings (described below), we performed three analyses, one comparing the SPVLs of EI men and all others, and another two stratifying based on different metrics for numbers of partners. Because our final sample sizes were quite small, we kept our statistical analysis purposefully simple; that is, we did not consider additional predictors of SPVL beyond sexual (e.g. host genotype), assuming that these other predictors should be uncorrelated with this behavioral attribute.

Results

One-generation model

Below we lay out the behavior observed in our simulations from this model. We note that key aspects of this behavior can also be demonstrated mathematically, and we include this derivation (provided to us by a reviewer) in Supplement section S9.

The model considering only one sex act demonstrated little, if any, difference in MSPVL between newly-infected EI and ER men (both values slightly below 5.4, Figure 2a). These values represent a rapid shift away from the source population mean of 4.5; individuals with higher SPVL transmit more easily, and this effect is not counter-balanced here by the trade-off of shorter life expectancy. Many more ER than EI men become infected (n = 1,493 vs. 128, Figure 2b).

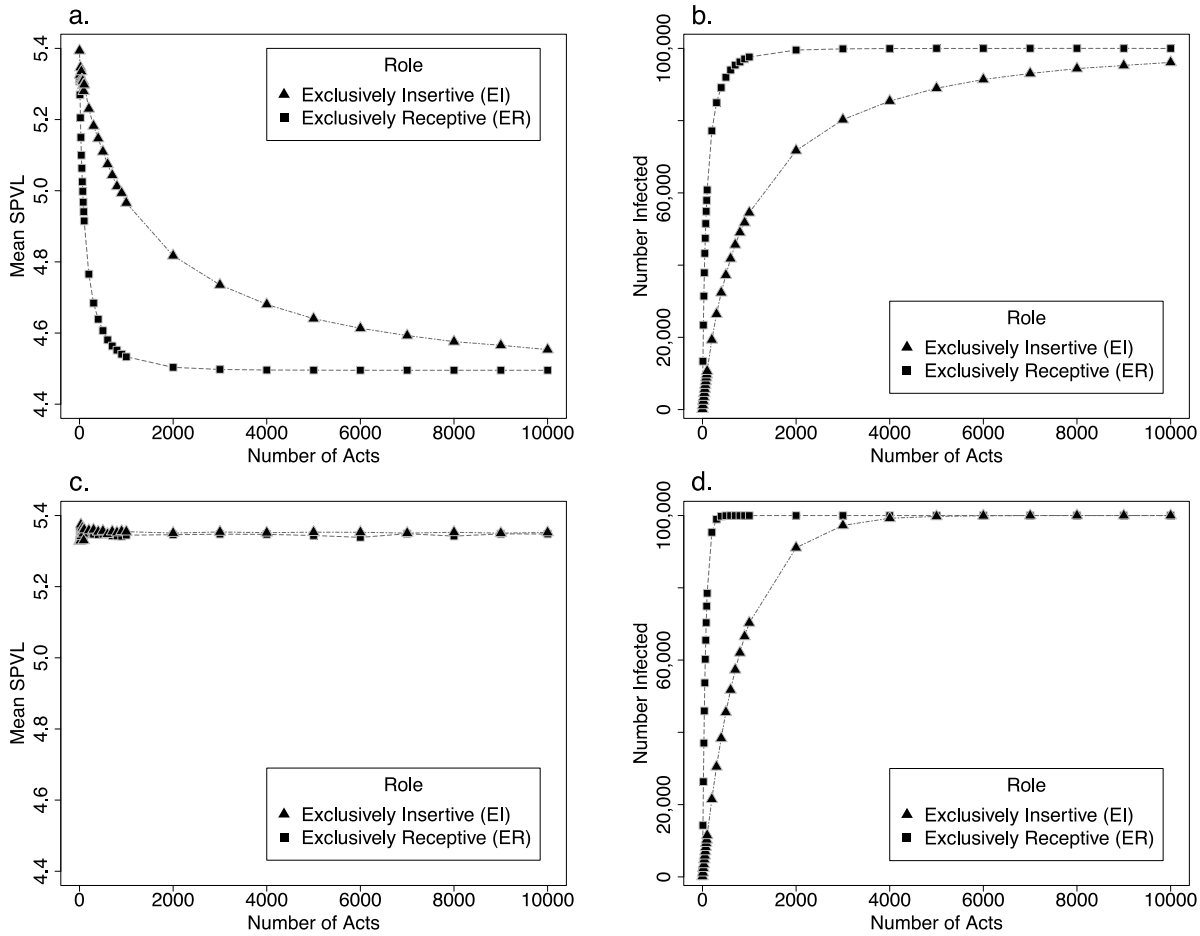
At the other extreme, when negative men have 10^4 acts with one partner, there is also little difference in MSPVL of newly-infected EI and ER men (4.55 vs. 4.50). These values, approximately equal to the source population's, reflect the fact that nearly every HIV-1-positive

man transmits to his one partner eventually, although transmissions generally take longer when the negative partner is insertive. MSPVL for EI men is slightly higher because there remain a few non-transmitting pairs involving receptive source partners with very low SPVL even after many acts.

Intermediate counts of coital acts do, however, yield a difference by role, with ER men averaging markedly lower SPVL. This difference peaks at 400 acts, with a 0.508 $\log_{10}$ difference between the two groups.

When we consider the same scenarios, but allow HIV-1-negative men to re-select partners between acts, we see a different pattern: MSPVL equals ~5.35 for both groups, for any number of coital acts (Figure 2c). However, the pattern of relative times until men become infected is similar to that of the previous model (Figure 2d). Contrasting this set of scenarios with those above, then, we see examples in which the same number of partners but different number of acts per partner leads to different MSPVL values by sexual role; however, different number of partners but the same number of acts per partner do not.

Figure 2: Results from one-generation model
Mean SPVL and number of individuals infected changes based on role and number of sex acts in the one-generation model. In each panel, role signifies the role of the initially HIV-1-negative partner. In 2a and 2b, there was no partner change: individuals stayed in the same relationship for the duration of the modeled time. In 2c and 2d, individuals selected a new partner with every act. (a) Mean SPVL for each role group, without partner change; (b) Number of individuals infected for each role group, without partner change; (c) mean SPVL for each role group, with partner change; (d) number of individuals infected for each role group, with partner change.

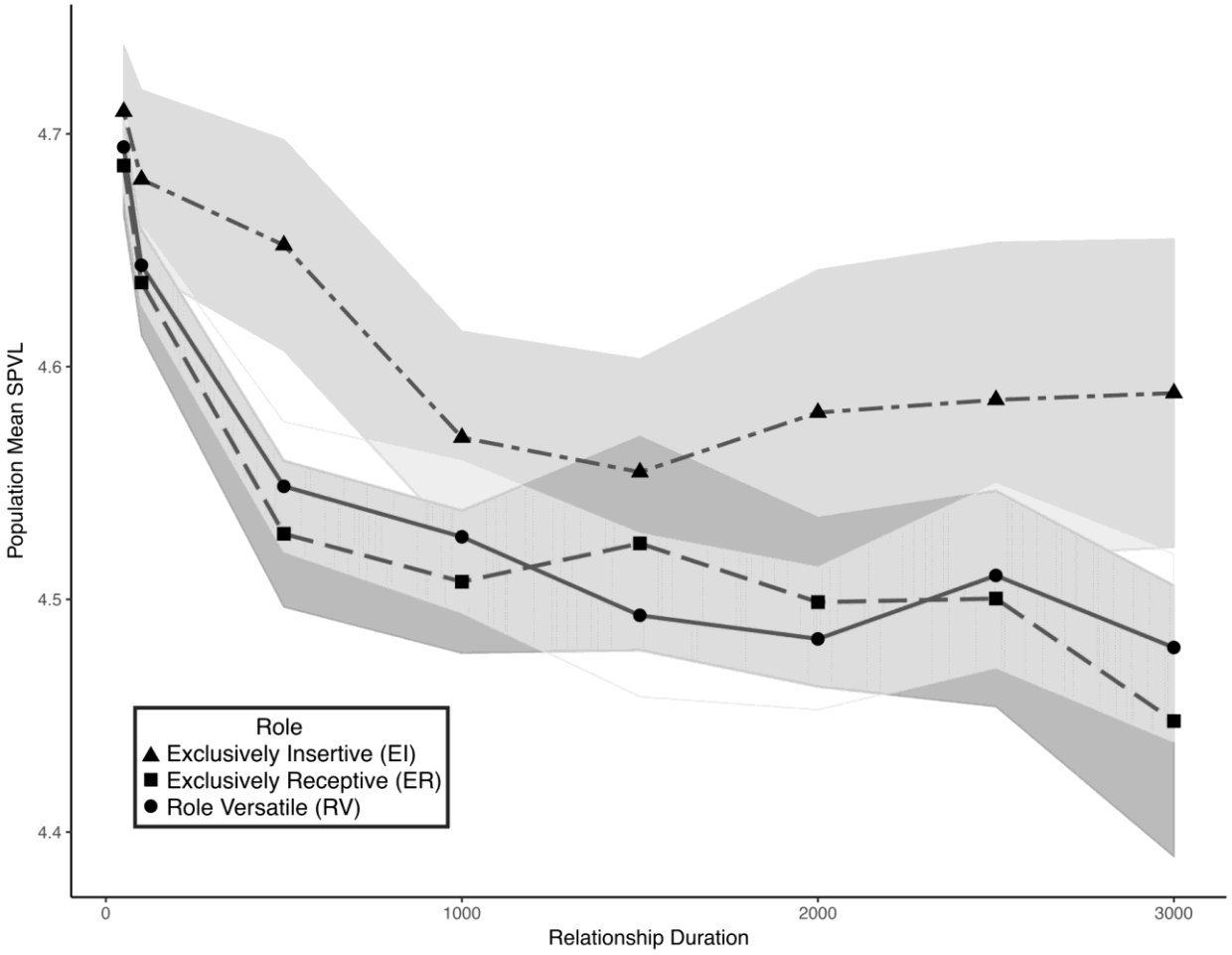


Network Model

Figure 3 shows results from our dynamic network model across different relationship lengths. Results show greater stochasticity than for the one-generation model; presumably this is at least in part because the explicit feedback added here (those newly infected are in the partner

pool for other HIV-uninfected men) allows for small random differences to become compounded. Consistent with the one-generation model, we see little, if any, difference between EI and ER men at short relationship durations. Differences appear at longer durations, for example at 500 days (corresponding to roughly 200 acts per relationship; 0.124 MSPVL difference). Other durations also show noteworthy differences by role, although some with overlapping confidence intervals. In contrast, RV men display SPVL values similar to those of ER men, presumably because their greatest risk (and most of their infections) comes from their acts of receptive AI. Differences between EI and ER men are generally smaller here than in the Bernoulli model for the same number of acts, where those comparisons are possible; for example, at around 1000 acts per relationship, the Bernoulli model displayed a difference of ~0.4 log10 SPVL, while the network model showed only ~0.1. Presumably this is because the added realism of the latter, i.e. partial heritability and evolutionary feedback between role groups. As with the one-generation model, here EI men are by far the least likely to become infected.

Figure 3: Results from dynamic network model
Data represent mean SPVL for each role group averaged across 50 simulations. Men are included if they are infected during years 2-5 of the simulation. Data are shown for 8 scenarios differing in mean relations durations (50, 100, 500, 1000, 1500, 2000, 2500 and 3000 days). There were on average 0.4 acts/day leading to roughly 20, 40, 200, 400, 600, 800, 1000, and 1200 acts per scenario. Shaded areas represent 95% confidence intervals around the mean values, using standard assumptions of normal variation across simulations.



MACS analysis

Since both models demonstrated that a difference in SPVL by sexual role was expected under some conditions, we proceeded with our empirical analyses. Given our model results, we hypothesized that EI men would have higher SPVL than either ER or RV men, combining the

latter two for the analysis and switching to one-tailed tests given the directionality of our hypothesis.

The combined sample of ER and RV men has a MSPVL of 4.29 and the EI men had a nearly identical 4.28 (Mann-Whitney U test, p=0.371). However, both of our models indicated that we should only expect a difference when considering men whose main risk comes from relationships containing many acts. We did not have access to data on acts per relationship, nor on relational duration. However, we had two different measures of numbers of AI partners reported by respondents, which we could use as proxies for acts per relationship, assuming that low partner counts correlate with higher acts per partnership. To add support to this supposition, we analyzed data from the two studies of MSM that formed the main sources for the behavioral parameters in our dynamic network model. Both yielded a strong and significant relationship in the expected direction; e.g. in one study (n=949), men with 1 partner in the last 6 months had a 56% chance of reporting 10+ acts per partner and a 19% chance of 1 act; for those with 5+ partners, the corresponding numbers were 11% and 54%, respectively (details in Supplement section S10). An additional literature review indicated that existing reports on this topic focus on acts per partnership per unit time, not acts in total, while our interest was in the latter given our model.

Each of our two proxy measures is imperfect in different ways, but provides some insight. The first was the reported number of partners in the 6 months prior to the first HIV-1-positive study visit. Given the short time frame, this measure showed relatively little variation, and is likely less reflective of long-term behavior. The other (available for the 344 men in the 1984 cohort only) was the estimated number of *receptive* AI partners (i.e. individuals the respondent had receptive sex with) a respondent had in the 2 years before and 6 months after

their baseline visit, a proxy for risk commonly used in analyses of MACS data (Detels et al., 1994; Herbeck et al., 2015). In this case, the longer duration gives a more stable estimate for partner acquisition rates; however, its limitation to receptive partners introduces some confounding with our main dependent variable, sexual role. We note that it is possible for a man we classify as EI (i.e. reporting no receptive partners) to have a value >0 for this metric (i.e. reporting receptive partners), since the two measures represent different times, potentially years apart. Given this caveat, we conducted two sub-analyses. First, we compared ER/RV men with ≤3 estimated baseline receptive partners to EI men with an estimated 0 baseline receptive partners, under the assumption that the latter represent men who are consistently insertive in the long-term. Second, we tried a more symmetric model, considering a ≤3-partner cutoff for each group. Finally, we tried different cutoffs (≤ 3 vs. 10 partners) for each analysis to see how sensitive our results were to this arbitrary cutoff and to balance the desire to limit to those with very few, long relationships with a need for larger sample sizes. We used non-parametric one-tailed Mann-Whitney tests given the small sample sizes and likely violation of distributional assumptions, but also repeated analyses using one-sided *t*-tests, with qualitatively similar findings.

Table 3 and Figure 4 show these results. When considering partners in the previous 6 months, MSPVL was nearly identical between EI men and others for both partnership count cutoffs; differences were not significant. However, when considering estimated number of receptive partners over the earlier 2.5-year span, EI men had significantly higher SPVL than others. For example, with the 10-partner cutoff for both groups, EI men had MSPVL of 4.51 and others had 4.19. This difference (~0.3 $\log_{10}$ copies/mL) is considered clinically significant; a

meta-analysis found it to translate into a 25% higher annual risk of progression to an AIDS-defining illness (Modjarrad et al., 2008). Results were qualitatively insensitive to cutoff.

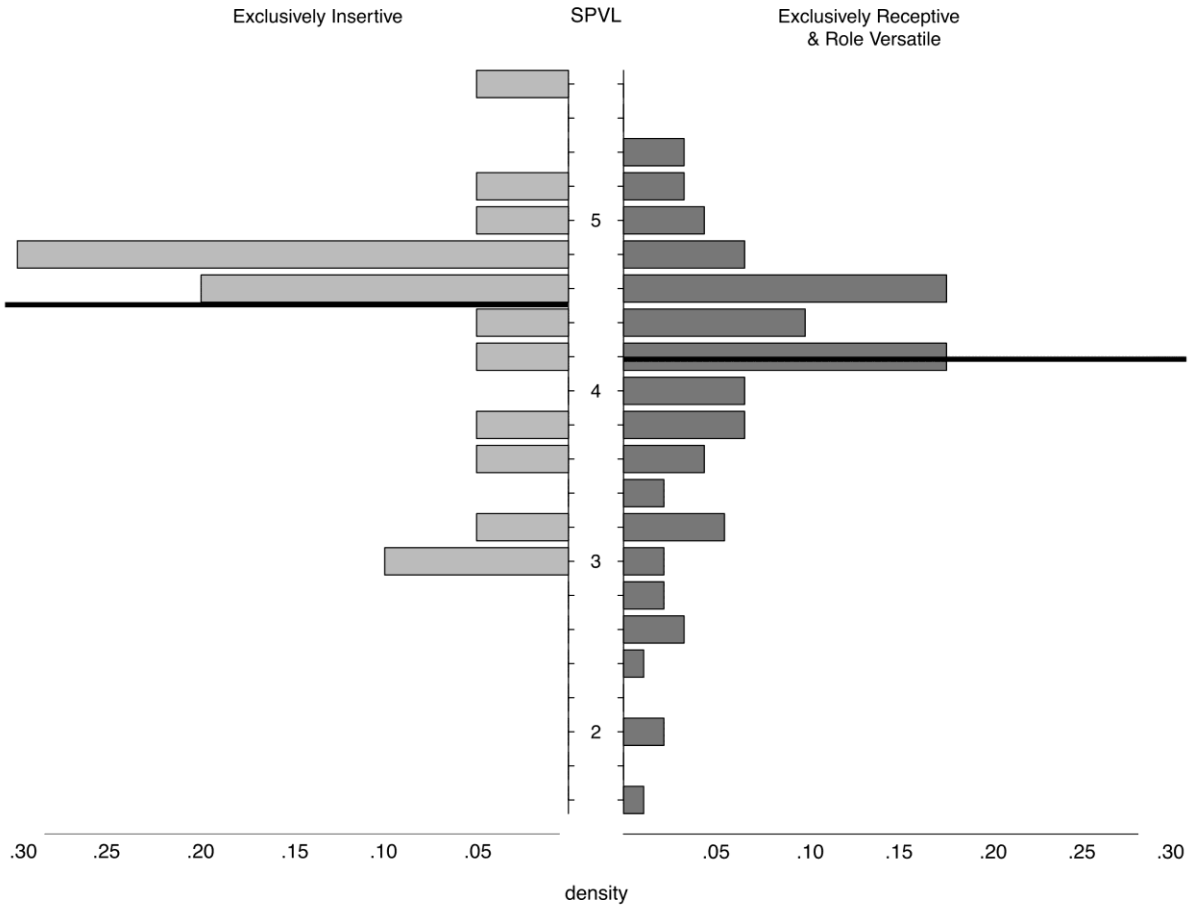
Table 3: Results of MACS role analyses

	Role	n	Mean SPVL	Pseudo-median SPVL (95% CI)	*p*-value
All individuals	EI	46	4.28	4.36 (4.08-4.61)	0.371
"	ER or RV	328	4.29	4.36 (4.28-4.44)	
6 mo. partner count ≤ 3	EI	30	4.20	4.28 (3.89-4.69)	0.554
"	ER or RV	110	4.33	4.42 (4.29-4.53)	
6 mo. partner count ≤ 10	EI	39	4.22	4.31 (3.99-4.56)	0.488
"	ER or RV	253	4.26	4.34 (4.24-4.43)	
30 mo. receptive partner count = 0	EI	7	4.65	4.82 (4.04-5.05)	0.027
30 mo. receptive partner count ≤ 3	ER or RV	33	4.05	4.17 (3.79-4.45)	
30 mo. receptive partner count = 0	EI	7	4.65	4.82 (4.04-5.05)	0.024
30 mo. receptive partner count ≤ 10	ER or RV	91	4.19	4.28 (4.10-4.43)	
30 mo. receptive partner count ≤ 3	EI	17	4.49	4.67 (4.02-4.93)	0.039
"	ER or RV	33	4.05	4.17 (3.79-4.45)	
30 mo. receptive partner count ≤ 10	EI	20	4.51	4.68 (4.09-4.88)	0.017
"	ER or RV	91	4.19	4.28 (4.10-4.43)	

Bold = significant at p=0.05. All distributions were compared using a two-sample Wilcoxon (a.k.a. Mann-Whitney) test with exact *p*-values, given the small sample sizes and potential violation of distributional assumptions in some cases. Means are those observed; pseudo-medians and confidence intervals were calculated using a one-sample Wilcoxon test. We also conducted a two-sample one-tailed *t*-test with Welch-Satterthwaite approximation (no assumption of equal variances) since this focuses more specifically on comparing means; results were qualitatively similar, although the fifth comparison became non-significant, at p=0.055. All analyses were conducted using the *stats* package in R, using default settings for all parameters not mentioned. Note that pseudo-medians are all higher than observed means given that the underlying distributions are left-skewed. Using the internal definitions of the MACS data set, "receptive partner count" refers to the number of partners with whom the respondent had receptive anal intercourse.

Figure 4: Distribution of SPVL by role at seroconversion, for men with lower partner numbers

Results shown here are for the sub-analysis comparing EI men (n=20) with ER or RV men (n=91) who each have an estimated 10 or fewer receptive partners in the 2.5 years around baseline. Role category is based on behavior in the first HIV-1-positive visit. The exclusively insertive men's mean = 4.51 and the exclusively receptive and role versatile men's mean = 4.19 (shown with dark lines). The small clustering at 3 for EI men and lack of tail below that might suggest an issue with detection threshold; however, this is not present in the ER/RV men, and we know of no explanation why detection thresholds would differ by sexual role.



Discussion

To our knowledge, no previous study has considered differences in SPVL by sexual role among MSM, despite the clinical and epidemiological significance of this virological measure, and numerous studies among heterosexuals. Our one-generation model demonstrated that we might expect exclusively insertive (EI) men to have higher MSPVL than others, but only when

partnerships are sufficiently long to involve numerous sex acts. In our dynamic simulation, which included many additional forms of realism, the impact of role on SPVL was smaller but still present at sufficiently long relationship durations. In the one-generation model, the gap closed again at very high (2000+) mean numbers of acts per relationship. We considered such high numbers for the sake of insight-building; for the more data-driven and computationally intensive dynamic model, we did not explore this range, and the gap in SPVL between EI men and others remained wide. It is crucial to remember, however, that in each case EI men were the least likely to become infected overall, as would be expected given the difference in transmission probabilities by role.

The logic behind these findings is subtle, and relies on consideration of two extremes: when there is only one act per relationship, and when there are very many (e.g. 10^4). In the former, transmission is biased towards those with high SPVL, but is biased equally by role. In the latter, nearly all partnerships eventually transmit, so there is no bias by SPVL or role. At intermediate numbers, the level of bias differs by role, as Figure 2 illustrated. Here all MSM acquire high SPVL strains disproportionately, but EI men do so more disproportionately than others (see also Supplement Section S9 for further elaboration).

Acute infection, with its increased transmission probability, complicates this idea. Short relationships mean greater opportunity to become infected and then infect others during a brief window, facilitating transmission from individuals with high VL because of acute infection, but not necessarily high SPVL. Notably, however, our models that did (dynamic) and did not (one-generation) include infection stages showed the same pattern at short relationships, indicating that acute infection is not the main driver of these patterns.

Results from the MACS data analysis provided partial confirmation for our models. The unstratified analysis failed to demonstrate a difference between groups. However, this included men with relationships of all lengths, while our model only predicted a difference for longer relationships; in the earliest cohort especially, many very short relationships likely predominated (Rotello, 1997). We conducted two subsets of stratified analyses focusing on men with few (and presumed longer) relationships, and these consistently demonstrated the predicted pattern of higher SPVL in EI men, with significance.

One early MACS study (Phair et al., 1992), although not considering role or SPVL, found that rapid progressors had more partners. We interpret this finding as consistent with our assumption that more partners suggests shorter relationships, and our model finding that shorter relationships should lead to higher SPVL and faster progression. However, we note that dual or superinfection could also generate this pattern (Gottlieb et al., 2004).

Our work provides indirect evidence to support the notion that some of the SPVL differences by sex in heterosexual transmissions might be influenced by differences in acquisition risk. This builds on recent findings that the transmission bottleneck leads to females being disproportionately infected by HIV-1 strains with amino acids residues associated with lower viral fitness (Carlson et al., 2014). It is worth noting that, even though some authors have found that the greater probability for male-to-female transmission than vice versa disappears after controlling for a variety of factors that foster greater acquisition probabilities in females (Hughes et al., 2012b), it is the unadjusted probabilities that represent the full set of environmental conditions shaping viral evolution.

This analysis has several limitations. We lacked a direct measure for acts per partnership, and our proxies were both imperfect; this adds noise to our analysis, and potentially bias related

to the fact that our measures of role and coital frequency were not independent, with ER men seeming to have more, and thus shorter, partnerships on average. Despite beginning with a large cohort, our final analyses involved small sample sizes. Ascertainment of sexual role was unlikely to have correctly classified everyone as it was based on reported partner counts instead of a direct survey question. Given the small sample sizes generated by our need for complete behavioral data and narrow seroconversion windows, we did not explore other predictors of SPVL that might have confounded our observed relationships; however, we note that, unlike analysis of SPVL in heterosexual transmission, where the insertive (male) and receptive (female) partners are expected to exhibit a host of systematic genetic and endocrinological differences, we have no such expectations for differences between MSM who exhibit different sexual roles. Our models did not consider that men likely have a mixture of relationship types (e.g. one long and many short), which might further complicate observed patterns. Furthermore, our models contained many parameters that were fixed at single values drawn from the literature, including the parameters governing the relationship between VL and transmission probability (Fraser et al., 2007b). Our qualitative findings might vary under different values for any of these, and we did not conduct sensitivity analyses to explore this. Many factors that might vary across populations, such as the numbers of sexual partners, the use of condoms, the presence of co-circulating STIs, or the level of antiviral treatment or more recently pre-exposure prophylaxis, could alter the evolutionary landscape for HIV-1 considerably. However, the impact of this limitation is tempered by the fact that our models served primarily to build the insights used to guide the empirical analysis.

Our Bernoulli model contained two comparisons: one in which we compared scenarios with the same number of partners but different numbers of acts per partner; and one in which we

compared scenarios with different numbers of partners but the same number of acts per partner. The former yielded differences in MSPVL by sexual role in some cases, while the latter did not. This led to us focusing on number of acts as our main explanatory variable for the empirical analysis, despite the fact that our actual measure was partner number, since we expect these to correlate (and demonstrated that they did in the main source studies that parametrized our network model). In reality, however, patterns of partner number and acts per partner are likely to be more complex than we fully explored, and interact with other network phenomena, e.g. through the presence of core groups—the tendency for those with many short-term partnerships to choose each other as partners disproportionately. We are in the process of conducting additional modeling work examining more complex relationships among these phenomena, and examining additional relationships between partner number and SPVL in the MACS data in light of these model findings.

Our results suggest that EI men, although less likely to become infected than men who engage in receptive AI, could be disproportionately infected by more virulent strains and might thus face worse outcomes, including as much as a 25% higher probability of progression to AIDS per year (Modjarrad et al., 2008). In the modern era, availability of treatment may mask these differences in many settings, although universal treatment is still far from a reality, even among MSM in developed settings (Singh et al., 2014). Analyses of VL measures from additional cohorts, especially cohorts with data on the number of both insertive and receptive acts per partnership in the period before seroconversion, could help confirm this finding, as would further work identifying viral selection at the transmission bottleneck (Carlson et al., 2014). Nonetheless, it appears that insertive men in long-term relationships now have an additional reason not to be complacent about their HIV risks.

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Chapter 2: Test-and-treat coverage and HIV virulence evolution among men who have sex with men

Title: Test-and-treat coverage and HIV virulence evolution among men who have sex with men

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Abstract

Background:

HIV set point viral load (SPVL) is the viral load (VL) established shortly after initial infection. SPVL is a proxy for HIV virulence: higher SPVLs are more likely to lead to transmission and to faster progression to AIDS or death. Three models of test-and-treat scenarios, mainly in heterosexual populations, found that increasing treatment coverage selects for viruses with higher virulence. Here, we examine the patterns of virulence evolution that occur in a population of men who have sex with men (MSM) with increasing test-and-treat coverage.

Methods:

We extended a stochastic, dynamic network model (EvoNetHIV), based in temporal ERGMs and using the statnet suite of R packages and the EpiModel package API. We varied relationship patterns (MSM pattern based on studies of US-based MSM vs. heterosexual pattern based on previous models), HIV transmission models (increasing vs. plateauing probability of transmission at very high VLs), and treatment roll-out scheme (test-and-treat scheme with a stochastic interval between infection and treatment and a scheme with a fixed interval between infection and treatment).

Results:

In the scenarios most similar to previously published models of heterosexual populations, which used the plateauing transmission function, we replicated the trends previously found: increasing treatment coverage led to increased mean population SPVLs (0.12 $\log_{10}$ increase in mean SPVL in the population between 20% and 100% treatment coverage). In contrast, in the scenarios reflecting an MSM population and using the increasing transmission function, increasing the proportion of individuals treated selected for viruses with *lower* mean SPVLs (0.16 $\log_{10}$ decrease in mean SPVL in the population between 20% and 100% treatment coverage).

Conclusions:

These findings emphasize the impact of sexual network conditions and transmission function details on predicted epidemiological and evolutionary outcomes. Our results suggest that, under some realistic conditions, effective test-and-treat strategies may *not* face the previously-reported tradeoff in which increasing coverage leads to the evolution of greater virulence and instead suggests that a virtuous cycle of increasing treatment coverage and diminishing virulence is possible.

Introduction

Pathogen evolution in the face of control measures is a pressing current issue. One particularly important example of this is HIV, which, as a retrovirus, can evolve extremely rapidly both in terms of virulence, or harm to the host, and in transmission risk. HIV virulence evolution in response to global treatment scale-up is important to consider, as evolution towards a more virulent form may require more intense precautions and control measures in the future. While HIV virulence evolution with increasing treatment coverage has been considered in heterosexual populations (Herbeck et al., 2016; Roberts et al., 2015b), as far as we can ascertain no published models of virulence evolution with increasing coverage have yet focused on populations of men who have sex with men (MSM). As this population accounted for an estimated 67% of new infections in the United States in 2016 (CDC Fact Sheet, 2018), estimating virulence evolution here is especially pressing.

HIV virulence can be tracked with the proxy measure of set point viral load (SPVL), the viral load (VL) established shortly after initial infection. SPVL can function as a proxy for virulence as it influences both disease progression and transmission potential; higher SPVLs are more likely to transmit (Fraser et al., 2007b; Hughes et al., 2012a) and result in faster progression to AIDS-defining illnesses (Modjarrad et al., 2008).

HIV transmission probability itself varies by stage of infection. In the acute phase, VL rapidly increases as the virus replicates, then decreases as the host immune system regains control. This phase lasts approximately three months and is marked by high risk of transmission, as VL drives transmission potential (Fraser et al., 2007b; Hughes et al., 2012a). VL increases gradually over many years in the chronic phase. This phase has a median duration of 9.4 years (95% CI 8.7,10.0) in MSM (Babiker et al., 2000) in the absence of treatment. Higher SPVLs are associated with both shorter time in this phase and higher risk of transmission (Modjarrad et al., 2008). Finally, in the AIDS phase VL (and transmission risk) quickly increases as the immune system can no longer control the virus. The stage of infection new transmissions occur in can also influence how viral virulence evolves. If there are more opportunities for the virus to transmit during the acute phase, for example, it will be less advantageous to the virus to keep individuals alive longer instead of evolving to have very high virulence and a greater chance of transmitting quickly, which can have sizable impacts on SPVL evolution (Goodreau et al., 2018c). In contrast, changes in the number of infections that occur during the AIDS phase have

less impact on SPVL evolution although may still have large impacts on prevalence and incidence (Goodreau et al., 2018c).

With treatment, an individual's VL can become undetectable. In this case, there is little or no risk of onward transmission (Rodger et al., 2016) and progression to AIDS is prevented (Sterne et al., 2005). Because of this, current treatment guidelines recommend immediate antiretroviral treatment (ART) initiation after a positive diagnosis, also known as test-and-treat (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016), a recommendation first given in 2015 (World Health Organization, 2015b). Treating infected individuals to prevent onward transmission is known as "treatment as prevention" (TasP). Although universal treatment is recommended, the proportion of persons living with HIV (PLWH) who are durably virally suppressed in the US is estimated at 49% (CDC, 2017). The care cascade leading to viral suppression is complex (testing and diagnosis, linkage to care, retention in care, ART adherence), and people are lost at each step. Even though retention in care remains a challenge, the overall proportion of PLWH who are receiving treatment is rising (CDC, 2017). Considering the indirect effects of HIV treatment on a large scale has therefore become more important.

Numerous researcher have modeled the effects of large scale test-and-treat campaigns on basic epidemiological outcomes such as incidence (Eaton et al., 2015), but fewer papers explore the effects of test-and-treat on virulence evolution (Herbeck et al., 2016; Roberts et al., 2015b; Smith and Mideo, 2017). Roberts et al. (2015b) explored virulence change with widespread test-and-treat campaigns with a simple deterministic two-strain model. Their model had one HIV strain with high SPVL and one with low SPVL to determine which strain is favored over the course of an epidemic. In order to prevent strain extinction, individuals infected with one strain of HIV had a small chance of passing on the other strain instead, which could complicate findings. Transmission coefficients for each strain were chosen to fix the epidemic peak 40 years after its start to correspond with observed epidemics in Botswana and South Africa. In the main analysis, individuals with higher SPVLs were treated sooner than those with lower SPVLs, which led to slightly decreased virulence. In a supplementary analysis, a test-and-treat scheme was approximated by starting treatment at a fixed time period after infection, ranging from 6 months to 4 years. With this treatment scheme, the more virulent strain predominated in all long-term scenarios as well as in those short-term scenarios that did not lead to virus extinction.

Herbeck et al. (2016) developed a stochastic agent-based test-and-treat model, designed to be comparable to the epidemic models described previously (Eaton et al., 2015) with prevalence and incidence trends based on South African data. They examined behavioral parameters in two ways: the primary model's behavioral parameters were based on a setting with a core group of individuals with a higher act rate, while the alternate model tested whether their predicted effects were robust to differences in scenarios by removing the core group and incorporating random mixing with lower average numbers of partners. Eligibility for ART was based on time since infection: all agents in a given scenario had the same time to initiation, which ranged from 1-6 years (in one-year increments) after date of infection depending on scenario. Each ART timing scenario was explored with different coverage levels, from 40-100% with 20% increments. For both the primary and alternate models, increasing treatment proportions led to increasing virulence. The maximum mean SPVL increase was equal to 0.4 $\log_{10}$ copies/mL 38 years after treatment rollout, which was accompanied by large reductions in incidence. The method of implementing ART here had the drawback of not explicitly incorporating testing rates or differences in length of time between infection and treatment initiation between individuals; this may impact the resulting epidemic, as it was impossible for anyone in acute infection to begin treatment. While it used heterosexual behavioral parameters, the model did not incorporate two sexes in agent mixing or allow for concurrent partnerships, which both have the potential to affect sexual networks and transmission dynamics in complex ways.

Finally, Smith and Mideo (2017) examined virulence change with expanding test-and-treat coverage with the added complexity of "leaky" therapy, in which treatment does not completely stop viral replication and agents receiving treatment can still transmit infection. The authors used a compartmental model with simplified HIV dynamics: there were no differences in transmission risk between HIV phases, all agents were homogenous except for infection and treatment status, and leaky treatment allowed infections with higher SPVLs to have a greater risk of transmission than lower SPVL viruses when under treatment. Here, increasing use of fully suppressive treatment caused mean population SPVL to increase and, when treatment was leaky, SPVL to evolve higher.

When considering questions about HIV spread, one must select a function that relates VL to the probability of transmission. Fraser et al. (2007b) and Hughes et al. (2012a) have both

estimated functions, based on transmission studies in heterosexual couples, that have been used to model the probability of HIV transmission given the infecting partner's VL. These have quite different forms, however, as the former plateaus at higher VLs (Figure 1, black lines) while the latter increases exponentially (Figure 1, gray lines). We will refer to these as the plateauing and increasing functions, respectively. Differences in the shape of the plateauing and increasing functions have large impacts on the likelihood of transmission at higher VLs, such as those in the acute and AIDS phases, as well as influencing transmission at moderate VLs where the functions also diverge. These shape differences also affect virulence evolution, as it becomes less advantageous for virulence to evolve to high levels with the plateauing function, as higher SPVLs only fuel shorter times to AIDS with no corresponding increase in transmission probability.

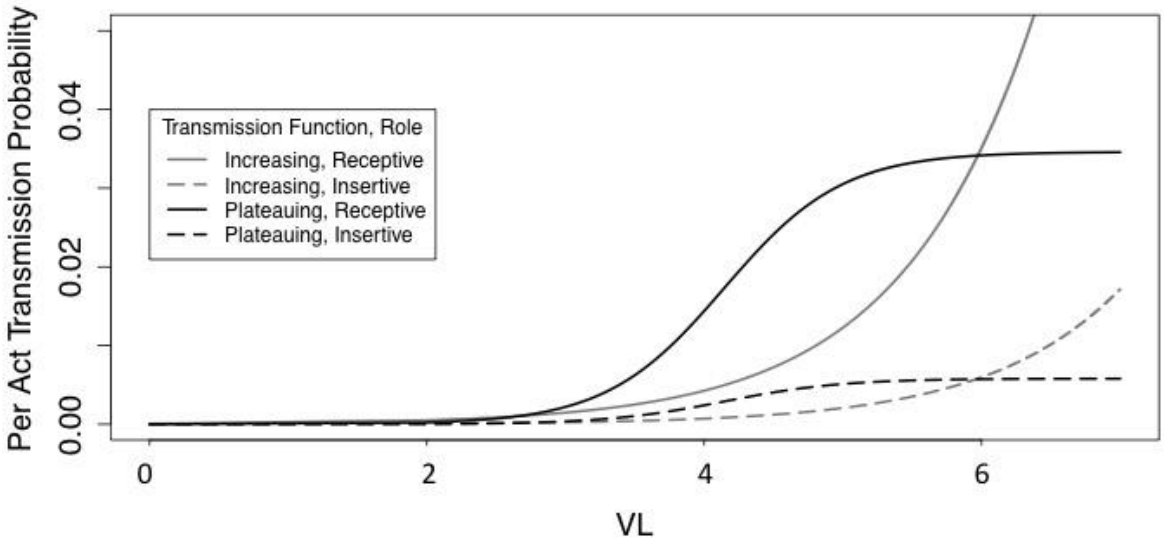

Figure 1: The plateauing (black, (Fraser et al., 2007b)) and increasing (gray, (Hughes et al., 2012a)) transmission functions, as implemented for MSM in EvoNetHIV. The increasing function shown here was converted from Hughes' original function, which was specified for penile-vaginal sex (full details in the appendix). As there is a difference in transmission risk between the insertive and receptive partners, both functions are plotted here with the role in the legend reflecting that of the negative partner. A plot showing the full range of transmission scenarios, including condom use and circumcision, can be found in the appendix.

Some of the difference in shape in transmission functions arises through the paucity of data about transmission at high VLs, since infecting partners in the discordant couples from the source partner studies are unlikely to have extremely high VLs at the time of transmission for a

number of reasons. Individuals whose partner had very high SPVLs would likely become infected before being recruited to a discordant partner study. Similarly, individuals would probably be past acute infection at the time of study entry. Sex is also less likely in the late AIDS phase, making transmissions there less probable. This is shown in one partner study as only 3 transmissions and 1% of follow-up time there occurred while the infected partner had very high VLs of ≥ 6 $\log_{10}$ copies/mL (Lingappa et al., 2010). At the other end of the scale, both the plateauing and increasing transmission functions may overestimate the number of infections at very low VLs; recently (and since both functions were published), the risk of transmission in a discordant couple in which the infected partner is virally suppressed was estimated to have an upper 95% confidence limit of 0.71/100 couple years of follow up for anal sex (Rodger et al., 2016). Small samples sizes in the studies (86 and 129 linked transmissions in the cohorts on which the increasing and plateauing functions were based, respectively, (Fideli et al., 2001a; Lingappa et al., 2010), methodological differences in those studies (see appendix) and noisy data also contribute to the overall differences in function shape.

Another factor to consider in modeling HIV spread and virulence evolution are relationship dynamics in the population of interest. These factors change the evolutionary landscape for HIV as they impact epidemic dynamics in different stages of infection (Goodreau et al., 2018a). Short mean relationship durations and high proportions of individuals with multiple partnerships occurring at the same time (concurrent partnerships) both allow individuals to become infected from one partner and transmit to another before leaving the highly infectious acute phase. As discussed above, if more transmissions occur early in the course of infection, very virulent viruses gain an evolutionary advantage, so that modeled populations with either of these traits tend to have higher mean population SPVLs (MPSPVLs). In contrast, average coital frequency in the modeled populations influenced transmissions across all stages of HIV infection, not concentrating in the acute phase. Modeling higher mean coital frequencies also led to higher MPSPVLs, although this effect was weaker than that of concurrency and relational duration. Overall, Goodreau et al. (2018a) found that relationship dynamics and network features that impact HIV transmission in the acute phase had the strongest effects on MPSPVL evolution, followed by those that impacted transmission in all stages of infection, and the weakest effects from those features that only impacted transmission in the AIDS phase.

Because HIV SPVL is partially heritable from the infecting partner (Alizon et al., 2010), shows large amounts of variation between individuals (Fraser et al., 2007b), and competes for survival and transmission, it fulfills the conditions for evolution via natural selection. We can thus consider a larger perspective on evolutionary tradeoffs (Ewald, 1983a, 2011b). The trade-off hypothesis posits that a pathogen's probability of transmission is linked to the duration of infection, which includes both recovery and mortality (Ewald 1983, Anderson & May 1982). This is seen in HIV as SPVL (the proxy for virulence) is linked to both rate of progression (Modjarrad et al., 2008) and probability of transmission (Fraser et al., 2007b; Hughes et al., 2012a). The virus faces a trade-off where evolving to have lower SPVL will result in more transmission opportunities with a lower chance of transmitting at each one, while evolving to a higher SPVL results in fewer chances to transmit but higher probabilities of transmission at each chance.

We set out to examine the patterns of virulence evolution that occur with increasing proportions of test-and-treat coverage with clinical and behavioral parameters tailored to MSM. It is important to model MSM specifically instead of extrapolating from models of heterosexuals as, in addition to high HIV burden, the MSM population also has high levels of testing and ART use. 71.1% of US MSM reported testing in the previous year in the 2014 National HIV Behavioral Surveillance data (Hall et al., 2017) and 52% of HIV-positive US MSM were virally suppressed in 2015 (CDC Fact Sheet, 2018). We began our analysis with these behavioral parameters and a test-and treat ART implementation scheme and tracked virulence evolution with the measure of MPSPVL change through time. We also followed epidemic progression with prevalence and incidence over time. We then examined the effects of heterosexual behavioral assumptions, treatment that began at a fixed interval after infection, and a different transmission scenario in order to facilitate comparison with the results of previous models, especially Herbeck et al. (2016). We confirmed that we could qualitatively replicate predictions about virulence evolution with key parameters similar to those used in Herbeck et al. (2016) in order to conclude that those specific parameters then create the differences driving the divergence in model predictions we find when using MSM behavioral parameters and another transmission scenario.

Methods

We extended EvoNetHIV, a stochastic, dynamic, network-based model previously described (Goodreau et al., 2018c; Herbeck et al., 2018; Stansfield et al., 2019), to predict MPSPVL, incidence, and prevalence changes with increasing levels of test-and-treat coverage in an MSM population. This model builds on the *EpiModel* (Jenness et al., 2016b) and *statnet* (Handcock et al., 2003) R packages and is available at github/EvoNetHIV/Test_and_Treat. Full methods for this model can be found in the appendix.

Our initial analysis (MSM/Increasing model, Table 1) featured parameter sets for relationship patterns designed to reflect an MSM population. Sexual behaviors were parameterized from two studies of Atlanta-area MSM conducted between 2010 and 2014 (Hernandez-Romieu et al., 2015; Sullivan et al., 2015) as interpreted in Goodreau et al. (2018a). The sexual behaviors in the Previous Literature/Plateauing model were parameterized from those in Herbeck et al. (2016)'s alternate model. We chose to parameterize our model after Herbeck et al. as their model was designed to correspond closely to many of the models that had previously examined test-and-treat's impacts on the HIV epidemic while also examining SPVL evolution. We parameterized sexual behaviors from the alternate model, instead of the primary model, as the primary model included a risk group and other factors that would complicate the analysis beyond the scope of this paper. The alternate model's virulence evolution results were equivalent to those in the primary model. While Herbeck et al. (2016)'s model was based on a heterosexual population, we used an MSM model. As we were able to replicate the direction of effect of treatment coverage on MPSPVL with our model, we did not pursue creating a heterosexual model. The MSM/Increasing and Previous Literature/Plateauing models differed in two key features: sexual behaviors (mean relationship duration and coital frequency), and the transmission function relating the VL of the HIV+ partner to the probability of HIV transmission. The remaining two models were chosen to consider each of these differences in isolation to aid in attributing observed differences to specific causes.

MODEL	Transmission Function	Relationship Duration (months)	Coital Frequency (acts/day)	Treatment Scheme	Treatment Coverage	Condom Use, Main Analysis	Condom Use, Sensitivity Analysis	Test Interval, Main Analysis	Test Interval, Sensitivity Analyses*
MSM/ Increasing	Increasing	3.3	0.2	Test & Treat	0-100%, 20% increments	50%	75%	2 years	1-6 years, 1 year increments
Previous Literature/ Plateauing	Plateauing	30.0	1.0	Test & Treat	"	"	0%	"	"
Previous Literature/ Increasing	Increasing	30.0	1.0	Test & Treat	"	"	0%	"	"
MSM/ Plateauing	Plateauing	3.3	0.2	Test & Treat	"	"	0%	"	"
MSM/ Increasing-Fixed Tx*	Increasing	3.3	0.2	Fixed Interval	"	"		"	"
Previous Literature/ Plateauing-Fixed Tx*	Plateauing	30.0	1.0	Fixed Interval	"	"		"	"
Previous Literature/ Increasing-Fixed Tx*	Increasing	30.0	1.0	Fixed Interval	"	"		"	"
MSM/ Plateauing Fixed Tx*	Plateauing	3.3	0.2	Fixed Interval	"	"		"	"

Table 1: Model parameter table. The main analysis consisted of the MSM/Increasing model, Previous Literature/Plateauing model, Previous Literature/Increasing model, and MSM/Plateauing model; 64 replicates were completed for each parameter set here, as well as for the condom use sensitivity analysis.
*Analyses varying the test interval and treatment scheme were completed with 16 replicates for each parameter set (results in Appendix).

We conducted analyses with two treatment schemes: a test-and-treat scheme in which agents tested for HIV every two years and immediately began treatment if found positive (following current World Health Organization test-and-treat guidelines (World Health Organization, 2015b)) and a fixed interval scheme in which the interval between infection and treatment start was fixed at two years to match Herbeck et al. (2016)'s model. Major differences between the two schemes include that those in acute infection have the possibility of being treated with test-and-treat but not in the fixed interval scheme, and that on average, those in the test-and-treat scheme will begin treatment one year after infection while those in the fixed interval scheme will always being treatment two years after infection. We present the test-and-treat results here; the results showing the fixed treatment scheme can be found in the appendix, as there was not a substantial difference in outcomes between the two schemes. Scenarios varying the testing intervals (or time between infection and treatment in the fixed interval schemes) from one to six years in one-year increments are also shown in the appendix.

Model parameters for sexual network structure, agent attributes, and behavior, apart from those described above, were acquired from the studies of Atlanta MSM previously referenced (Hernandez-Romieu et al., 2015; Sullivan et al., 2015) as derived in Goodreau et al. (2018a). Agents in the model possessed many attributes, most importantly SPVL, which was fixed for each individual, and current VL, which varied with time and treatment status. Agent's initial CD4+ cell count depended on SPVL and rate of progression to AIDS depended on SPVL and treatment status. Separable temporal exponential random graph models (STERGMs), as implemented in *statnet*, were used to model sexual network structure (Krivitsky and Handcock, 2014b). This framework allows relationships to form and break stochastically while preserving many network parameters, including momentary mean degree (the average number of partners, here 0.7). Within partnerships, coital acts occur stochastically and cease during the latter half of the AIDS phase. Condom use per coital act occurred stochastically with a probability of 50% (Goodreau et al., 2018a). Relationships dissolved with a constant hazard based on modeled relationship duration.

Given a serodiscordant act, transmission depended on donor's current VL, each partner's sexual role, condom use, and the HIV-negative partner's circumcision status (if he was the insertive partner). Individual SPVL had both inherited and non-inherited factors, with heritability equal to 0.36 (Hollingsworth et al., 2010a). The inherited factor comes from the infecting partner

with the addition of a random mutational parameter, while the non-inherited factor follows a normal distribution representing environmental and host contributions. Mean SPVL in the initial population was 4.5 $\log_{10}$ copies/mL (Herbeck et al., 2012).

Treatment in the models began ten years after model time started and continued to the end of modeled time. We decided to focus on two-year test intervals as MPSPVL evolution patterns were clearest here and remained similar to those found at the other tested intervals. We modeled incomplete coverage by assigning an individual attribute ("treatable") with probability dependent on the scenario's coverage. If an agent was HIV+, had a detectable VL at the time of the test, and was within the treatable proportion of the simulation, they began treatment immediately in order to simulate a test-and-treat scheme. With treatment, an agent's VL exponentially decayed and became undetectable.

The initial population included 10,000 individuals between 18 and 55 years old. HIV prevalence at the beginning of the simulation was 10%. Simulations lasted 50 years with one-day time steps. Arrival into the model population followed a Poisson distribution set to give 1% annual population growth. Departures ensued through aging out of the population, AIDS mortality, and background mortality. We tracked viral virulence evolution with MPSPVL change through time, as well as epidemiological factors of prevalence and incidence through time.

While we recognize that calculating inferential statistics for simulated data is a topic for debate, we believe it can be valuable if the number of replicated simulations is fixed in advance, especially at levels that are on the order of the number of observations in a typical empirical study of similar phenomena. This follows Ferguson et al. (2006); Goodreau et al. (2018c); Yang et al. (2009); and others. We calculated 95% confidence intervals for variables of interest in each parameter set. We present most variable values for years 30-50, the second half of modeled time after treatment begins in year 10. This allows MPSPVL evolution to take place for a substantial amount of time so that the effects are more apparent. Plots of values from years 10-30 can be found in the appendix.

Results

Basic epidemiological features such as incidence and prevalence showed dramatic differences between models (Figure 2). The models with the plateauing transmission function (Previous Literature/Plateauing and MSM/Plateauing) had the highest prevalence and incidence;

0% treatment mean prevalence at year 50 equaled 47.9% and 46.4%, respectively, and mean yearly percent incidence equaled 9.6 and 9.5, respectively. In contrast, the models with the increasing transmission function (MSM/Increasing and Previous Literature/Increasing) had mean prevalence equal to 13.1% and 32.5% and mean yearly percent incidence equal to 2.2 and 5.5, respectively. Prevalence and incidence in all scenarios decreased with increasing treatment proportions, but the magnitude of this decrease varied between scenarios. Incident MPSPVL also changed through time depending on the model parameters, showing the evolution of viral virulence. These changes reflected both trends with increasing treatment coverage as well as overall differences between models.

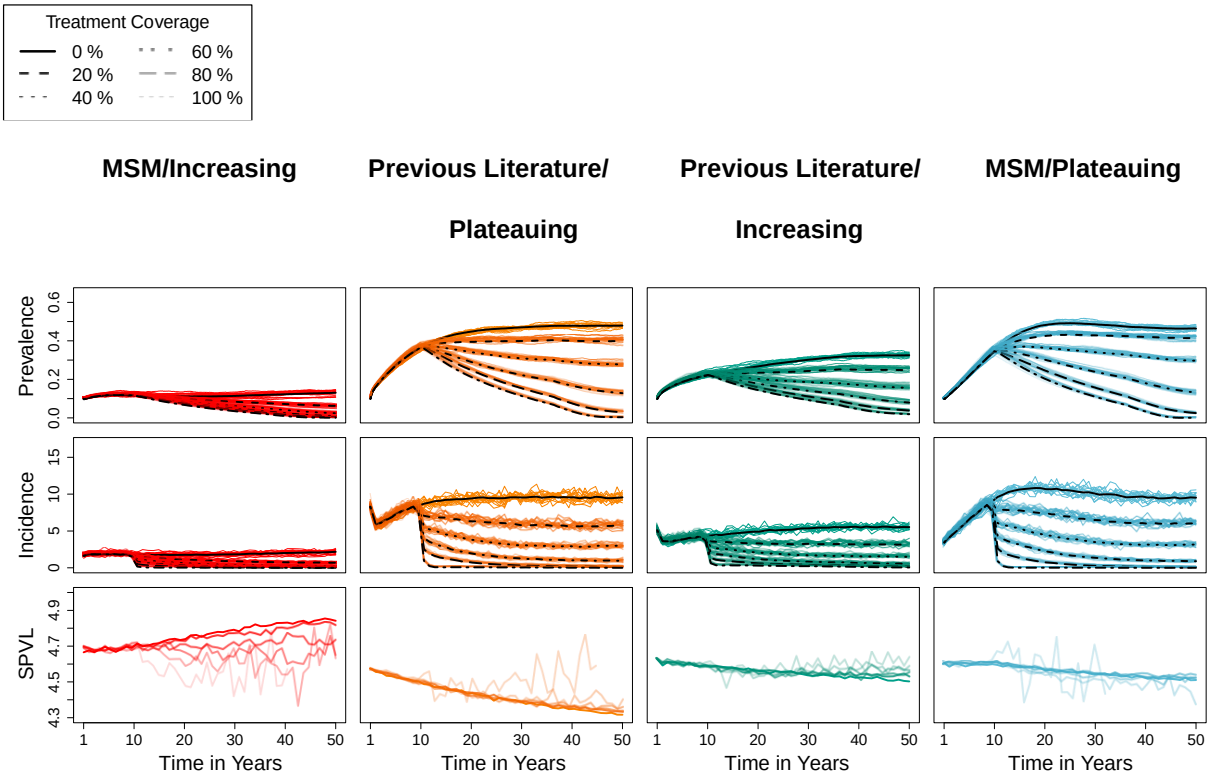

Figure 2: Prevalence, Incidence, & SPVL between years 1-50. Treatment began year 10.
Prevalence & Incidence Plots: Each black line is the mean of 64 simulations. Thin lines show individual simulations.
SPVL plots: each line is the mean of 64 simulations; lines end when 50% of simulations had no incident infections.

The MSM/Increasing model and Previous Literature/Plateauing model produced qualitatively different results with respect to our key question of interest: the direction of SPVL evolution in the face of increasing test-and-treat coverage (Figure 3). In the MSM/Increasing

model, increasing test-and-treat coverage selected for viruses with lower MPSPVLs (MPSPVL = 4.79 $\log_{10}$ copies/mL (CI 4.76-4.82) at 20% coverage and 4.58 $\log_{10}$ copies/mL (CI 4.46-4.71) at 100% coverage, 0.21 $\log_{10}$ decrease). In contrast, in the Previous Literature/Plateauing model, we found that higher test-and-treat coverage led to higher MPSPVL (MPSPVL = 4.35 $\log_{10}$ copies/mL, (CI 4.34, 4.37) at 20% coverage and 4.56 $\log_{10}$ copies/mL (CI 4.48, 4.64) at 100% coverage, 0.20 $\log_{10}$ copies/mL *increase*). This result replicated the direction of effect in Herbeck et al. (2016) but differed in magnitude as the authors found a 0.4 $\log_{10}$ copies/mL increase. The remaining two models had much less MPSPVL change with increasing treatment, although the Previous Literature/Increasing model showed a consistent monotonic trend upwards (0.07 $\log_{10}$ copies/mL decrease and 0.02 $\log_{10}$ copies/mL increase between the 20% and 100% treatment scenarios in the Previous Literature/Increasing and MSM/Plateauing models respectively). Patterns in MPSPVL change with increasing treatment proportion were not all linear; there appeared to be a threshold effect in the Previous Literature/Plateauing model with a larger jump in MPSPVL between 80-100% treatment than in previous proportions. In contrast, in the MSM/Increasing model there was a more continual decline in MPSPVL.

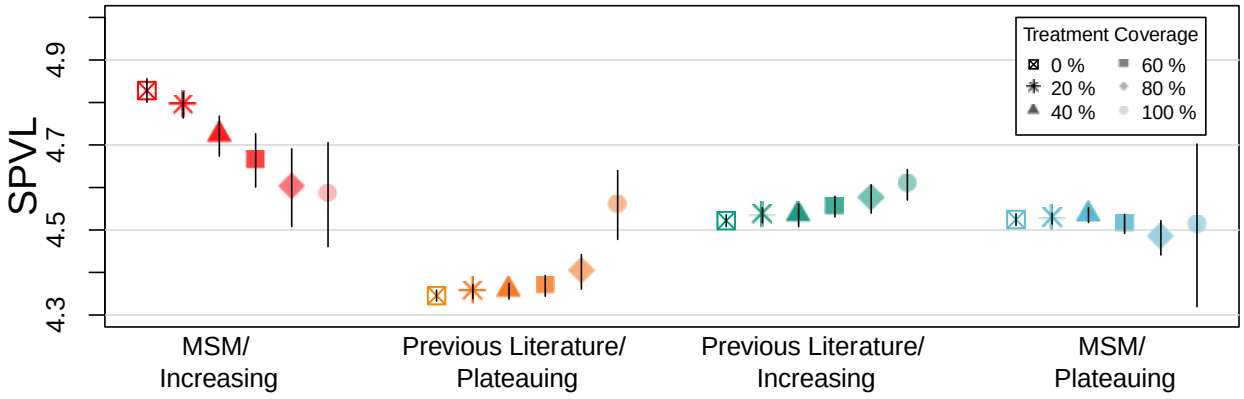

Figure 3: Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 64 simulations. Bars show 95% confidence intervals.

Factors that influence trends in mean population SPVLs with increasing treatment coverage can include timing of transmission (Figure 4). The Previous Literature/Plateauing model had the most dramatic increases in the proportion of transmissions in the infecting partner's acute phase, as 13.8% (CI 13.6,14.1) of transmissions occurred there with 20%

treatment coverage while 26.8% (CI 23.1, 30.5) occurred with 100% treatment coverage. In contrast, there was little difference in the MSM/Increasing model with increasing treatment coverage (7.1% (CI 6.8, 7.4) transmissions with 20% treatment coverage, 5.4% (CI 2.4, 8.5) with 100% treatment coverage). The proportion of transmissions that occurred in the infecting partner's AIDS phase with increasing treatment coverage showed mixed effects, as the Previous Literature/Plateauing and Previous Literature/Increasing models had a more linear decline in transmissions in the infecting partner's AIDS phase, while the MSM/Increasing and MSM/Plateauing models showed a threshold effect with little decrease until the 80% or 100% treatment coverage level.

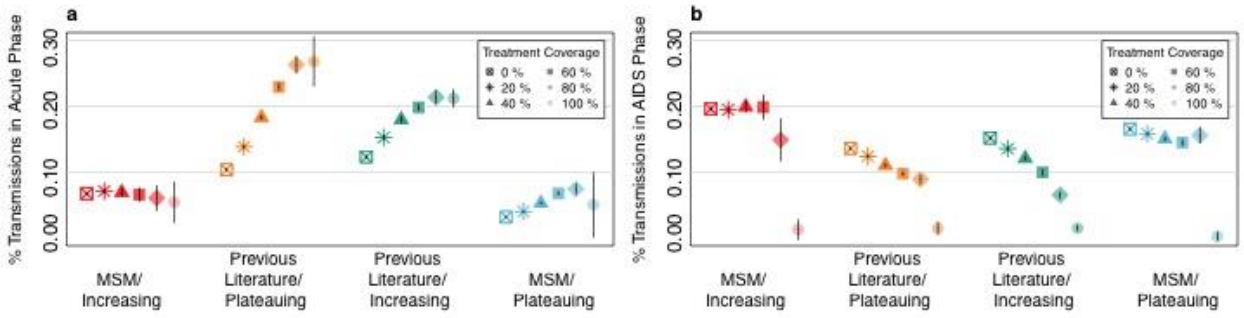

Figure 4: The proportion of transmissions that occur during the infecting partner's acute phase (a) and AIDS phase (b) between years 30 and 50. Each point is the mean of 64 simulations. Bars show 95% confidence intervals.

One possible explanation for the pattern seen in MPSPVL with increasing treatment coverage in different models is simple reversion to the mean. The MSM/Increasing model had the highest MPSPVL while the Previous Literature/Plateauing model had the lowest for the scenario with no treatment (for which details of the care cascade would be irrelevant to explaining differences between models); some form of reversion to the mean with higher coverage could in theory cause the effects seen in these models, and complicate our ability to interpret the trends across the four scenarios. To test this hypothesis, we ran sensitivity analyses varying condom use in order to observe trends in MPSPVL with increasing treatment coverage when the overall MPSPVL levels are more similar (Figure 5). While all main scenarios had 50% condom use, distributed randomly in acts, for this sensitivity analysis we changed the MSM/Increasing model to have 75% condom use in order to decrease overall MPSPVL and changed the remainder of the models to have 0% condom use to increase it. We found no change

in the direction of the MSM/Increasing model's trend with lower overall MPSPVL. The Previous Literature/Increasing and MSM/Plateauing models had similar overall MPSPVL levels to the MSM/Increasing model and showed a more pronounced trend toward higher MPSPVLs with higher treatment coverage than in the main analysis. Only overall MPSPVL in the Previous Literature/Plateauing model did not change substantially with decreased condom use, but neither did its trend with increasing treatment coverage. As the direction of the MPSPVL trends in each model did not change, and the MSM/Increasing, Previous Literature/Increasing, and MSM/Plateauing models now cross each other, we concluded that the pattern of decreasing MPSPVL with increasing coverage in the MSM/Increasing model is not indicative of simple reversion to the mean. The lack of change in the Previous Literature/Plateauing model may be due to the large number of sex acts and higher chance of transmission of low VL viruses with the plateauing function: if almost all serodiscordant partnerships resulted in transmitting HIV even with low VLs, there would be less scope for change with lower condom use.

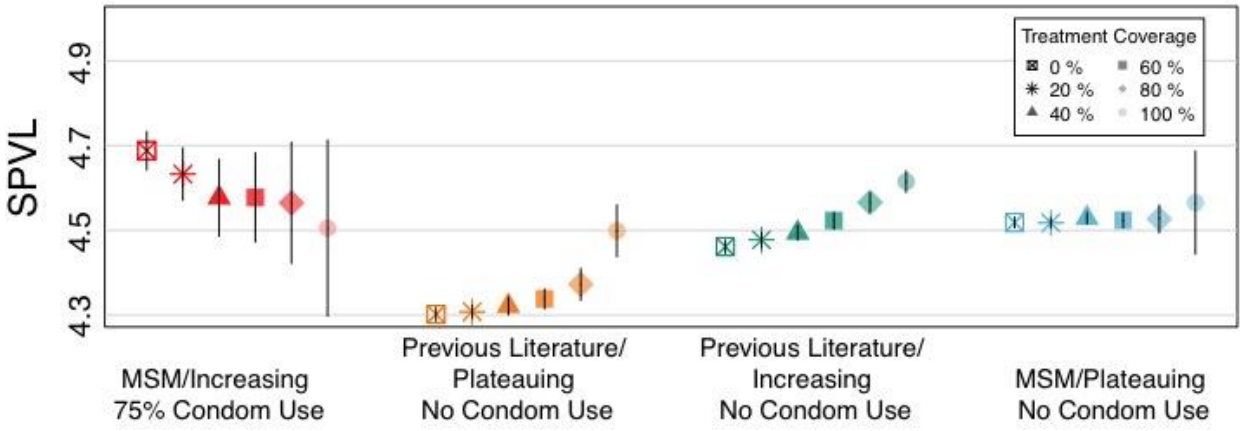

Figure 5: Mean population set point viral load trends with changed condom use of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 64 simulations. Bars show 95% confidence intervals.

Discussion

As test-and-treat coverage expands around the world, understanding how HIV virulence will respond to this expansion, especially in highly affected groups such as US MSM, is becoming more important in order to predict incidence changes and potential clinical consequences for those not on treatment. The impact of expanding treatment campaigns in

reducing new infections could be diminished if increasing test-and-treat coverage caused virulence, and consequent probability of transmission, to increase.

In contrast to the previous literature, however, our MSM/Increasing model predicted that, with higher test-and-treat coverage, HIV virulence would decrease. To isolate the causes of this discrepancy we first replicated the direction of effect found in the previous literature, then varied parameters relating to sexual behaviors, the transmission function, and treatment initiation in order to investigate the underlying cause of the differences in results. We found that the influence of these parameters varied in relation to how they impacted overall MPSPVL as well as transmission at different stages in the disease course. To disentangle the many moving parts, we first consider the Previous Literature/Plateauing model then each other model, changing one factor at a time. Each of the factors to consider in as virulence trends change with increasing treatment coverage is shown in the causal diagram (Figure 6).

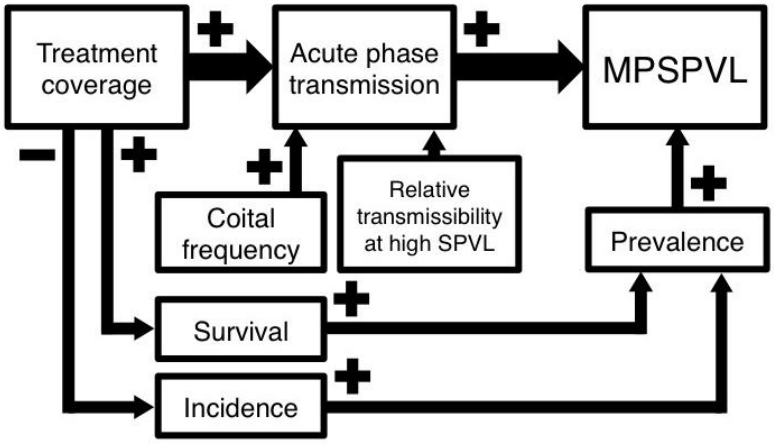

Figure 6: Causal diagram showing the relationship between model factors and MPSPVL change. Arrow size shows strength of the effect. The relative transmissibility at high SPVL refers to the probability of transmission at high VLs. The plateauing transmission function creates more variability in the proportion of transmissions in the acute phase than does the increasing transmission function.

Virulence trends with increasing treatment coverage

In the Previous Literature/Plateauing model, increasing treatment coverage led to increasing virulence (Figure 3). As a higher proportion of individuals were treated, more transmissions shifted to occurring early in the course of infection before treatment was initiated (Figure 4a). This model had extremely high coital frequency (mean = 1 act/day), which contributed to the high proportion of transmissions that occurred in the acute phase, as early

transmission was made more probable given the high number of transmission opportunities that would exist. Treatment disproportionately removes people in the later stages of HIV from the infectious population, as they have a higher probability of having tested positive and of becoming virally suppressed. As discussed above, shifting more transmissions to occurring during acute and early infection would select for more virulent viruses, as there is now a great deal of benefit to being more contagious and no corresponding decrease in length of time one is infectious (as this time period is now controlled by treatment initiation, not agent death), as discussed in Herbeck et al. (2016). The Previous Literature/Plateauing model had a much larger change in the proportion of transmissions occurring in the acute phase than the other models, so it shows the effect of this shift most clearly.

The Previous Literature/Increasing model had the same high coital frequency and high proportion of transmissions in the acute phase. However, it also used the increasing transmission function, instead of the plateauing function. The change in transmission function to the increasing function accounted for the smaller amount of variation in proportion of transmissions in the acute phase for the Previous Literature/Increasing model and the correspondingly smaller upward trend in MPSPVL.

The MSM/Plateauing model, in contrast, shared the plateauing function with the Previous Literature/Plateauing model but had a much lower coital frequency. The lower coital frequency means that there would be fewer transmission opportunities in the acute phase and therefore fewer transmissions. While there is a small increase in the number of transmissions that occur during the acute phase, the effect on MPSPVL is weak enough to be balanced by the large difference in prevalence between the treatment coverage levels. Higher prevalence levels in the simulations with lower treatment coverage led to higher MPSPVL, replicating effects found in Goodreau et al. (2018c). One likely explanation for this pattern is that with high prevalence, there are fewer susceptible individuals in the population, so more virulent viruses' increased transmission probabilities are beneficial enough to outweigh mortality costs. This effect is weaker than that of shifting transmissions to the infecting partner's acute phase, but as there was only a small difference in acute phase transmissions here, prevalence differences caused MPSPVL to have very little change with increasing treatment coverage.

Finally, in the MSM/Increasing model, low coital frequency and the increasing transmission function combined to lead to little change in acute phase transmissions. Missing

that strong effect, changing prevalence between treatment coverage levels led to decreasing MPSPVL with increasing treatment coverage.

Overall virulence differences between models

The trends in virulence change with increasing treatment coverage seen above occur in the context of overall MPSPVL differences between models. These patterns are similar to effects observed in in Goodreau et al. (2018c)'s simulation analysis and are shown in a causal model (Figure 7). First, models with shorter relationship durations had higher MPSPVLs. One likely explanation for this pattern is that with shorter relationship durations, only more virulent viruses are likely to be able to transmit before the partnership dissolves. In longer relationships with more overall coital acts, however, less virulent viruses have a greater chance of transmitting (Stansfield et al., 2019). Second, models with the plateauing transmission function had lower MPSPVLs than those with the increasing transmission function. Presumably this occurred because there is less advantage to a very virulent virus with the plateauing function, as increasing viral SPVL will increase mortality without increasing the probability of transmission, as discussed above. With the increasing transmission function, increasing SPVL leads to increased probability of transmission, which can outweigh the effects of increasing mortality.

Figure 7: Causal diagram showing the relationship between model factors and overall MPSPVL. Arrow size shows strength of the effect. The relative transmissibility at high SPVL refers to the probability of transmission at high VLs, e.g. the increasing transmission function has high transmissibility here and subsequently higher MPSPVLs while the plateauing transmission function has lower transmissibility and lower MPSPVLs.

The MSM/Increasing model had both factors that lead to higher MPSPVLs being more advantageous and evolved in that direction. The Previous Literature/Plateauing model had both factors that lead to lower MPSPVLs being more beneficial and evolved correspondingly. The other two models have effects in opposite directions and so remain closer to the initial MPSPVL value of 4.5 $\log_{10}$ copies/mL.

Limitations of our analysis include that agents did not cease treatment and were perfectly adherent to treatment once it was initiated. A small number of infections (mean over all simulations = 2.6%) occurred while an agent was virally suppressed. While this is likely to be an overestimation of transmission potential at very low VLs (Rodger et al., 2016), it reflects the increasing and plateauing transmission functions. Our network model was quite simple, in order to emphasize the effects of relationship duration, and did not include features such as age-related homophily, changing relationship duration with age, or other complex features. We based the previous literature sexual partnership parameters on Herbeck et al. (2016)'s alternate model, which had very high coital frequency, limiting the generalizability of our previous literature model to heterosexual populations.

Our results highlight the immense impacts of the exact details of behavior, virological, and biological processes in understanding fundamental public health outcomes.. By varying sexual behaviors and the HIV transmission function between parameter sets—sexual behaviors that all came from published models and transmission functions estimated from data—we generated huge differences in the effect of increasing treatment coverage on virulence. Transmission function especially had huge effects on prevalence and incidence estimates. Each transmission function has some biological plausibility and, given the ethics of future research, we may never know which more accurately estimates the relationship between viral load and probability of transmission. However, this relationship is of fundamental importance in understanding HIV spread. Thoughtfulness in parameterization and transparency about parameter choices are imperative in modeling studies, as small assumptions can lead to huge outcome differences.

With data-derived modeling assumptions and an MSM population, we found that MPSPVL either does not change or decreases with higher ART coverage. As treatment coverage has increased worldwide, this is good news as it shows that the hypothesized tradeoff between higher treatment prevalence and increasing virulence is not assured and public health programs need not contend with increasing transmission probability and other side effects of the hypothesized increased virulence. While patient outcomes will always come before evolutionary concerns in recommending treatment, it is reassuring to note that despite uncertainty in transmission function, our results suggest that, under some realistic conditions, vigorous test-and-treat strategies may *not* need to face a tradeoff in which increasing treatment coverage fuels

evolution of greater virulence, and may instead may begin a virtuous cycle of higher rates of treatment leading to less HIV virulence.

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Chapter 3: Pre-exposure prophylaxis coverage and HIV virulence evolution among men who have sex with men

Title: Pre-exposure prophylaxis coverage and HIV virulence evolution among men who have sex with men

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Abstract

Background:

HIV set point viral load (SPVL) is the viral load (VL) established shortly after the initial peak in VL subsides. It is a proxy for HIV virulence: higher SPVLs lead to faster progression to AIDS and increase the probability of transmission. Pre-exposure prophylaxis (PrEP) involves HIV-negative individuals utilizing HIV treatment in order to reduce their risk of acquisition. One previous compartmental model suggested that HIV virulence would increase with increasing PrEP coverage. Here, we examine the patterns of virulence evolution in a population of men who have sex with men (MSM) with different proportions of PrEP coverage.

Methods:

We extended a stochastic, dynamic network model (EvoNetHIV), based on temporal ERGMs implemented using the *statnet* suite of R packages and the EpiModel package API. We compared runs with no PrEP coverage to runs with 20-100% coverage for those eligible under behavioral guidelines established by the US Centers for Disease Control and Prevention. To reflect heterogeneity in behaviors that impact PrEP eligibility, we included longer and shorter relationship duration groups. We also included sensitivity analyses varying risk compensation behavior, assortative mixing within groups, and PrEP adherence differences by group.

Results:

HIV SPVL decreased as PrEP coverage increased. In the scenario with no PrEP coverage, mean population SPVL (MPSPVL) was 4.84 $\log_{10}$ copies/mL (95% CI 4.80, 4.88) with no PrEP, while in the scenario with PrEP for all those eligible, MPSPVL was 4.59 $\log_{10}$ copies/mL (95% CI 4.52, 4.67). This relationship was robust to sensitivity analyses.

Discussion:

These findings emphasize the impact of PrEP on predicted HIV virulence evolution. Our results suggest that increasing PrEP coverage does not promote the evolution of greater virulence. Instead we find that providing PrEP to all those eligible may actually select for lower virulence, amplifying the effects of PrEP to make HIV transmission less likely to all members of the population.

Introduction

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy in which HIV-negative people take anti-retroviral medication in order to reduce their risk of HIV acquisition. The current formulation in the United States involves one pill per day containing emtricitabine and tenofovir disoproxil fumarate (Grant et al., 2010), and when taken as directed reduced the probability of HIV acquisition by 95% or more (Grant et al., 2014; McCormack et al., 2016; Molina et al., 2017). As PrEP coverage increases around the world, it is important to consider the potential evolutionary effects it may have on HIV viral virulence. If PrEP expansions cause virulence increases, individuals not on PrEP, or those not fully adherent, would be more likely to have increased acquisition risks which could dull the effects of the interventions. Conversely, if increasing PrEP coverage led to decreased viral virulence, the effects of an intervention in reducing acquisition risk would be amplified and extended to all members of the population, not only those taking PrEP.

HIV virulence can be estimated using the proxy measure of set point viral load (SPVL), the viral load (VL) established soon after initial infection. SPVL influences both transmission potential and pace of disease progression: higher SPVLs are associated with faster progression to AIDS-defining illnesses (Modjarrad et al., 2008) and are more likely to transmit (Fraser et al., 2007b; Hughes et al., 2012b). Because SPVL is associated with both transmission probability and disease progression, the virus faces a tradeoff as it evolves towards higher or lower SPVL. It can either evolve to have higher infectiousness and shorter survival time after infection or lower infectiousness and longer survival time. In each case there is a tradeoff because the effects conflict: slower disease progression means there will be more opportunities to transmit but a lower chance of transmission at each one, while the opposite is true for faster disease progression with fewer chances to transmit but a higher probability of transmission at each chance.

PrEP coverage has steadily increased in the United States since its introduction. Between 2014 and 2017, the proportion of men who have sex with men (MSM) reporting PrEP use in the Center for Disease Control's (CDC) National HIV Behavioral Surveillance (NHBS) rose from 6 to 35% (Finlayson et al., 2019). This is not evenly spread across all groups, as 42% of white men reported 2017 PrEP use while only 26% of black men did. PrEP use is also concentrated in the United States and Sub-Saharan Africa, which account for 71% and 15% of worldwide PrEP users respectively (Fitch et al., 2018).

Modeling work has delved into the effects of PrEP coverage on epidemiological markers and risk groups. For example, Abbas et al. (2013) found that combining antiretroviral therapy (ART) interventions with PrEP prevent more infections than either intervention singly. Kessler et al. (2014) found that, in New York City, prioritizing PrEP to MSM created a large reduction in new infections and, compared to providing PrEP for all persons at risk, retained 79% of the effect at 15% of the cost. When examining the impact of the CDC's PrEP guidelines, Jenness et al. (2016c) found that there was a monotonic decline in both incidence and prevalence in the population when PrEP coverage begins. In UK MSM, Punyacharoensin et al. (2016) found that PrEP was a key factor in reducing incidence.

Viral load (VL) evolution with PrEP coverage has also been explored with mathematical modeling. In a compartmental model, Smith and Mideo (2017) tested several assumptions about treatment and PrEP. They found that as PrEP and treatment coverage increased, both overall virulence in their population and, in some cases, prevalence also increased. Further, virulence increased even more if treatment or PrEP was imperfectly effective. However, this model simplified HIV dynamics across a number of dimensions, which may limit the generality of its findings. For instance, all agents were homogenous except for infection, treatment, and PrEP status, including in terms of behavior; however, heterogeneity in behavior is key to the targeting of PrEP to those at high risk first (Centers for Disease Control and Prevention, 2017; Jenness et al., 2016c). Treatment caused infected agents to have their SPVL decreased by 1-2 $\log_{10}$ reductions, down to a minimum value of 2.6 $\log_{10}$ copies/mL for agents starting with the mean SPVL. While modifying SPVL in this way allows for treated agents to have slower progression to AIDS and a reduced transmission rate, it does not allow for treatment to result in undetectable (i.e. < 1.7 $\log_{10}$ copies/mL) or untransmittable VLs, which are now well-established (Rodger et al., 2016). Efficacy is uniformly applied across all agents receiving PrEP within a scenario; however, this lack of population heterogeneity, along with the collapsing of effectiveness and adherence into one measure, limits the conclusions one can draw. Condom use or risk compensation were not modeled despite their impact on PrEP's ultimate effectiveness in a population. Finally, all transmissions were assumed to occur during the chronic phase of infection and relationships are not included in the model. This approach has a few drawbacks: timing of HIV transmission within the disease course can impact SPVL evolution, as can relationship dynamics in the population (Goodreau et al., 2018c; Stansfield et al., in progress),

which will be absent if all infections are assumed to occur in the chronic phase and relationships are not modeled.

In this analysis, we modeled HIV transmission and viral evolution in an MSM population to determine the patterns of virulence evolution with different levels of PrEP coverage. We included VL dynamics that vary by state of infection and allow for those on treatment to achieve undetectable and untransmittable VLs. We modeled relationships and behavioral heterogeneity in relationship duration. Our model included heterogeneity in PrEP adherence and subsequent differences in effectiveness by adherence level. We also conducted several sensitivity analyses to see how robust our findings were to a variety of assumptions about risk compensation behaviors, PrEP adherence in relation to risk groups, and assortative mixing within risk groups.

Methods

We extended EvoNetHIV, a stochastic, dynamic, network-based model that has been described previously (Goodreau et al., 2018c; Herbeck et al., 2018; Stansfield et al., 2019), to predict mean population SPVL (MPSPVL), incidence, and prevalence changes with increasing levels of PrEP coverage in an MSM population. This model builds on the *EpiModel* (Jenness et al., 2016b) and *statnet* (Handcock et al., 2003) R packages and is available at github/EvoNetHIV/PrEP. Full methods for this model can be found in the appendix.

Our analysis featured relationship parameters designed to reflect an MSM population. Sexual network structure, relationship behaviors, and agent attributes were parameterized from two studies of Atlanta-area MSM conducted between 2010 and 2014 (Hernandez-Romieu et al., 2015; Sullivan et al., 2015) as interpreted in Goodreau et al. (2018a). Our simulated population included main and short relationship duration groups. In Goodreau et al. (2018a)'s analysis, probability of one-time acts per week was broken into quintiles, with the highest quintile having 66% of the one-time acts. In our model, there was a short relationship duration group comprising 20% of the population with mean relationship duration (36 days) adjusted to reflect the top quintile group for one-off acts and a main group comprising 80% of the population reflecting the other four quintiles (mean relationship duration = 62 days). In relationships with one member of each group, relationship duration was additive on the log scale (mean relationship duration = 47 days).

Treatment was administered based on a test-and-treat scheme following current World Health Organization test-and-treat guidelines (World Health Organization, 2015b). Agents tested annually (Helms et al., 2009) and began treatment upon a positive diagnosis. Treatment coverage was 60%, which was the mean of black and white men virally suppressed for one year in Buchacz et al. (2018) reflecting the approximately equal sizes of these populations in the Atlanta area, matching our other parameter sources (Goodreau et al., 2017).

PrEP eligibility was based on CDC guidelines and agents' behavior over the prior six months. Current CDC guidelines recommend PrEP initiation for MSM with behavioral indications including condomless anal intercourse (CAI) outside monogamous partnerships, CAI in HIV status-unknown monogamous partnerships, and anal intercourse (AI) in serodiscordant partnerships (Centers for Disease Control and Prevention, 2017). Agents were eligible for PrEP in our model if they were at an HIV test visit, did not have diagnosed HIV, had at least one partner in the previous 6 months, and were not in a monogamous, recently tested partnership. Additionally, they needed to be in a relationship with a disclosed positive partner or have had either CAI with a status unknown partner or any AI with two or more partners. PrEP coverage was varied between 0-100% of eligible agents, in 20% increments. PrEP coverage began ten years into modeled time. The appropriate percentage of eligible agents began PrEP at that time; agents could start PrEP at any test visit at which they were determined eligible if the coverage fraction had not been exceeded. Once an agent began PrEP, they continued until they were deemed no longer eligible, with eligibility assessed at each HIV testing visit. Adherence was fixed and reflected weekly dose levels based on an open-label demonstration project (Liu et al., 2016) as interpreted in Jenness et al. (2016c). In our model, 62% of agents were highly adherent with >4 doses/week, 10% had 2-3 doses/week, 7% had <2 doses/week, and 21% were non-adherent, with 0 doses. PrEP efficacy corresponded to the agents' adherence level, and was 95%, 81%, 31%, and 0% respectively (Grant et al., 2014).

We conducted analyses varying several components of the model, to see how robust our findings were to a variety of assumptions about behavior on PrEP and simulation design. These analyses are described in Table 1. We varied the function that related viral load in an infecting partner to the probability of transmission (see Stansfield et al. (in progress)), considering both an increasing transmission function based on Hughes et al. (2012b) and a plateauing transmission based on Fraser et al. (2007b) . For full details of the transmission functions, see the appendix.

We added in assortative mixing between two groups (90% of ties were within groups). In the baseline model, individual-level condom use propensities were combined to form couple-level probabilities with the mean of individual levels. We also conducted sensitivity analyses using the maximum or minimum individual-level propensity in each couple.

Table 1: Simulation design. If not specified in a specific column, each simulation had the same design as the baseline simulation in that column.

Model	Transmission Function	Risk compensation linked to PrEP adherence	Relationship duration group linked to PrEP adherence	Assortative mixing based on group membership	Condom compromise method
1 (baseline)	Increasing	None	None	None	Mean
2	Plateauing				
3				90% of ties formed in group	
4		Low adherence groups had more RC			
5		High adherence groups had more RC			
6		Low adherence groups had more RC		90% of ties formed in group	
7		High adherence groups had more RC		90% of ties formed in group	
8			Short relationship duration group had low PrEP adherence		
9			Short relationship duration group had high PrEP adherence		
10			Short relationship duration group had low PrEP adherence	90% of ties formed in group	
11			Short relationship duration group had high PrEP adherence	90% of ties formed in group	
12					Maximum
13					Minimum

We varied risk compensation as it was linked to PrEP adherence. Here, risk compensation was simulated as a decrease in individual condom use propensities. The relationship between risk compensation with condom use and PrEP adherence is not necessarily straightforward. One can imagine two countervailing phenomena: one in which individuals who are highly adherent to PrEP correctly assess their decreased risk of HIV acquisition and reduce their condom use accordingly, and another in which individuals have challenges in both PrEP adherence and in maintaining condom use. One study found that young MSM who had the highest rates of receptive CAI were also the least adherent to PrEP (Newcomb et al., 2018). However, this effect is unlikely to be universal so we explored both options and modeled scenarios in which the individuals who were the most adherent and the least adherent to PrEP had the most risk compensation. In the baseline simulation, individual propensities for condom use formed a truncated normal distribution centered at 50% with a standard deviation of 0.0373 drawn from condom use rates in Goodreau et al. (2017). In risk compensation scenarios where the most adherent group had the most risk compensation, those taking >4 doses/week had no condom use, those with 2-3 doses/week had individual condom use propensities centered at 10%, those with <2 doses/week had propensities centered at 20%, and those with 0 doses/week had propensities centered at 50%. The pattern was the same in risk compensation scenarios where the least adherent group had the most risk compensation, with no condom use in the 0 doses/week group, and condom use propensities centered at 10%, 20%, and 50% in the <2 doses/week, 2-3 doses/week, and 4+ doses/week groups respectively.

We also examined scenarios in which group membership was linked to PrEP adherence. When the shorter-relationship-duration group also had higher PrEP adherence, this could reflect individuals accurately assessing their HIV risk and adjusting the PrEP adherence accordingly. Conversely, when the shorter-relationship-duration group had lower PrEP adherence, this could reflect individuals whose life circumstances make both long-term relationships and regular PrEP adherence more difficult. In both of these simulations, proportions of individuals in each adherence group in the total population were equal to those described in Liu et al. (2016) as interpreted in Jenness et al. (2016c). In the simulation in which the shorter-relationship-duration group had lower PrEP adherence, there were no shorter-relationship-duration group members in the 4+ or 2-3 doses/week groups, 20% of group members were in the <2 doses/week group, and 80% of group members were in the 0 doses/week group. In the simulation in which the shorter-

relationship-duration group had higher PrEP adherence, 80% of group members were in the 4+ doses/week group and 20% of members were in the 2-3 doses/week group.

The initial population included 10,000 individuals between the ages of 18 and 55. HIV prevalence at the simulation start was 10%. Simulations lasted 50 years with one-day time steps. We examined viral evolution using MPSPVL change through time and epidemiological factors using prevalence and incidence. We calculated 95% confidence intervals for MPSPVL differences between simulations. While calculating inferential statistics on simulated data is a practice for debate, we believe it can be valuable when the number of observations is fixed in advance. This follows from Ferguson et al. (2006); Goodreau et al. (2018c); Yang et al. (2009); and others.

Results

In the baseline simulations (Model 1), prevalence briefly rose then fell through time while incidence declined slowly in the absence of PrEP (Figure 1). As more agents were diagnosed, began treatment, and thus lived longer with HIV, prevalence initially rose even as incidence was dropping. Prevalence and incidence showed expected declines in both the main group and risk group with increased PrEP coverage. With no PrEP, mean prevalence was 14% by year 50 and mean incidence was 0.80 per 100 person-years. When all those eligible for PrEP received it, however, mean prevalence was 1% and mean yearly percent incidence was 0.02 per 100 person-years. This pattern of declining prevalence and incidence with increasing PrEP coverage was repeated with all other parameter sets.

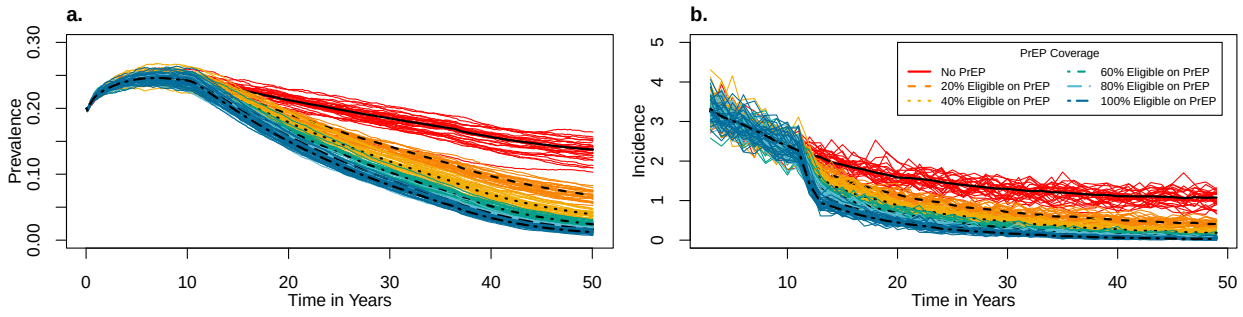

Figure 1: Prevalence (a) and incidence (b) between year 1-50. PrEP coverage began in year 10. Each black line is the mean of 112 simulations. Thin lines show individual simulations.

Mean incident population SPVL was also lower with higher PrEP coverage (Figure 2). While mean population incident SPVLs increased through time with no PrEP or lower PrEP

coverage levels, with PrEP coverage of 80-100% mean population SPVL declined over time. The mean incident population SPVL between years 40 to 50 declined linearly with increasing coverage, ranging from 4.84 $\log_{10}$ copies/mL (95% CI 4.80, 4.88) with no PrEP to 4.59 $\log_{10}$ copies/mL (95% CI 4.52, 4.67) with all those eligible for PrEP receiving it.

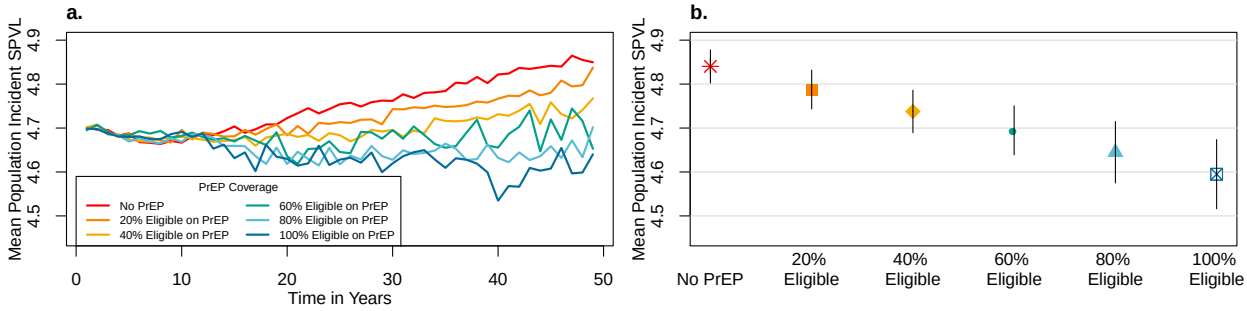

Figure 2: Mean population incident SPVLs changes with PrEP coverage increases. PrEP began in year 10. A: Mean population incident SPVL change through time. Each line is the mean of 112 simulations. B: Mean population SPVLs of those infected in years 40-50. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals.

Given that these results directly contrast with those of Smith and Mideo (2017), we calculated additional metrics in order to disentangle possible causal mechanisms. First, we examined the proportion of the population that is susceptible, which was mainly made up of uninfected individuals not on PrEP but also included a fraction of those on PrEP (although multiple levels of adherence mean that the least adherent individuals have the most risk of acquisition, those with high adherence retain a small chance of becoming infected). When more eligible individuals were on PrEP, there were fewer susceptible individuals in the population (Figure 3). The amount of time an infected person had been infected when they transmitted HIV to a susceptible partner also increased as PrEP coverage increased (Figure 4). The mean time a person was infected when transmitting to a susceptible partner between years 40 to 50 increased linearly as PrEP coverage increased, from 5.26 years (95% CI 5.10, 5.42) with no PrEP to 9.84 years (95% CI 9.02, 10.67) when all those eligible for PrEP received it.

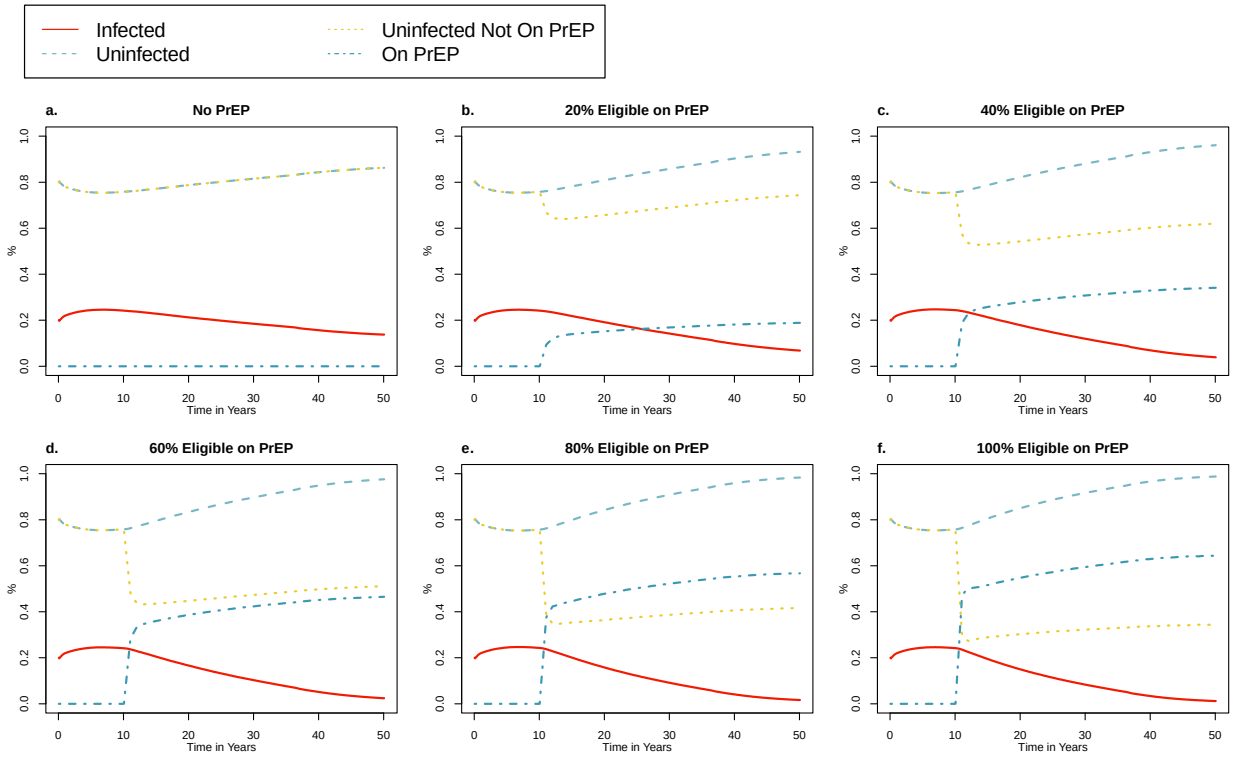

Figure 3: Proportion of total individuals in the population infected, uninfected, uninfected and not on PrEP, and on PrEP between years 1-50. The uninfected population was composed of HIV-negative individuals not on PrEP and those on PrEP. Each line is the mean of 112 simulations. Due to adherence levels, some of those on PrEP remain susceptible to HIV infection.

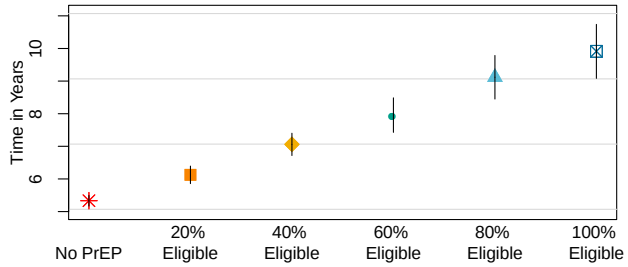

Figure 4: Mean time an infected person was infected when transmitting to a susceptible partner in years 40-50. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals.

Most of our sensitivity analyses showed very similar patterns across analyses. When using the plateauing transmission function (Fraser et al., 2007b) instead of the increasing transmission function (Hughes et al., 2012b) in Model 2, increasing PrEP coverage continued to lead to lower MPSPVLs (Figure 5). The magnitude of this difference was smaller than when

using the increasing transmission function, consistent with previous work (Goodreau et al., 2018c; Stansfield et al., in progress).

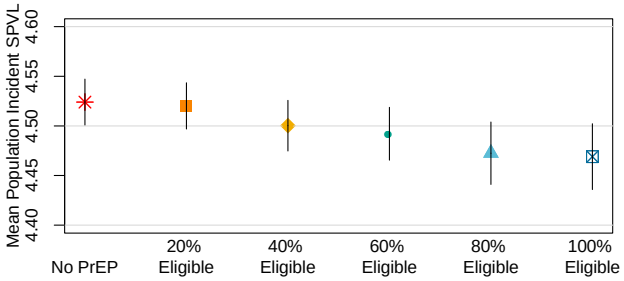

Figure 5: Mean population SPVLs of those infected in years 40-50 in Model 2, the simulation with the plateauing transmission function. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals. Note change of scale from other SPVL plots.

The addition of assortative mixing between the shorter-relationship-duration and main groups (Model 3) continued to generate declining MSVP with increasing PrEP coverage, although with some evidence for a slight threshold effect between 20% and 40% coverage levels (Figure 6).

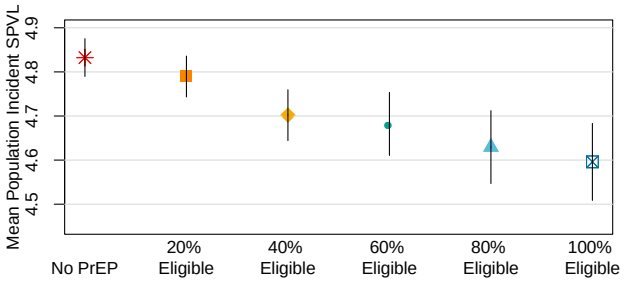

Figure 6: Mean population SPVLs of those infected in years 40-50 in Model 3, the simulation with assortative mixing within groups: 90% of relationships were formed between members of the same group. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals.

In sensitivity analyses varying risk compensation and PrEP adherence (Models 4-7, Figure 7), PrEP coverage increases also caused MPSPVL decreases. There was a linear decrease in MPSPVL with increasing PrEP coverage when individuals with lower PrEP coverage had higher levels of risk compensation with or without assortative mixing (Figure 7a, c). When individuals with higher PrEP adherence also had higher levels of risk compensation (Figure 7b,

d), MPSPVL decreased slightly more between 20% and 40% coverage (without assortative mixing) and between 20% and 60% coverage (with assortative mixing) than between other coverage levels.

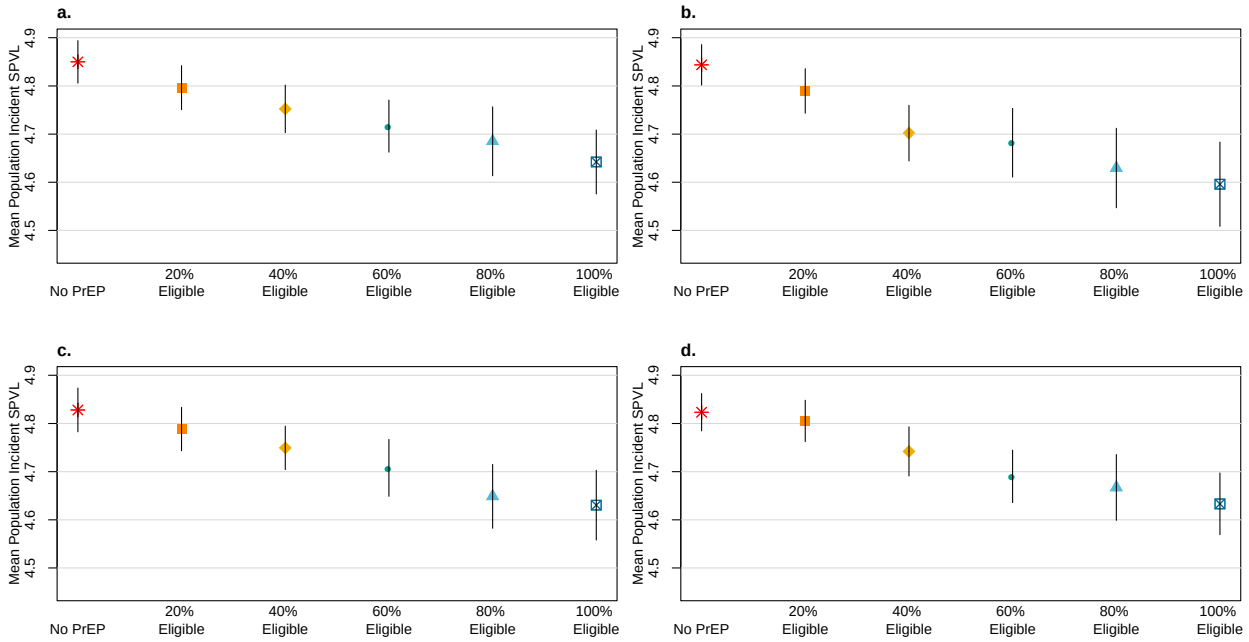

Figure 7: Mean population SPVLs of those infected in years 40-50. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals. A: Model 4, individuals with lower PrEP adherence had higher levels of risk compensation. B: Model 5, individuals with higher PrEP adherence had higher risk compensation. C: Model 6, individuals with lower PrEP adherence had higher levels of risk compensation and assortative mixing was in effect. D: Model 7, individuals with higher PrEP adherence had higher risk compensation and assortative mixing was in effect.

When PrEP adherence levels varied with group membership (Models 8-11), the effect of PrEP coverage on MPSPVL was more complicated (Figure 8). When the shorter-relationship-duration group had higher PrEP adherence or had lower PrEP adherence without assortative mixing, the results were similar to those found previously, with monotonic declines and some possible small threshold effects (Figure 8 a, b, d). In contrast, when the shorter-relationship-duration group had lower PrEP adherence and assortative mixing, MPSPVL remained flat across PrEP coverage levels (Figure 8c). We therefore probed this scenario further by considering the relationship duration groups separately (figures in appendix); the main group showed lower MPSPVLs with higher PrEP coverage resembling previous scenarios, while the shorter-

relationship-duration group had very low PrEP adherence, high incidence, and no relationship between PrEP coverage and MPSPVL level.

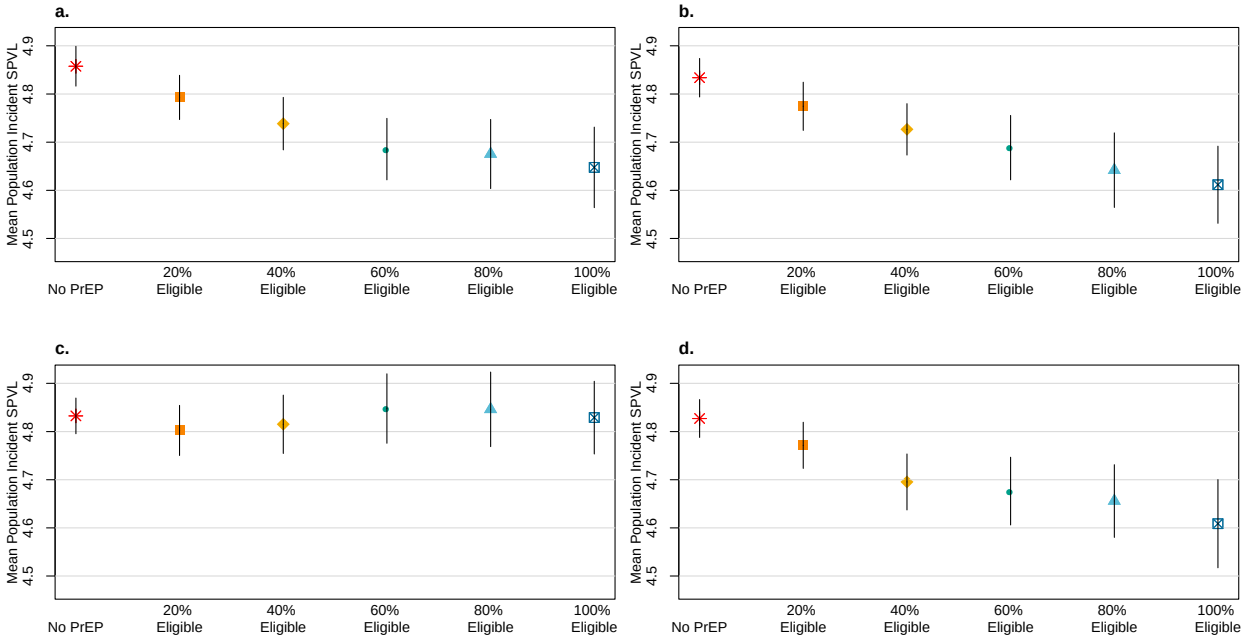

Figure 8: Mean population SPVLs of those infected in years 40-50. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals. A: Model 8, shorter-relationship-duration group had lower PrEP adherence. B: Model 9, shorter-relationship-duration group had higher PrEP adherence. C: Model 10, shorter-relationship-duration group had lower PrEP adherence and assortative mixing was in effect. D: Model 11, shorter-relationship-duration group had higher PrEP adherence and assortative mixing was in effect.

Changes in the condom compromise method (Models 12-13, figures in appendix) did not lead to differences from the baseline simulation in the pattern of MPSPVL decreases with PrEP coverage increases.

Discussion

The relationship between PrEP coverage increase and subsequent MPSPVL decrease follows from a viral trade-off: HIV can either evolve to become more virulent, with correspondingly higher probability of transmission and shorter time to AIDS, or less virulent, with lower probability of transmission but longer time to AIDS. When more individuals are on PrEP, there are fewer susceptible people in the population (Figure 3), as being on PrEP and adherent removes the individual from the pool of susceptibles. With fewer susceptible people in the population, it takes an infected person longer to encounter a susceptible person and transmit

infection (Figure 4) and it becomes more advantageous to the virus to allow a longer disease course. This progression is shown in a causal diagram in Figure 9; which is why here, infected individuals had longer times between infection and transmission to an uninfected partner when there was higher PrEP coverage in the population. The traits both depend on VL and thus are linked, so when a longer disease course is more advantageous, SPVL must decrease.

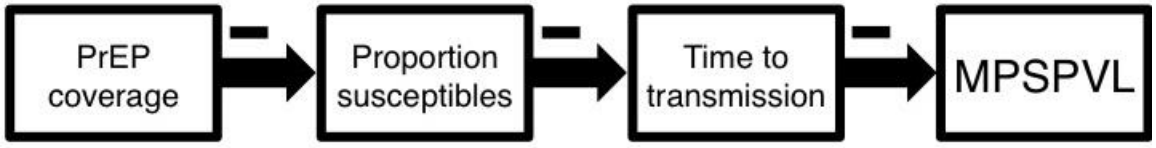

Figure 9: Causal diagram showing the relationship between PrEP coverage, the proportion of individuals in a population who are susceptible, the amount of time an infected person has been infected when they transmit infection, and mean population SPVL

The changes in MPSPVL with increasing PrEP coverage may stem from the alterations in the population when susceptible individuals can move to an uninfectable state. When there are both susceptible and unsusceptible individuals in a population, this would serve to lower the overall transmission rate. The theoretical literature on virulence evolution suggests that the transmission rate and duration of infection (which includes both mortality and recovery) are related through a trade-off curve (Figure 10). Evolution favors pathogen strains that move toward the boundary of the curve, but once a pathogen reaches the boundary transmission rate can only change if mortality or recovery also change. Under some simplifying assumptions and with random mixing, the most evolutionarily optimal pathogen virulence level is expected to be found at the intersection with a line passing through the origin and tangent to the curve (Bull and Lauring, 2014; van Baalen and Sabelis, 1995). For HIV, duration of infection is determined solely by mortality as there is no recovery. Lowering the transmissibility of HIV through PrEP will serve to shift the trade-off curve so that mortality is also lower. Lower mortality necessitates lower SPVL as these are linked (Modjarrad et al., 2008).

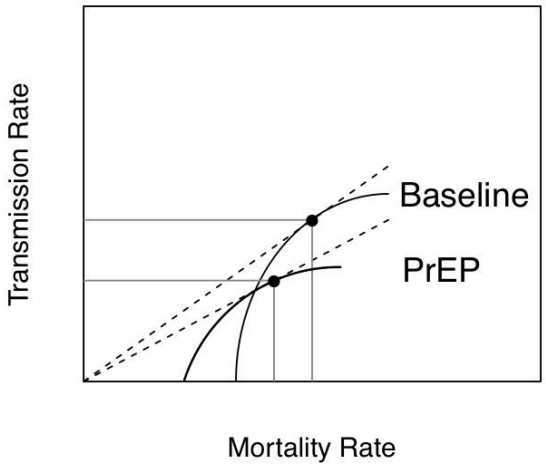

Figure 10: Diagram of a trade-off curve (solid lines) relating transmission rate and duration of infection for both a baseline population with no PrEP and a population with PrEP. Duration reflects mortality as HIV does not permit recovery. With several simplifying assumptions in place, the evolutionarily optimal virulence level will be at the intersection of this curve and a tangent line containing the origin (dotted line). As PrEP reduced the transmissibility of HIV by removing individuals from the susceptible population, the trade-off curve is also shifted.

Our finding that MPSPVL decreased with higher PrEP coverage was robust to sensitivity analyses across a variety of assumptions. While the magnitude of the change was much smaller when using the plateauing transmission function instead of the increasing transmission function (as in the baseline simulations), the direction of effect remained the same. This contrasts with the findings in Smith and Mideo (2017), as they also used the plateauing transmission function but found increased MPSPVL with increasing PrEP coverage. While the HIV transmission function can greatly impact the relationship between treatment and MPSPVL (Stansfield et al., in progress), this shows that this factor was not the driving force in the differences observed between these models. The model in Smith and Mideo (2017) also causes HIV prevalence to increase with increasing treatment and PrEP coverage in some cases, which could contribute to the difference in effects found as HIV prevalence decreased with increasing PrEP in all cases here. Smith and Mideo (2017) also found HIV to be evolutionarily unstable when PrEP is highly effective, so mainly discussed low efficacy PrEP (efficacy = 0.2), while we modeled a range of PrEP adherence and subsequent efficacy levels, which could also give rise to large differences in model predictions.

One persistent concern about PrEP is risk compensation, where PrEP use among MSM leads to increased CAI (Lal et al., 2017) . If risk compensation occurs mainly in those who are very adherent to PrEP, this may not lead to HIV incidence increases, although it remains a concern for other STIs. However, if those whose PrEP adherence is insufficient to protect them against HIV acquisition are also those with more risk compensation, this could lead to higher HIV incidence. Although one might imagine that those with high adherence would have the most risk compensation (since they know they are already protected), one longitudinal cohort study of young MSM in Chicago (Newcomb et al., 2018) found that those on PrEP with the most receptive CAI were also the most likely to be *non-adherent*. Despite this potential, the relationship between PrEP coverage and MPSPVL remains similar to that in the baseline simulation, although some simulations that varied risk compensation had a less linear and more sigmoidal relationship between the factors.

Finally, we found an interesting interaction effect when considering both PrEP adherence linked to risk group, and assortative mixing by risk group. Neither alone was sufficient to alter the inverse relationship between PrEP coverage and MSPVL, but when both were present that relationship became effectively flat. When the shorter-relationship-duration group had high PrEP adherence, adherence in the main group was not depressed enough to have an impact on MPSPVL patterns. However, when the shorter-relationship-duration group also had lower PrEP adherence, adherence in this group was low enough to eliminate any impact of PrEP on acquisition risk. Rising prevalence coupled with a small pool of potential partners led to incidence in this group becoming very high. As the main group had much lower incidence, individuals who became infected in the shorter-relationship-duration group comprised the majority of new infections. This dwarfed the impact of PrEP on MPSPVL when considering the overall population. However, when the groups were considered individually, the relationship between PrEP coverage and MPSPVL in the main group remained consistent with that in the baseline model.

Limitations of our analysis include the fact that agents in our model do not change their PrEP adherence patterns and are perfectly adherent to ART. We use a simple network model, which does not account for phenomena such as either differential relationship length or assortative mixing by age. Agents remain in their relationship duration group until they exit the model. We do not consider potential drug resistance, which would limit the effectiveness of

increasing PrEP coverage. This factor may be partially mitigated as we assume that fully adherent PrEP is 95% effective, which seems likely to be an underestimate (Grant et al., 2014; McCormack et al., 2016; Molina et al., 2017); this gap between our assumed PrEP efficacy and the actual rate implicitly allows for a small number of virus acquisitions due to drug resistance.

We found that in an MSM population, as PrEP coverage increased, HIV virulence decreased. As PrEP coverage increases in the US and worldwide, this is hopeful as it suggests that coverage increases will contribute to declines in both incidence and virulence, making onward transmission to those both on and off PrEP less likely, adding to both the effectiveness and cost-effectiveness of this intervention.

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Conclusion

This dissertation examined factors inherent in HIV acquisition and virulence evolution in a US MSM population. Simulation remains the only way to estimate these effects, as current ART recommendations do not allow for SPVL measurement.

Virulence impacts on public health

While decision-making surrounding individual treatment and PrEP use in the real world will of course be guided by patient outcomes, the results in this dissertation help to overturn previously modeled trade-offs in higher ART and PrEP coverage and higher virulence evolution. As I have shown that increasing treatment and PrEP coverage can lead to lower virulence levels becoming more evolutionarily advantageous, this points the way for secondary positive effects that have been previously unaccounted for. These effects on SPVL evolution can amplify the influences of treatment and PrEP interventions to positively affect the entire population: when virulence decreases, there is a lower risk of acquisition to everyone.

Virulence evolution with contrasting pressures

This dissertation also explores how virulence evolves differently when infected individuals are removed from the model through treatment than when susceptibles are removed from the model through PrEP use (Figure 1). HIV does not permit recovery, so without treatment or PrEP, can be thought of as having two states: one can either be susceptible to the virus or infected with it, and movement is only allowed *from* the susceptible category *to* the infected category. With the introduction of treatment, infected individuals can move to a new category with no possibility of transmission to susceptible individuals. In contrast, PrEP allows susceptible individuals to move into a new category with little risk of acquisition. The effect of these moves on transmission potential is especially important when one considers acute phase transmissions. In the acute phase, infected individuals have high VL and so have a high probability of transmission if they are in a serodiscordant relationship. Adding treatment coverage does not greatly diminish infections here, as individuals are less likely to have tested positive and began treatment while in this phase. In contrast, removing individuals from the pool of susceptibles by increasing PrEP coverage means that they will not be available to become

infected in their partners' acute phase. While different modeling assumptions result in different proportions of infections occurring during the acute phase with increasing treatment coverage, the same effects are not seen with PrEP coverage. This may explain why the effects of increasing PrEP coverage on SPVL evolution were more robust to modeling assumptions than were the effects of increasing treatment coverage.

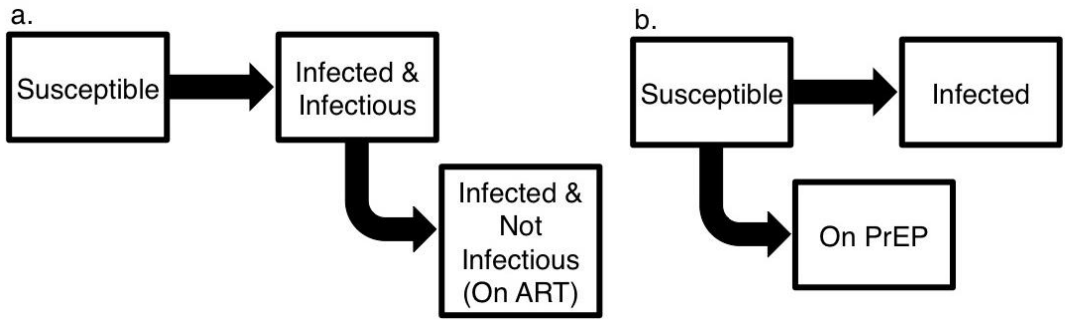

Figure 1: Causal model of the effects on the modeled population of introducing ART (A) or PrEP use (B).

Model assumptions

One aspect common to all chapters here is that model assumptions determine outputs. This is most clearly shown in the second chapter, when the direction of the modeled effect reversed when assumptions about the transmission function and relationship patterns were changed. The effects of assumptions about relationship factors could also be seen in the first chapter, where the number of coital acts serodiscordant agents had (encompassing coital frequency and relationship durations) played a large role in the virulence of the viruses they acquired. While the effects of increasing PrEP coverage in the third chapter were largely robust to model assumptions, there was a much smaller effect seen when the transmission function was varied. Careful consideration of and transparency about model assumptions are imperative in order to create realistic and replicable models.

Future Work

While questions of the impact of PrEP coverage increases on virulence evolution will be difficult to examine with population data given that SPVL information can no longer be collected from patients, the impact of ART coverage increases (if measured before test-and-treat

recommendations began) may be possible to capture. This would give a real world look at how changing the evolutionary environment of HIV impacts SPVL change.

One limitation of this work was in estimating heritability with a fixed value. There have been a wide range of estimates of the heritability of HIV SPVL between partners. Although much of this effect may be due to researchers estimating heritability with different measures, the precise value of heritability remains an open question. It may also shift with changing environments. Continuing to examine the effects of changing evolutionary environments on both heritability and HIV virulence evolution may give new insights into future virulence changes.

Chapter 1 Supplementary Appendix

Sexual role and HIV-1 set point viral load among men who have sex with men

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1. Model overview

We developed both a Bernoulli model of one generation of HIV-1 transmission from a founder population and a stochastic dynamic network model of HIV transmission. Model code for both is accessible at https://github.com/EvoNetHIV/RoleSPVL; the one generation Bernoulli model can be found under RoleSPVL/OneGenModel and is discussed in section 9.

The majority of this technical supplement focuses on the dynamic network model. *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.

In the description below, all references to viral load (VL) and set point viral load (SPVL) are $\log_{10}$ copies/mL, unless otherwise noted. *EvoNetHIV* is programmed in the R software language (R Development Core Team, 2008).

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.

2. Sexual network

2.1 Empirical data

Additional details regarding study design and analysis are available in Jenness et al. (2016c) and Goodreau et al. (2017).

2.2 Network structure

The sexual network consists of a population of MSM. 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. Two men with incompatible sexual role (i.e., two exclusively insertive

men or two exclusively receptive men) are prohibited from forming a partnership. All existing relationships have a constant and equal daily probability of dissolution.

Separable temporal exponential random graph models (STERGMs) (Krivitsky and Handcock, 2014b), as implemented in the statnet (Handcock et al., 2003) and EpiModel software suites, were used to estimate the networks. 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.

Table 2.1. Model parameters utilized in network estimation

Model parameter	**Value**	**Source(s) and notes**
Momentary mean degree	0.70	Jenness et al. (2016d) 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. (2017); based on data from the InvolveMENt and MAN Project studies
Relationship duration (days)	50, 100, 500, 1000, 1500, 2000, 2500, 3000 days	Relationship duration = 50 days. This was calculated as the weighted mean of the relationship durations for main, casual, and one-time sexual networks in the data presented in Jenness et al. (2016d). Other values were included as an exploration of this key variable on outcomes of interest.

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) to account for the changing size of the network as the simulation progresses.

3. Sexual behaviors and agent attributes

Coital acts are determined among agents in a serodiscordant relationship at each time step. Among these partnerships, the number of coital acts per partnership at a given time step is assigned according to a Poisson draw with mean 0.4 acts/day, except in late-stage AIDS when it is 0. Circumcision status is assigned to every agent at model entry, with 85% probability of being circumcised.

Table 3.1. Model parameters specifying sexual behaviors and agent attributes

Model parameter	**Value**	**Source(s) and notes**
Mean sex acts per day	0.40	0.20 is a reanalysis of parameters in a previous study of MSM with multiple relational types (Goodreau et al., 2017) for a single relational type; based on data from the InvolveMENt and MAN Project (Hernandez-Romieu et al., 2015) studies. We used an arbitrary increase factor of 2 to account for the fact that rates of condomless anal intercourse early in the AIDS epidemic were likely higher than when these data were collected
Circumcision probability	0.85	Mean from two previous modeling studies among MSM. Jenness et al. (2016d); Goodreau et al. (2012a)

4. HIV transmission

The risk of HIV transmission to the uninfected agent is determined for each sex act according to characteristics of the coital act and characteristics of the agents engaged in the coital act. We begin with the model from Fraser et al. (2007b). This is an increasing Hill function that depends on the maximum infection rate per year (0.317), the slope of increasing infectiousness by viral load (1.02), and the viral load at which infectiousness is half of the maximum (4.14 $\log_{10}$ copies/mL or 13,938 copies per mL). We back-calculated an approximate per-act maximum transmission probability (0.002) from Fraser's annual estimate based on previous work (Herbeck et al., 2014). 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), 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, as 2.9 and 17.3, respectively. Collectively, the probability of transmission per act can thus be described as:

$$P(transmission) = \beta(V) = \frac{[0.002 * (viral\ load^{1.02})]}{(13938^{1.02}) + (viral\ load^{1.02})} * (0.22)^{\mathrm{I}[condom]} *$$

$$(2.9)^{\mathrm{I}[insertive\ \mathrm{AI}]} * (17.3)^{\mathrm{I}[receptive\ \mathrm{AI}]} * (0.53)^{\mathrm{I}[circumcised]*\mathrm{I}[insertive\ \mathrm{AI}]}$$

with viral load in this equation referring to absolute viral load, not log10, as per the source model.

Where I[·] is an indicator function, with I[insertive AI], I[receptive AI] and I[circumcised] referring to the HIV-negative member of the partnership, and I[condom] referring to the use of a condom by the insertive partner during the act. We note that the effects of these modifiers are unlikely to be independent of viral load, such that the true function involves more complex interactions; however, in the absence of research that has demonstrated the nature of these interactions, we adopt this form, with the expectation that its impacts on our qualitative findings are minimal.

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

Model parameter	**Value**	**Source(s) and notes**
Maximum infection rate per year	0.317	Fraser et al. (2007b)
Slope of increasing infectiousness by viral load	1.02	Fraser et al. (2007b)
Viral load at which infectiousness is half of the maximum	13,938 copies per mL (absolute scale)	Fraser et al. (2007b)
Per-act maximum transmission probability (approximate)	0.002	Back-calculated from Fraser et al. (2007b) in Herbeck et al. (2014)
Relative risk of transmission for circumcision	0.53	Hughes et al. (2012a)
Relative risk of transmission for condom use	0.22	Hughes et al. (2012a)
Relative risk of transmission for insertive anal intercourse	2.9	Derived from Patel et al. (2014) (see text)
Relative risk of transmission for receptive anal intercourse	17.3	Derived from Patel et al. (2014) (see text)

5. Set point viral load

Throughout this section, viral load is expressed in $\log_{10}$ copies/ml. Set point viral load (SPVL) in infected agents at model initialization is generated as a normal distribution:

$$viral_{spvl,i} \sim N\left(\mu_{spvl,t_0}, \sigma^2_{spvl,t_0}\right)$$

where:

$\mu_{spvl,t_0} = 4.5$ $\log_{10}$ copies/mL

$\sigma^2_{spvl,t_0} = 0.8$ $\log_{10}$ copies/mL

For infections after the start of the model, SPVL is calculated as a combination of viral genotype and environmental (a combination of undefined host and non-viral) factors. For infected agent *i*, the viral contribution to SPVL equals:

$$viral_{spvl,i} = h^2\left(viral_{spvl,infector} + \epsilon\right)$$

where h^2 is the heritability coefficient, set here at 0.36, following Hollingsworth et al. (2010), and consistent with the Fraser et al. meta-analysis (2014). Note that while the value of h^2 is set as a model input and employed to modulate the influence of viral genotype on the similarity in SPVL between transmission pairs, heritability is a population-level measure that can change over time and across populations. The ϵ is the assumed normally distributed stochastic mutational variance, $\epsilon \sim N(0,\ 0.01)$. Mutational variance was initially included in the model with the intention of making it a function of time since infection, thus providing a means for heritability to decline slightly with time since infection for the initially infected partner. However, this was

never implemented; thus, the mutational variance term as included did not add anything to the model mathematically that could not have been included in the environmental contribution to SPVL. Nonetheless, we explain it here, and note that its value is very small and should thus have negligible impact on our results; moreover, we confirmed that our base model demonstrated a heritability of ~0.36 as an output population measure with this and all other forms of complexity in the model.

The stochastic environmental contribution is normally distributed:

$$env_{spvl,i} \sim N(0, \sigma^2_{env})$$

$where\ \sigma^2_{env} = (1 - h^2)\sigma^2_{spvl,t_0}$, and σ^2_{spvl,t_0} equals the variance in SPVL at time 0.

Individual SPVL is then the sum of the viral and environmental contributions:

$$spvl_i = env_{spvl,i} + viral_{spvl,i}.$$

However, SPVL values are constrained to a minimum of 2 $\log_{10}$ copies/mL and a maximum of 7 $\log_{10}$ copies/mL; in the rare distances that calculations fall below or above this range, they are reset to 2 or 7, respectively.

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

Model parameter	**Value**	**Source(s) and notes**
Mean $\log_{10}$ SPVL at model initialization	4.5	Fraser et al. (2007b) ; Korenromp et al. (2009)
Heritability of SPVL across transmissions (h^2)	0.36	Hollingsworth et al. (2010b)
Initial variance of $\log_{10}$ SPVL (σ^2_{spvl,t_0})	0.8	Herbeck et al. (2012)
Mutational variance (ϵ)	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.

6. Viral dynamics

Throughout this section, we define viral load *VL* and set-point viral load *SPVL* in terms of $\log_{10}$ copies/mL for simplicity, although our model code expresses them in a mixture of absolute and $\log_{10}$ units.

Upon infection, viral load starts at the initial value VL_0 = -4 $\log_{10}$ copies/mL or 0.0001 copies/mL) and grows linearly at rate r_0 for the first 21 days according to the formula:

$$VL(t) = VL_0 + r_0 t$$

where *t* indicates the number of days since initial infection. Robb et al. (2016) 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:

$$VL_{peak} = 4.639 + 0.495 * SPVL$$

where the values of 4.639 and 0.495 are based on regression data given in Robb et al. (2016). We then set $r_0 = (VL_{peak} - VL_0)/21$ separately for each individual in order to obtain peak viral load on day 21 for everyone. We chose to correlate the up-slope from infection to peak viral load instead of utilizing a fixed slope as both Prince et al. (2012) and Selhorst et al. (2017) found correlations between SPVL and viral "replication capacity," the growth rate of the virus in culture (p=0.02 and 0.045 respectively). These differences in replication capacity would predict different up-slopes, not different peak viral loads.

After viral load reaches peak, it then decays biphasically. The first phase has a duration of 11 days, in which viral load decays linearly according to the following formula:

$$VL(t) = VL_{peak} - \frac{(t-21)}{11} * (VL_{peak} - VL_{32})$$

where viral load at t=32 is a weighted mean of VL_{peak} and SPVL:

$$VL_{32} = 0.714 * SPVL + 0.286 * VL_{peak}$$

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

$$VL(t) = VL_{32} - \frac{(t - 32)}{58} * (VL_{32} - SPVL)$$

In the chronic phase of HIV infection, an agent's viral load increases at a constant annual rate of 0.06 $\log_{10}$ copies/mL, calculated as follows

$$VL(t) = SPVL + \ 0.06 * \frac{t - 90}{365}$$

SPVL is here defined as the viral load at the beginning of the chronic phase, before viral load begins to rise. Viral load trajectory continues until an agent initiates antiretroviral treatment or enters the AIDS stage, defined by CD4+ cell count less than 200 cells/mm^3. During the AIDS stage, the agent's viral load increases linearly by 0.001782 per day:

$$VL(t) = 0.001782 + VL(t - 1)$$

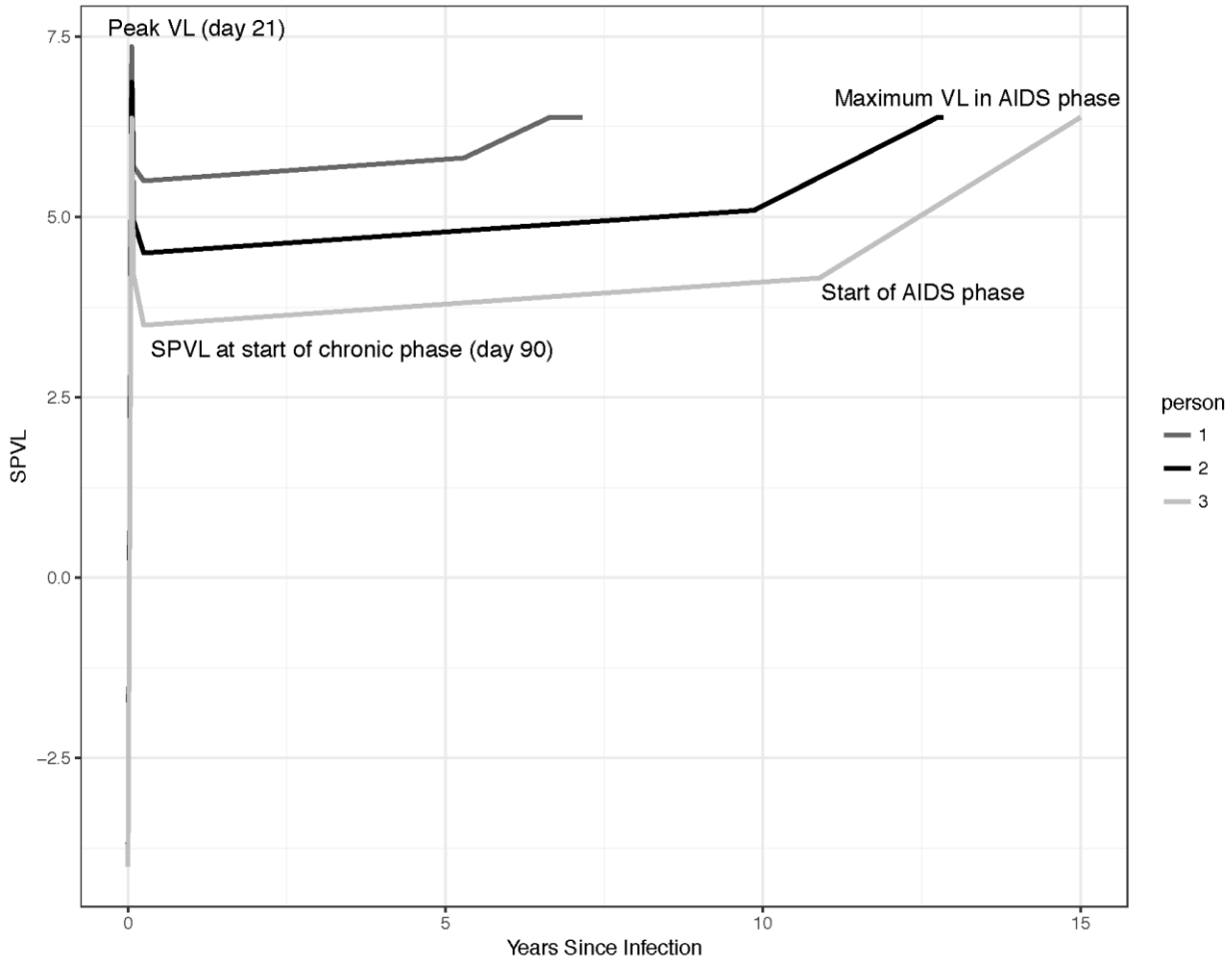
Viral load in AIDS increases up to a maximum viral load of 6.38 $\log_{10}$ copies/mL.

Table 6.1. Model parameters utilized in viral load dynamics

Model parameter	**Value**	**Source(s) and notes**
Viral load at day 0 of infection	-4 $\log_{10}$ copies/mL (0.0001 copies/mL)	Approximately equal to 1 virion / body, assuming ~10,000 mL of blood and lymph
Duration of acute infection	90 days	Fiebig et al. (2003)
Duration of viral growth	21 days	Lindback et al. (2000)
Duration of phase 1 decay	11 days	Lindback et al. (2000)
Duration of phase 2 decay	58 days	Constrained as the duration of acute infection (90 days) minus each of the other two components of that phase—viral growth (21 days) and phase 1 decay (11 days)
Relative weighting in the mean used to calculate VL_{32}	71.4% SPVL 28.6% VL_{peak}	Calculated to reflect that viral load decays more quickly in phase 1
Log_{10} viral load progression rate during chronic phase	0.06 per year	Approximated from Fiebig et al. (2003); Geskus et al. (2007)
Log_{10} viral load progression rate during AIDS phase	0.001782 per day	Viral load increases linearly until maximum viral load in AIDS is reached
Maximum viral load in AIDS (CD4+ cell count <200)	6.38 $\log_{10}$ copies / mL (=2.4×10^6 copies/mL)	Piatak et al. (1993)

Figure 6.1 Example viral load dynamics

Viral load dynamics for three individuals with SPVLs of 3.5, 4.5, and 5.5 $\log_{10}$ units and chronic and AIDS phase durations corresponding to values from Table 7.2, which give the mean time spent at each CD4+ cell count value for each SPVL. These were chosen as both parameters are stochastic when modeled.



7. Disease progression

CD4+ cell count values determine the additional risk of death among infected agents. Values are categorized as CD4+ $\geq$ 500 cells/mm^3, 500 < CD4+ $\leq$ 350, 350 < CD4+ $\leq$ 200, and CD4+ < 200. Agents are assigned a CD4 category probabilistically according to their set point viral load (Cori et al. (2015); Table 7.1). No agents are assigned a CD4+ cell count category of less than 200 cells/mm^3 upon initial infection.

Table 7.1. Probability of assignment to CD4+ cell count category stratified by set point viral load

Set point viral load ($\log_{10}$ copies/mL)	CD4+ cell count level (cells/mm^3)		
	$\geq$ 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

We note that the two categories of highest viral load are included for the sake of completion, so that any individual who does evolve into this zone will have an associated CD4+ cell count

value. However, these persons are very rare in the model and die quickly, limiting the persistence of their viral genotype in the population.

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

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

Set point viral load ($\log_{10}$ copies/mL)	CD4+ cell count level (cells/mm^3)			
	≥ 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

8. Vital dynamics

8.1 Model initialization

The epidemic model is initialized with a population size of 5,000 agents. We initially began the model with an age distribution derived from the CDC WONDER database for United States males for the years 1999-2003 (Centers for Disease Control and Prevention, 2015). However, because our model represents a highly selective population with large HIV burden and high AIDS mortality because of lack of treatment, this age distribution is very different than the one generated by the model, and we considered the dramatic change in age distribution as a possible source of artifacts. Thus, we simulated our based model through a burnin period until the age distribution stabilized, and then began again with that age distribution as our initial one.

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 model parameters are used. Each new agent enters the model uninfected with age 18.

8.3 Exits

Age-specific annual non-AIDS mortality rates for US males ages 18-55 were obtained from the CDC WONDER database for the years 1999-2003 (Centers for Disease Control and Prevention, 2015). We converted these annual mortality rates to daily probabilities. Natural deaths occur

randomly according to each agent's age-specific probability of death. HIV-infected agents with CD4+ cell count greater than 200 cells/mm^3 have an increased probability of death that is dependent on their CD4+ cell count category. Deaths due to AIDS occur when an agent's time in CD4+ cell count category 4 (CD4+ < 200 cells/mm^3) 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	5,000	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,	Modified from CDC WONDER (Centers for Disease Control and Prevention, 2015)

	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	
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 (Centers for Disease Control and Prevention, 2015)
Additional probability of death with CD4+ cell count > 500 cells/mm^3	0.0000112 per day	The values in CASCADE, 2011 (Writing Committee for the CASCADE

		Collaboration, 2011) are for men with mean age 30. Rates presented here therefore subtract 0.0014, the natural mortality rate for North American males aged 30 (Centers for Disease Control and Prevention, 2015), to estimate an excess death rate associated with this CD4+ cell count category.
Additional probability of death with CD4+ cell count 350-500 cells/mm^3	0.0000148 per day	See note above
Additional probability of death with CD4+ cell count 200-350 cells/mm^3	0.0000333 per day	See note above

9. Mathematical derivation of one-generation model

The following derivation that provides a formal proof for the main findings of our one-generation model was provided to us during the review process by Dr. Chris Wymant of the University of Oxford:

Let $g(v)$ be the population-level viral load probability distribution function, i.e. the probability of having a viral load in the range $[v_1, v_2)$ is $\int_{v1}^{v2} g(v)dv$. Let $T(v)$ be the per-act transmission probability for a donor with viral load v, defined for a particular category of recipient with a particular susceptibility (to be revisited shortly). Consider a serodiscordant partnership at its point of initiation, in which the HIV+ individual is drawn randomly from the population. The (infinitesimal) probability that the HIV+ individual has viral load v is therefore $g(v)dv$. After N sexual acts, the probability of transmission in this partnership is $\sum_{n=1}^{N}\left(1-T\left(v\right)\right)^{n-1}T\left(v\right)$. Although this is equivalent to the simpler and more familiar form $1-\left(1-T\left(v\right)\right)^{N}$, we use the former as it simplifies the final step of the derivation below. From this it follows that:

Pr(transm. occurred during N acts and donor had viral load v) = $g\left(v\right)dv\sum_{n=1}^{N}\left(1-T\left(v\right)\right)^{n-1}T\left(v\right)$

Pr(transm. occurred during N acts) = $\int_{v'} g\left(v'\right)\sum_{n=1}^{N}\left(1-T\left(v'\right)\right)^{n-1}T\left(v'\right)dv'$

Pr(donor had viral load v | transm. occurred during N acts) = $\frac{g\left(v\right)dv\sum_{n=1}^{N}\left(1-T\left(v\right)\right)^{n-1}T\left(v\right)}{\int_{v'} g\left(v'\right)\sum_{n=1}^{N}\left(1-T\left(v'\right)\right)^{n-1}T\left(v'\right)dv'}$

For example:

Pr(donor had viral load v | transm. occurred during 1 act) = $\frac{g\left(v\right)dvT\left(v\right)}{\int_{v'} g\left(v'\right)T\left(v'\right)dv'}$

Pr(donor had viral load v | transmn. occurred during 2 acts) = $\dfrac{g(v)\,dv\big(2-T(v)\big)T(v)}{\int_{v'} g(v')\big(2-T(v')\big)T(v')\,dv'}$

Pr(donor had viral load v | transmn. occurred during ∞ acts) = $\dfrac{g(v)\,dv}{\int_{v'} g(v')\,dv'}$

We can consider a different category of recipients having a different susceptibility by scaling $T(v)$ by a viral-load-independent relative risk factor, α say, with $\alpha < 1$ for lower susceptibility. The above recipient viral load distributions for a single act and for an infinite number of acts are both invariant under a rescaling of $T(v)$, i.e. are independent of the recipient's susceptibility. However, for an intermediate number of acts (e.g. $N = 2$ which has the simplest equation, shown above), multiplying $T(v)$ by a constant α shifts the distribution. For T being a monotonically increasing function of v, $\alpha < 1$ shifts the recipient viral load distribution to higher values.

Consider now that a new partner is drawn for each sex act. Define $p = \int_{v'} g(v')T(v')\,dv'$, which is the fixed probability of transmission in any act (for the same kind of recipient):

Prob(transm. occurred during N acts) = $\sum_{n=1}^{N}(1-p)^{n-1}\,p$

Prob(transm. occurred during N acts and donor had viral load v) = $\sum_{n=1}^{N}(1-p)^{n-1}g(v)T(v)$

Prob(donor had viral load v | transmission occurred during N acts) = $\dfrac{\sum_{n=1}^{N}(1-p)^{n-1}g(v)T(v)}{\sum_{n=1}^{N}(1-p)^{n-1}\,p}$

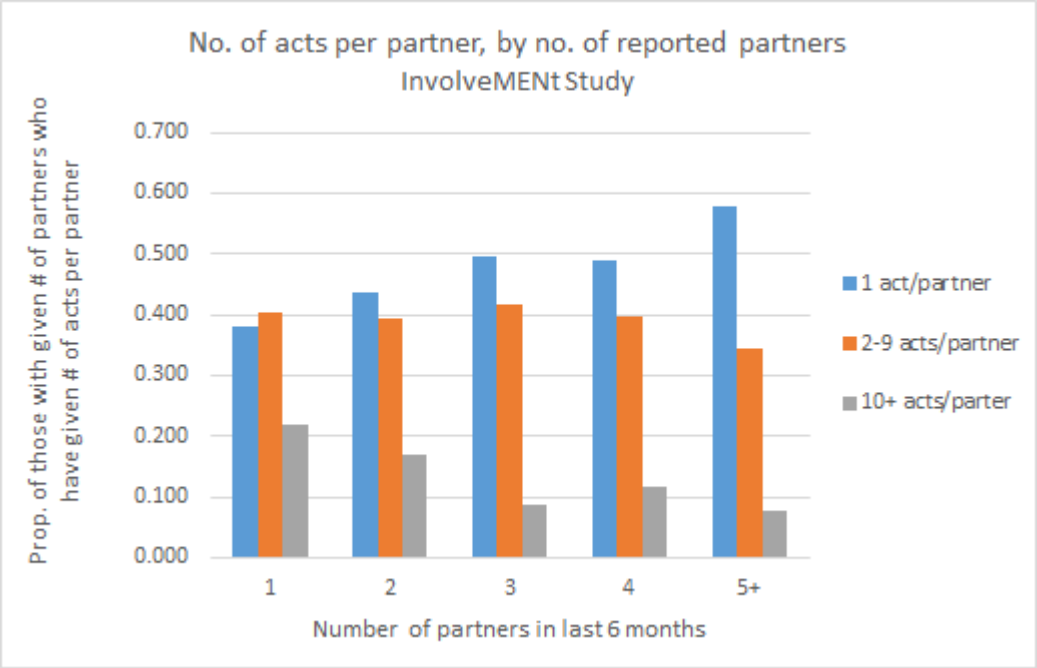
$$= \frac{g(v)T(v)}{\int_{v'} g(v')T(v')dv'}$$

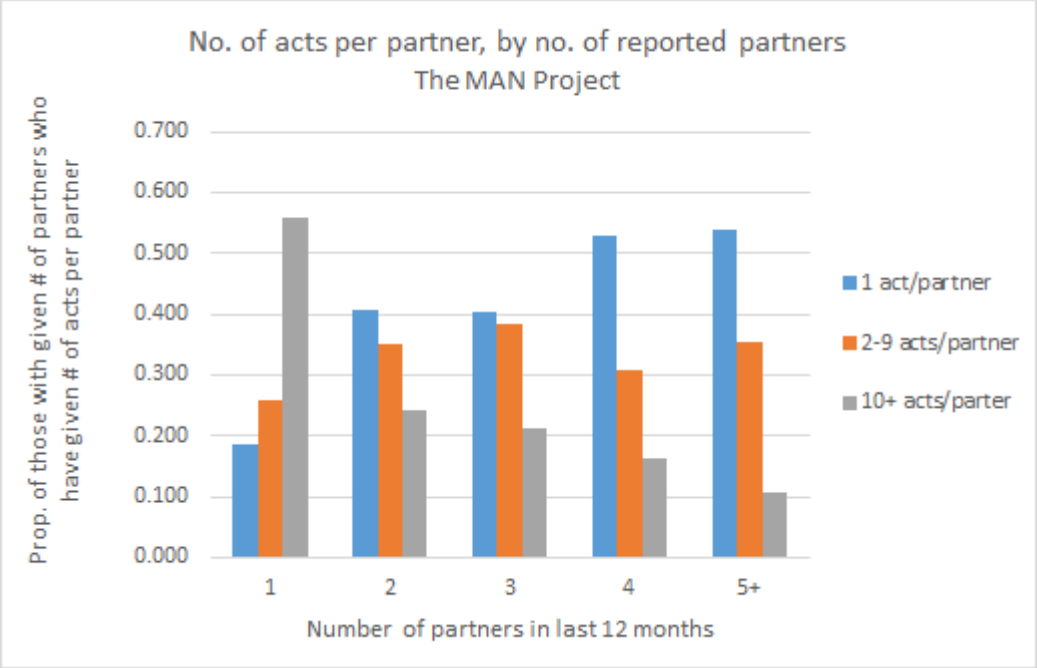
This is the same recipient viral load distribution as the previous case when we restricted partnerships to a single act; it is independent of a rescaling of $T(v)$, i.e. of the recipient's susceptibility.

10. Supplementary analysis of partner number and acts per partner

Our models demonstrated that one should expect a difference in mean SPVL (MSPVL) between EI and ER men only when considering relationships that have more than one act, and that the differences should get larger with more acts (until narrowing again after a very large number of acts). Because the MACS data did not include a measure for the number of sexual acts with each partner, we used partner number as a proxy, assuming that having more partners correlates with having lower numbers of acts per partner. Although this relationship seems intuitive, it was also worth confirming that this correlation does, indeed, exist in other behavioral studies of MSM. In this vein, we analyzed unpublished data from the two studies that provided most of the behavioral parameters for our dynamic network model: InvolveMENt (Sullivan et al., 2015) and the MAN Project (Hernandez-Romieu et al., 2015). Each was based in the Atlanta area, and each asked men to report on their numbers of male partners and number of acts of sexual intercourse with each partner. For InvolveMENt, reports were for the last 6 months and partner count was top-coded at 5; for MAN Project, the corresponding figures were 10 months and 10 partners. In both studies, acts were top-coded at 10. Given this, we considered five partner counts in each study (men with 1, 2, 3, 4, and 5+ partners reported) and compared these on the

proportion of men reporting an average of 1 act with their partners, 2-9 acts, or 10+ acts. The figures below reveal that in each study, the expected pattern holds: as one has more partners, one becomes increasing likely to have just 1 act per partner, and progressively less likely to average >10 acts per partner. The pattern is especially strong in the MAN Project, where a wider time window was considered. Given the top-coding and binning, we conducted a non-parametric Kruskall-Wallis one-way analysis of variance for each study, with partner number as the indepedent variable and mean acts per partner as the dependent variable ($p<0.0001$ for both studies).




No. of acts per partner, by no. of reported partners
The MAN Project
Prop. of those with given # of partners who have given # of acts per partner
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
1
2
3
4
5+
Number of partners in last 12 months
1 act/partner
2-9 acts/partner
10+ acts/parter

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Chapter 2 Supplementary Appendix

Test-and-treat coverage and HIV virulence evolution among men who have sex with men

Table of Contents

1. Supplementary Figures

1.1 Test & Treat Analyses

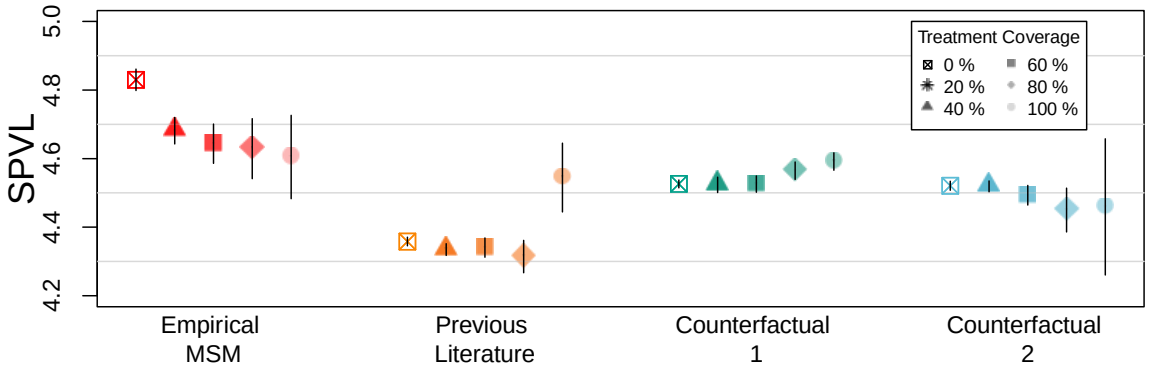

Fig. 1: Test & Treat runs with 1-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

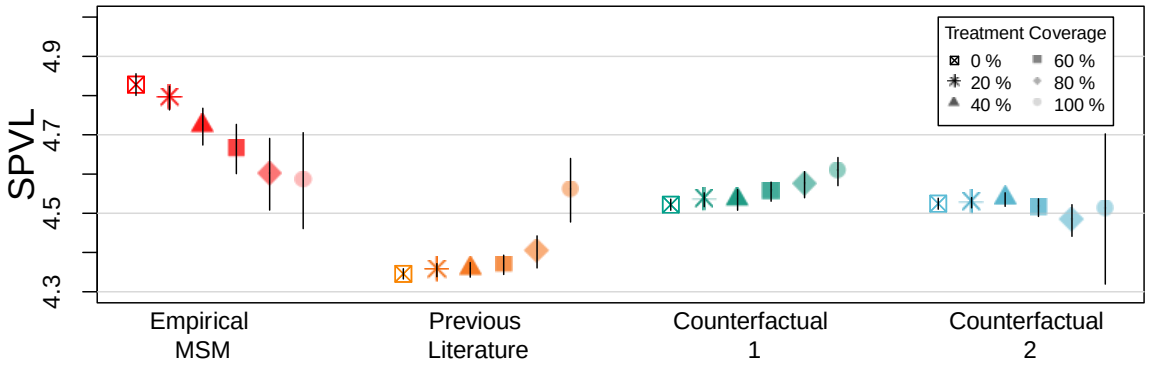

Fig. 2: Test & Treat runs with 2-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 64 simulations. Bars show 95% confidence intervals. (Figure is shown in main manuscript, here for purposes of comparison)

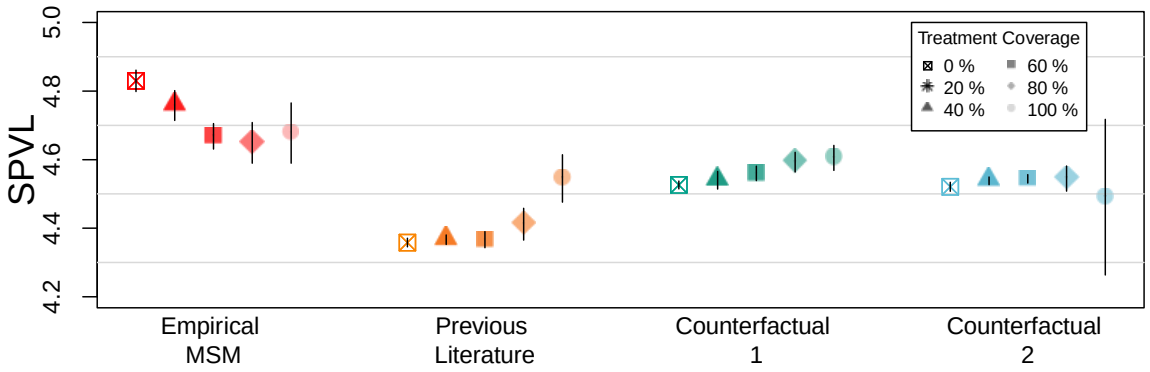

Fig. 3: Test & Treat runs with 3-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

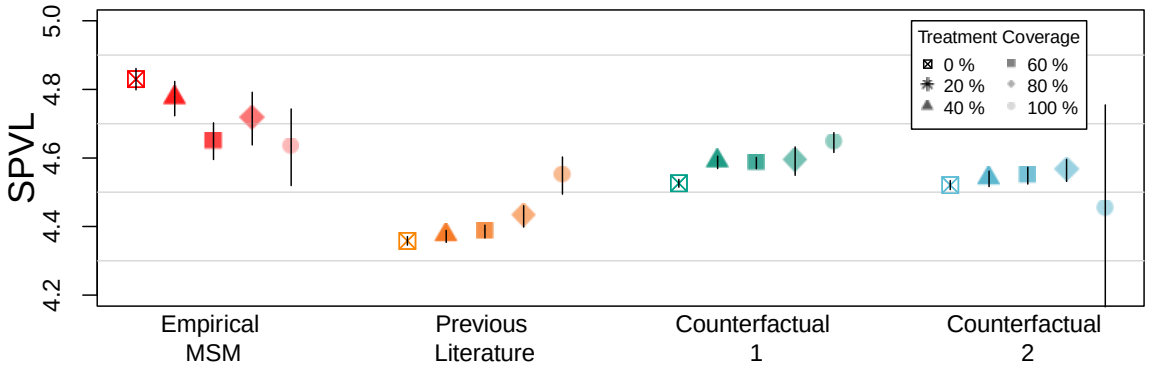

Fig. 4: Test & Treat runs with 4-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

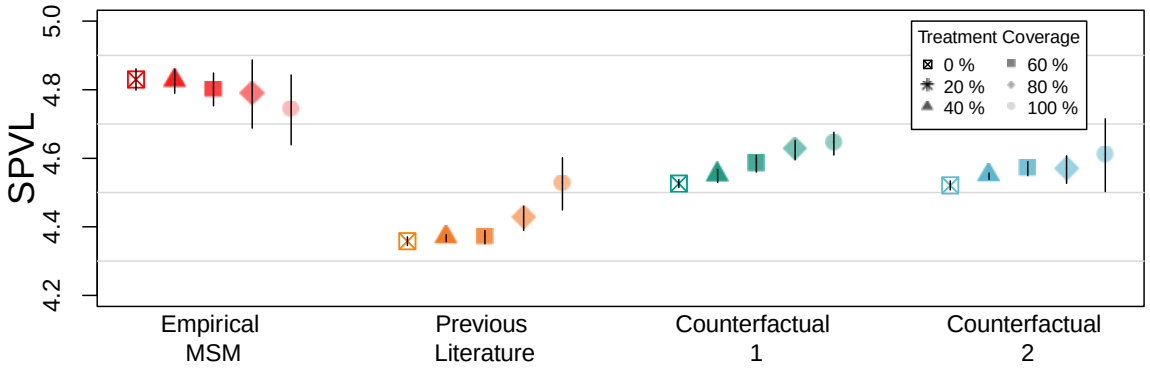

Fig. 5: Test & Treat runs with 5-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

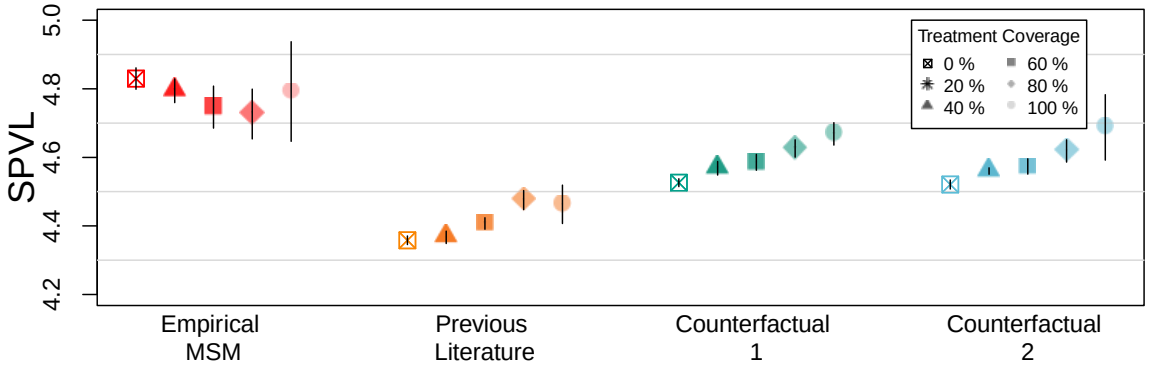

Fig. 6: Test & Treat runs with 6-year test interval. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

1.2 Fixed Interval Treatment Analyses

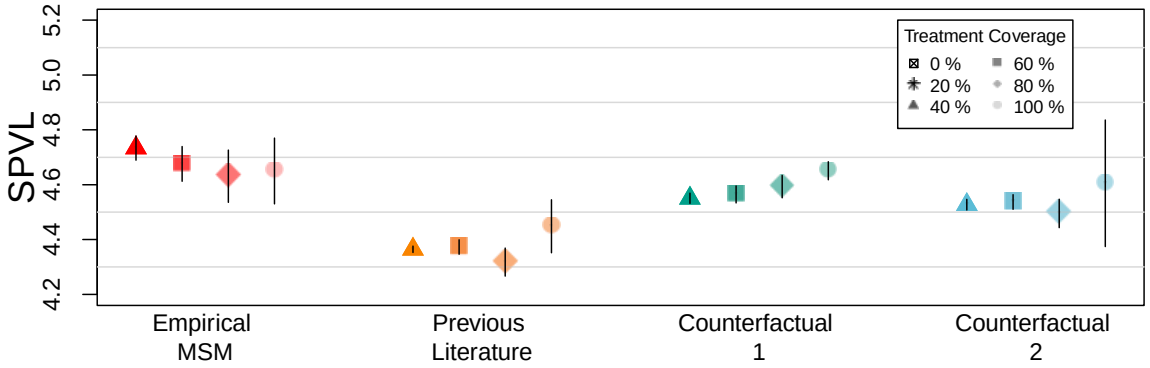

Fig. 7: Fixed interval runs with 1-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

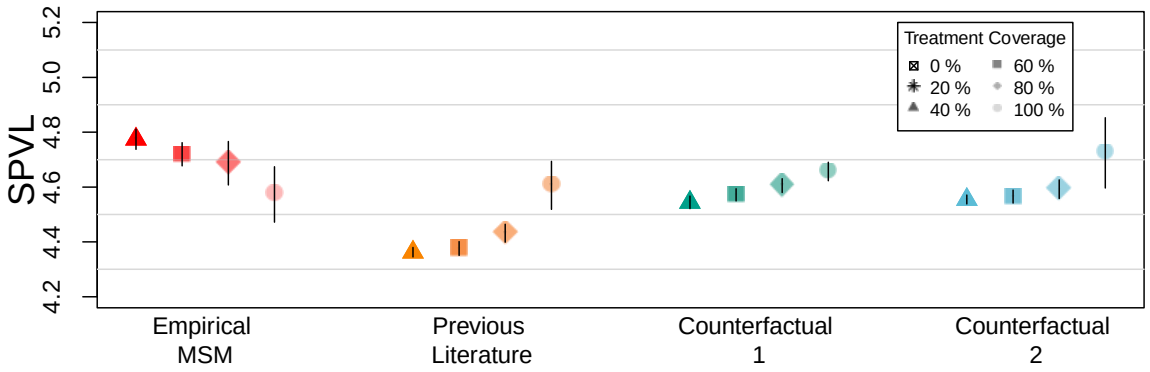

Fig. 8: Fixed interval runs with 2-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

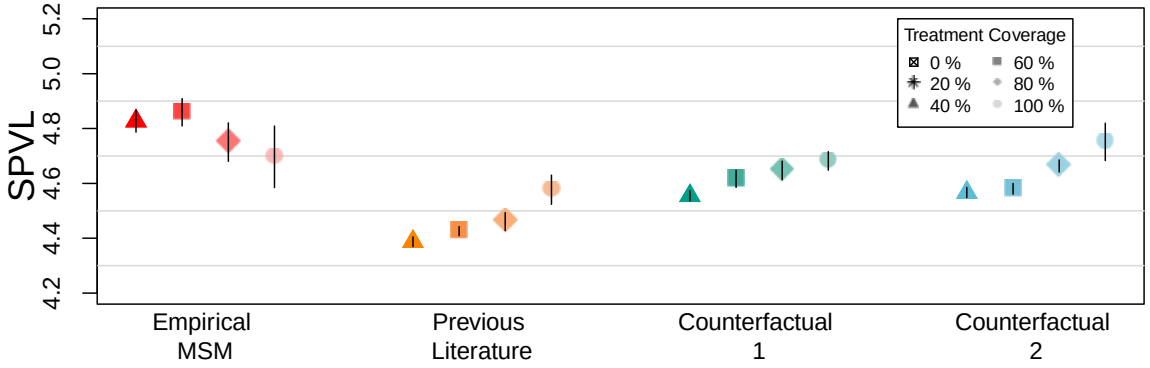

Fig. 9: Fixed interval runs with 3-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

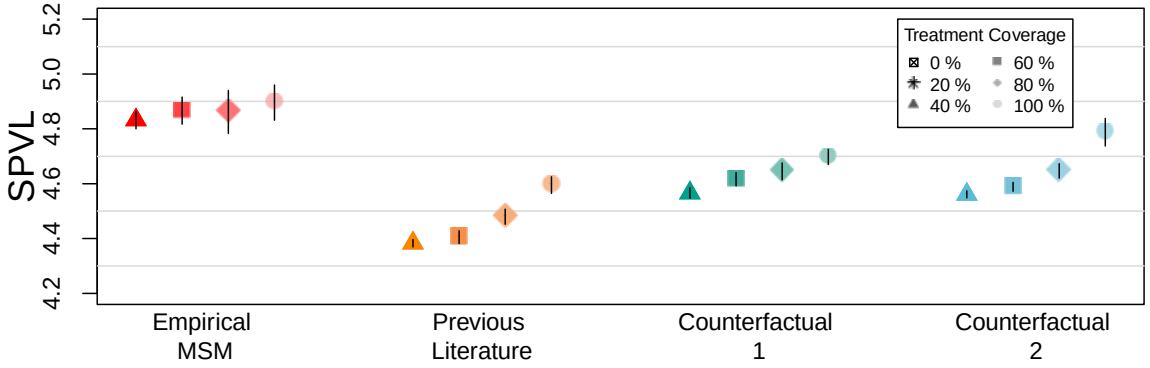

Fig. 10: Fixed interval runs with 4-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

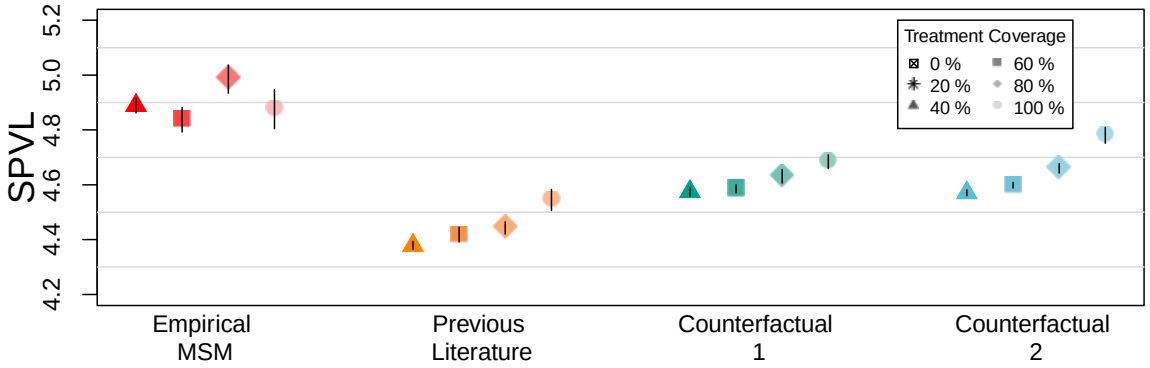

Fig. 11: Fixed interval runs with 5-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 11. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

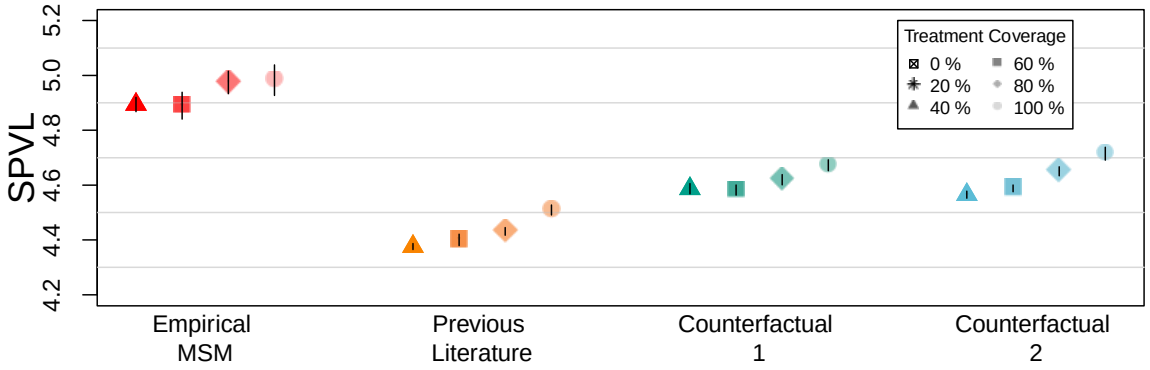

Fig. 12: Fixed interval runs with 6-year interval between infection and treatment initiation. Mean population SPVLs of those infected in years 30-50. Treatment began in year 10. Each symbol is the mean of 16 simulations. Bars show 95% confidence intervals.

2. Transmission Function Methodological Differences

The plateauing function (Fraser et al., 2007b) is based on data from the Zambian transmission study (Fideli et al., 2001a). This study followed 1022 serodiscordant cohabiting couples for between 2 and 67 months between 1994 and 2000; there were 129 linked transmissions. HIV status was assessed quarterly. The data used to create the plateauing transmission function consisted of SPVLs for index cases in partnerships, the overall mean duration of observation, and information about whether the initially uninfected partner became

infected (Fraser et al., 2007b). It did not have information about duration of observation of individual partnerships. They created an infection hazard per unit time instead of per serodiscordant sex act, as there were inconsistencies in the reported unprotected sex act frequencies.

The increasing function (Hughes et al., 2012a) is based on a prospective study of 3297 serodiscordant couples in the Partners in Prevention Herpes Simplex Virus (HSV)/HIV Transmission Study; there were 86 linked transmissions and data were collected between 2004 and 2007 (Lingappa et al., 2010). HIV positive partners in this study were infected with HSV-2, which does not hinder its generalizability as 60-90% of people living with HIV worldwide are also infected with HSV-2 (Weiss, 2004). This study enrolled couples in eastern and southern Africa and followed them for up to 24 months. HIV tests for negative partners and plasma RNA measurements for positive partners were performed quarterly and number of acts and condom use was assessed monthly. The authors considered many covariates to fit a model that included condom use and time-varying plasma HIV-1 RNA concentration and found a 2.89 increase in the per-act risk of transmission for each $\log_{10}$ increase in plasma HIV-1 RNA concentration. They found no evidence of a saturation effect or plateauing relationship between VL and risk of transmission, although only 3 transmissions and 1% of follow-up time occurred while the infected partner had very high VLs of ≥ 6 $\log_{10}$ copies/mL.

3. Model overview

Note: This and subsequent sections of the appendix are derived from earlier versions of the EvoNetHIV methodological appendix, updated to reflect the parameters and methods specific to this analysis.

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. For R scripts to run the models in this paper see https://github/EvoNetHIV/Test_and_Treat. In the description below, all references to VL and SPVL are $\log_{10}$ copies/mL, unless otherwise noted. *EvoNetHIV* is programmed in the R software language (R Development Core Team, 2008).

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.

4. Sexual network

4.1 Empirical data

Additional details regarding study design and analysis are available in Jenness et al. (2016c) and Goodreau et al. (2017).

4.2 Network structure

The sexual network consists of a population of MSM. Parameters include mean momentary degree (0.70, i.e., average number of relationships a man is in at a cross-section of time), coital frequency, and mean relational duration. Two men with incompatible sexual role (i.e., two exclusively insertive men or two exclusively receptive men) are prohibited from forming a partnership. All existing relationships have a constant and equal daily probability of dissolution.

Separable temporal exponential random graph models (STERGMs) (Krivitsky and Handcock, 2014b), as implemented in the *statnet* (Handcock et al., 2003) and EpiModel (Jenness et al., 2016b) software suites, were used to estimate the networks. 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.

Table 4.1. Model parameters utilized in network estimation

Model parameter	**Value**	**Source(s) and notes**
Momentary mean degree	0.70	Jenness et al. (2016d) 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. (2018a); based on data from the InvolveMENt (Sullivan et al., 2015) and MAN Project (Hernandez-Romieu et al., 2015) studies
Relationship duration (months), Empirical MSM analysis	3.3	Calculated as a compromise between the weighted mean of the mean relationship durations of the main, casual, and one-time sexual networks (54 days) and the main and casual sexual networks (212 days) from Goodreau et al. (2018a).
Relationship duration (months), Previous Literature analysis	30	Herbeck et al. (2016)'s alternate model

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) to account for the changing size of the network as the simulation progresses.

5. Sexual behaviors and agent attributes

Coital acts are determined among agents in a serodiscordant relationship at each time step. Among these partnerships, the number of coital acts per partnership at a given time step is assigned according to a Poisson draw with mean of 0.2 or 1 acts/day, which terminated in late-stage AIDS. Circumcision status is assigned to agents at model entry with 85% probability.

Table 5.1. Model parameters specifying sexual behaviors and agent attributes

Model parameter	**Value**	**Source(s) and notes**
Mean sex acts per day, Empirical MSM analysis	0.20	0.20 is a reanalysis of parameters in a previous study of MSM with multiple relational types (Goodreau et al., 2017) for a single relational type; based on data from the InvolveMENt (Sullivan et al., 2015) and MAN Project (Hernandez-Romieu et al., 2015) studies
Mean sex acts per day, Previous Literature Analysis	1.0	Herbeck et al. (2016)'s alternate model
Circumcision probability	0.85	Mean from two previous modeling studies among MSM. Jenness et al. (2016d); Goodreau et al. (2012a)

6. HIV transmission

6.1 Increasing Function

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 a model that provides a functional form that includes numerous covariates, and relative risk estimates for those covariates (Hughes et al., 2012a). However, the published results did not include an estimate for the base value of the function (λ), 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 a meta-analysis (Patel et al., 2014), which provides risk estimates 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:

$$P(transmission) = 1 - (1 - \lambda)^{e^{X\beta}}$$

where

$$X\beta = \ln(2.89) * (viral\ load - 4.0) + \ln(2.9) * insertive + \ln(17.3) * receptive + \ln(0.53) * circumcised + \ln(0.22) * condom$$

Table 6.1. 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 $\log_{10}$ increase in viral load	2.89	Hughes et al. (2012a)
Relative risk of condom use	0.22	Hughes et al. (2012a)
Relative risk of circumcision	0.53	Hughes et al. (2012a)
Relative risk of insertive anal intercourse	2.9	Derived (see text) from Patel et al. (2014)
Relative risk of receptive anal intercourse	17.3	Derived (see text) from Patel et al. (2014)

6.2 Plateauing Function

The Plateauing Function followed the model from Fraser et al. (2007b). This is an increasing Hill function that depends on the maximum infection rate per year (0.317), the slope of increasing infectiousness by viral load (1.02), and the viral load at which infectiousness is half of the maximum (13,938 copies per mL). We back-calculated an approximate per-act maximum transmission probability (0.002) from Fraser's annual estimate based on previous work (Herbeck et al., 2014). 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), 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.

$$P(transmission) = \beta(V) = \frac{[0.002 * (viral\ load^{1.02})]}{(13938^{1.02}) + (viral\ load^{1.02})} * (condom * 0.22) * (insertive * 2.9) * (receptive * 17.3) * (circumcised * 0.53)$$

Table 6.2. Model parameters determining HIV transmission probability per serodiscordant coital act

Model parameter	**Value**	**Source(s) and notes**
Maximum infection rate per year	0.317	Fraser et al. (2007b)
Slope of increasing infectiousness by viral load	1.02	Fraser et al. (2007b)
Viral load at which infectiousness is half of the maximum	13,938 copies per mL	Fraser et al. (2007b)
Per-act maximum transmission probability (approximate)	0.002	Back-calculated from Fraser et al. (2007b) in Herbeck et al. (2014)
Relative risk of circumcision	0.53	Hughes et al. (2012a)
Relative risk of insertive anal intercourse	2.9	Derived from Patel et al. (2014) (see text)
Relative risk of receptive anal intercourse	17.3	Derived from Patel et al. (2014) (see text)

7. Set point viral load

Set point viral load (SPVL) in infected agents at model initialization is generated as a combination of viral (viral genotype) and environmental (a combination of undefined host and non-viral) factors. For infected agent *i* present at the start of the model, the viral contribution to SPVL is drawn from a normal distribution:

$$viral_{spvl,i} \sim N(\mu_{spvl,t_0}, \sigma^2_{viral,t_0})$$

$\mu_{spvl,t_0} = 4.5$ $\log_{10}$ copies/mL

$\sigma^2_{viral,t_0} = h^2\ \sigma^2_{spvl,t_0}$,

where h^2 is the heritability coefficient, set here at 0.36, following Hollingsworth et al. (2010), and consistent with the Fraser et al. meta-analysis (2014), and σ^2_{spvl,t_0} is the variance of the distribution of SPVL in the initial population at model start. Note that this while the value of h^2 is set as a model input and employed to modulate the influence of viral genotype on the

similarity in SPVL between transmission pairs, heritability is a population-level measure that can change over time and across populations.

For infections after model start, the viral component for newly infected agent *i* is:

$$viral_{spvl,i} = viral_{spvl,infector} + \epsilon$$

where ϵ is the assumed normally distributed stochastic mutational variance, $\epsilon \sim N(0,\ 1e-4)$.

The stochastic environmental contribution is normally distributed and is calculated similarly for the initial population and subsequent infections:

$$env_{spvl,i} \sim N(0, \sigma^2_{env})$$

$\sigma^2_{env} = (1 - h^2)\sigma^2_{spvl,t_0}$.

SPVL is then the sum of the viral and environmental contributions, constrained to a minimum value of 2 $\log_{10}$ copies/mL and a maximum value of 7 $\log_{10}$ copies/mL:

$$spvl_i = env_{spvl,i} + viral_{spvl,i}.$$

Table 7.1. Model parameters utilized in the assignment of set point viral load

Model parameter	**Value**	**Source(s) and notes**
Mean $\log_{10}$ SPVL at model initialization	4.5	Fraser et al. (2007a); Korenromp et al. (2009); (Herbeck et al., 2008)
Heritability of SPVL across transmissions (h^2)	0.36	Hollingsworth et al. (2010b)
Variance of $\log_{10}$ SPVL	0.8	Herbeck et al. (2012)
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.

8. Viral dynamics

Upon infection, viral load, *V*, grows exponentially at rate r_0 for the first 21 days according to the formula

$$V(t) = V_0 e^{r_0 t}$$

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) 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

$$V_{peak} = 4.639 + 0.495 * log_{10}(SPVL)$$

where the values of 4.639 and 0.495 are based on regression data given in Robb et al. (2016). 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:

$$V(t) = V_{peak}\left(\frac{V_{32}}{V_{peak}}\right)^{\frac{(t-21)}{11}}$$

where viral load at t=32 is a weighted geometric mean of V_{adj_peak} and SPVL:

$$V_{32} = SPVL^{0.714} * V_{peak}^{0.286}$$

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

$$V(t) = V_{32}\left(\frac{SPVL}{V_{32}}\right)^{\frac{(t-32)}{58}}$$

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

$$V(t) = SPVL * e^{0.14*\frac{t-90}{365}}$$

This trajectory continues until an agent initiates antiretroviral treatment or enters the AIDS stage, defined by CD4 less than 200 cells/mm^3. During the AIDS stage, the agent's viral load increases linearly by 1.004112-fold per day:

$$V(t) = 1.004112 * V(t-1)$$

Viral load in AIDS increases up to a maximum viral load of 6.38 $\log_{10}$ copies/mL.

Table 8.1. 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 et al. (2000)
r_0	1.19367006	Model-calibrated to replicate viral dynamics in Lindback et al. (2000)
Duration of exponential viral growth	21 days	Lindback et al. (2000)
Duration of phase 1 decay	11 days	Lindback et al. (2000)
Duration of phase 2 decay	58 days	Lindback et al. (2000)
Duration of acute infection	90 days	Fiebig et al. (2003)
Viral load progression rate, natural log	0.14	Geskus et al. (2007)
Maximum viral load in AIDS (CD4<200)	2.4×10^6 copies/mL = 6.38 $\log_{10}$ copies / mL	Piatak et al. (1993)

9. Disease progression

CD4 values determine the additional risk of death among infected agents. Values are categorized as CD4 ≥ 500 cells/mm^3, 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); Table 7.1). No agents are assigned a CD4 category of less than 200 cells/mm^3 upon initial infection.

Table 9.1. Probability of assignment to CD4 category stratified by set point viral load

Set point viral load ($\log_{10}$ copies/mL)	CD4 level (cells/mm^3)		
	≥ 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

We note that the two highest categories are included for the sake of completion, so that any individual who does evolve into this zone will have an associated CD4 value. However, these

persons are very rare in the model and die quickly, limiting the persistence of their viral genotype in the population.

In the absence of antiretroviral treatment, infected agents progress through CD4 categories probabilistically according to an exponential 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) and personal communication; Table 7.2).

Table 9.2. Mean time (in years) spent in each CD4 category stratified by set point viral load

Set point viral load (log_{10} copies/mL)	CD4 level (cells/mm^3)			
	≥ 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

10. Vital dynamics

10.1 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 (Centers for Disease Control and Prevention, 2015). 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.

10.2 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.

10.3 Exits

Age-specific annual mortality rates for US males ages 18-55 were obtained from the CDC WONDER database for the years 1999-2003 (Centers for Disease Control and Prevention, 2015). 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/mm^3 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/mm^3) is completed according to disease progression described in Section 7.

10.4 Aging

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

Table 10.1. 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 (Centers for Disease Control and Prevention, 2015)
Age-specific annual mortality	0.0011, 0.0012, 0.0013,	CDC WONDER (Centers for

rates	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	Disease Control and Prevention, 2015)
Additional probability of death with CD4 > 500 cells/mm^3	0.0000112 per day	The values in CASCADE, 2011 (Writing Committee for the CASCADE Collaboration, 2011) are for men with mean age 30. Rates presented here therefore subtract 0.0014, the natural mortality rate for North American males aged 30 (Centers for Disease Control and Prevention, 2015), to estimate an excess death rate associated with this CD4 category.
Additional probability of death with CD4 350-500 cells/mm^3	0.0000148 per day	See note above
Additional probability of death with CD4 200-350 cells/mm^3	0.0000333 per day	See note above

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Chapter 3 Supplementary Appendix

Pre-exposure prophylaxis coverage and HIV virulence evolution among men who have sex with men

Table of Contents

1. Supplementary Figures

1.1 Shorter-relationship duration group

These plots show the incidence, prevalence, and mean SPVL of those infected in years 30-50 in Model 10, the model in which the shorter-relationship-duration group had lower PrEP adherence and assortative mixing, broken down by group membership.

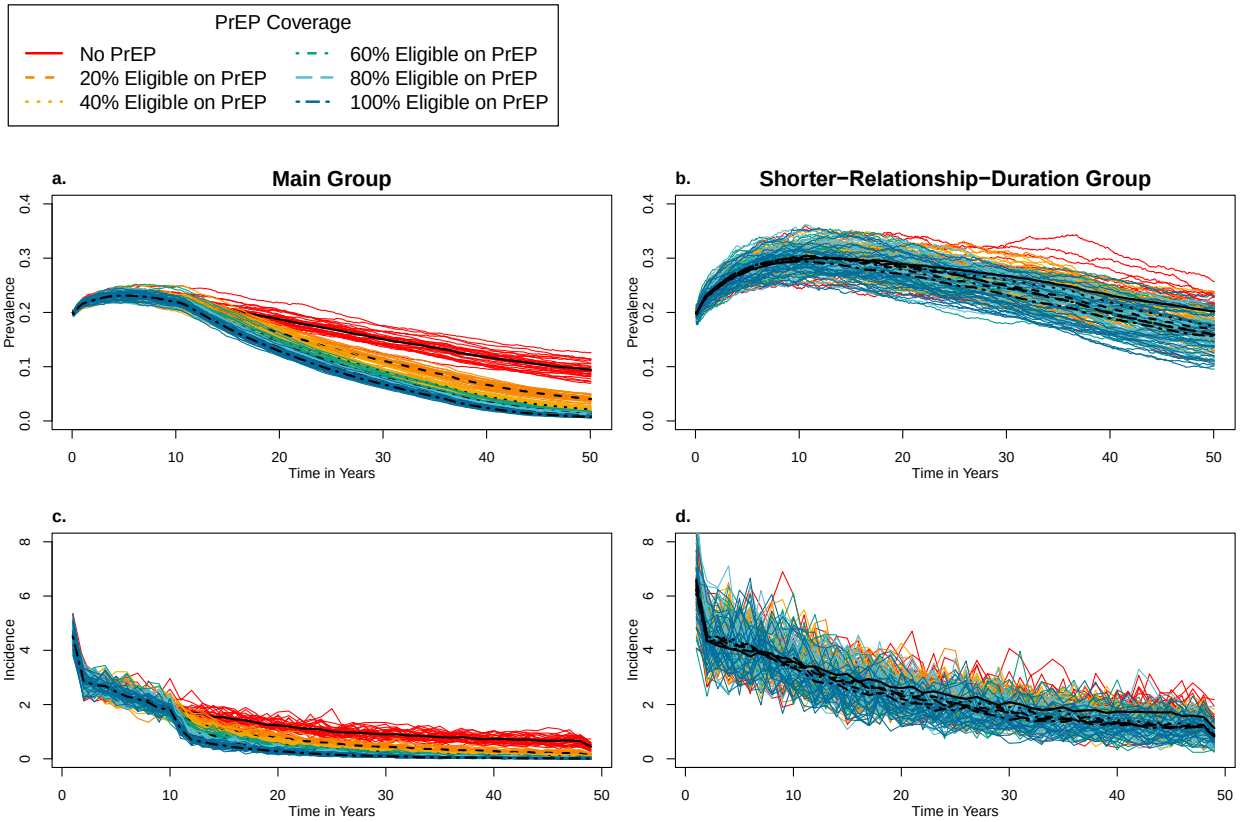

Fig. 1: Prevalence (a,b) and incidence (c,d) between year 1-50. PrEP coverage began in year 10. Each black line is the mean of 112 simulations. Thin lines show individual simulations. The main group is shown in plots A and C while the shorter-relationship duration group is shown in plots B and D.

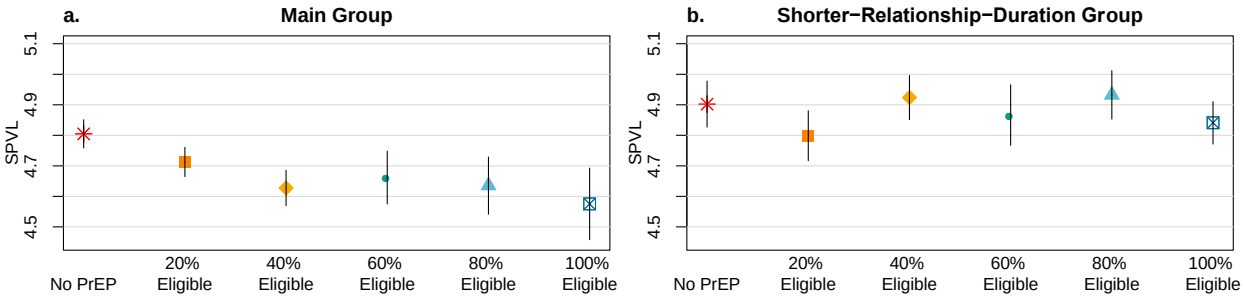

Fig. 2: Mean population SPVLs of those infected in years 40-50. Note change of scale from majority of SPVL figures. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals. A: Main group. B: shorter-relationship-duration group.

1.2 Condom compromise method sensitivity analyses

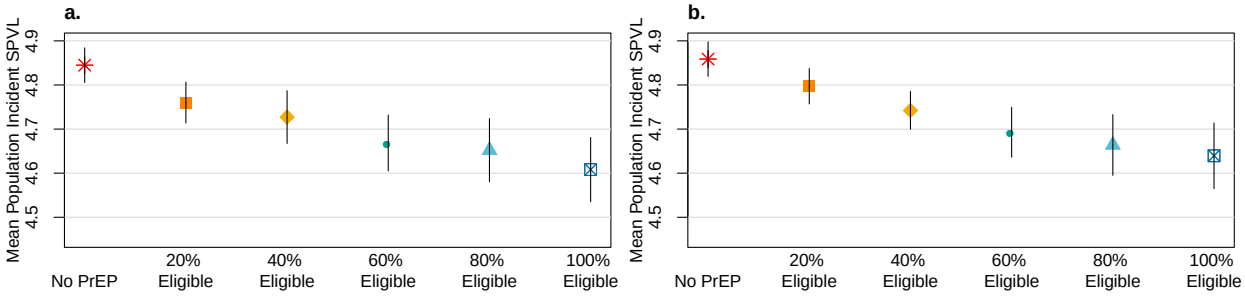

Fig. 3: Mean population SPVLs of those infected in years 40-50. PrEP began in year 10. Each symbol is the mean of 112 simulations. Bars show 95% confidence intervals. A: Model 12, maximum individual condom probability used. B: Model 13, minimum individual condom probability used.

2. Transmission Function Methodological Differences

Note: This and subsequent sections of the appendix are derived from earlier versions of the EvoNetHIV methodological appendix, updated to reflect the parameters and methods specific to this analysis.

The plateauing function (Fraser et al., 2007b) is based on data from the Zambian transmission study (Fideli et al., 2001a). This study followed 1022 serodiscordant cohabiting couples for between 2 and 67 months between 1994 and 2000; there were 129 linked transmissions. HIV status was assessed quarterly. The data used to create the plateauing transmission function consisted of SPVLs for index cases in partnerships, the overall mean duration of observation, and information about whether the initially uninfected partner became infected (Fraser et al., 2007b). It did not have information about duration of observation of individual partnerships. They created an infection hazard per unit time instead of per serodiscordant sex act, as there were inconsistencies in the reported unprotected sex act frequencies.

The increasing function (Hughes et al., 2012a) is based on a prospective study of 3297 serodiscordant couples in the Partners in Prevention Herpes Simplex Virus (HSV)/HIV Transmission Study; there were 86 linked transmissions and data were collected between 2004 and 2007 (Lingappa et al., 2010). HIV positive partners in this study were infected with HSV-2, which does not hinder its generalizability as 60-90% of people living with HIV worldwide are also infected with HSV-2 (Weiss, 2004). This study enrolled couples in eastern and southern Africa and followed them for up to 24 months. HIV tests for negative partners and plasma RNA

measurements for positive partners were performed quarterly and number of acts and condom use was assessed monthly. The authors considered many covariates to fit a model that included condom use and time-varying plasma HIV-1 RNA concentration and found a 2.89 increase in the per-act risk of transmission for each $\log_{10}$ increase in plasma HIV-1 RNA concentration. They found no evidence of a saturation effect or plateauing relationship between VL and risk of transmission, although only 3 transmissions and 1% of follow-up time occurred while the infected partner had very high VLs of ≥ 6 $\log_{10}$ copies/mL.

3. Model overview

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. For R scripts to run the models in this paper see https://github/EvoNetHIV/Test_and_Treat. In the description below, all references to VL and SPVL are $\log_{10}$ copies/mL, unless otherwise noted. *EvoNetHIV* is programmed in the R software language (R Development Core Team, 2008).

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.

4. Sexual network

4.1 Empirical data

Additional details regarding study design and analysis are available in Jenness et al. (2016c) and Goodreau et al. (2017).

4.2 Network structure

The sexual network consists of a population of MSM. Parameters include mean momentary degree (0.70, i.e., average number of relationships a man is in at a cross-section of time), coital frequency, and mean relational duration. Two men with incompatible sexual role (i.e., two exclusively insertive men or two exclusively receptive men) are prohibited from forming a partnership. All existing relationships have a constant and equal daily probability of dissolution.

Separable temporal exponential random graph models (STERGMs) (Krivitsky and Handcock, 2014b), as implemented in the *statnet* (Handcock et al., 2003) and EpiModel (Jenness et al., 2016b) software suites, were used to estimate the networks. 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.

Table 4.1. Model parameters utilized in network estimation

Model parameter	**Value**	**Source(s) and notes**
Momentary mean degree	0.70	Jenness et al. (2016d) 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. (2018a); based on data from the InvolveMENt (Sullivan et al., 2015) and MAN Project (Hernandez-Romieu et al., 2015) studies
Relationship duration (months), Empirical MSM analysis	3.3	Calculated as a compromise between the weighted mean of the mean relationship durations of the main, casual, and one-time sexual networks (54 days) and the main and casual sexual networks (212 days) from Goodreau et al. (2018a).
Relationship duration (months), Previous Literature analysis	30	Herbeck et al. (2016)'s alternate model

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) to account for the changing size of the network as the simulation progresses.

5. Sexual behaviors and agent attributes

Coital acts are determined among agents in a serodiscordant relationship at each time step. Among these partnerships, the number of coital acts per partnership at a given time step is assigned according to a Poisson draw with mean of 0.2 or 1 acts/day, which terminated in late-stage AIDS. Circumcision status is assigned to agents at model entry with 85% probability.

Table 5.1. Model parameters specifying sexual behaviors and agent attributes

Model parameter	Value	Source(s) and notes
Mean sex acts per day, Empirical MSM analysis	0.20	0.20 is a reanalysis of parameters in a previous study of MSM with multiple relational types (Goodreau et al., 2017) for a single relational type; based on data from the InvolveMENt (Sullivan et al., 2015) and MAN Project (Hernandez-Romieu et al., 2015) studies
Mean sex acts per day, Previous Literature Analysis	1.0	Herbeck et al. (2016)'s alternate model
Circumcision probability	0.85	Mean from two previous modeling studies among MSM. Jenness et al. (2016d); Goodreau et al. (2012a)

6. HIV transmission

6.1 Increasing Function

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 a model that provides a functional form that includes numerous covariates, and relative risk estimates for those covariates (Hughes et al., 2012a). However, the published results did not include an estimate for the base value of the function (λ), 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 a meta-analysis (Patel et al., 2014), which provides risk estimates 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:

$$P(transmission) = 1 - (1 - \lambda)^{e^{X\beta}}$$

where

$$X\beta = \ln(2.89) * (viral\ load - 4.0) + \ln(2.9) * insertive + \ln(17.3) * receptive + \ln(0.53) * circumcised + \ln(0.22) * condom$$

Table 6.1. 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 $\log_{10}$ increase in viral load	2.89	Hughes et al. (2012a)
Relative risk of condom use	0.22	Hughes et al. (2012a)
Relative risk of circumcision	0.53	Hughes et al. (2012a)
Relative risk of insertive anal intercourse	2.9	Derived (see text) from Patel et al. (2014)
Relative risk of receptive anal intercourse	17.3	Derived (see text) from Patel et al. (2014)

6.2 Plateauing Function

The Plateauing Function followed the model from Fraser et al. (2007b). This is an increasing Hill function that depends on the maximum infection rate per year (0.317), the slope of increasing infectiousness by viral load (1.02), and the viral load at which infectiousness is half of the maximum (13,938 copies per mL). We back-calculated an approximate per-act maximum transmission probability (0.002) from Fraser's annual estimate based on previous work (Herbeck et al., 2014). 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), 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.

$$P(transmission) = \beta(V) = \frac{[0.002 * (viral\ load^{1.02})]}{(13938^{1.02}) + (viral\ load^{1.02})} * (condom * 0.22) * (insertive * 2.9) * (receptive * 17.3) * (circumcised * 0.53)$$

Table 6.2. Model parameters determining HIV transmission probability per serodiscordant coital act

Model parameter	Value	Source(s) and notes
Maximum infection rate per year	0.317	Fraser et al. (2007b)
Slope of increasing infectiousness by viral load	1.02	Fraser et al. (2007b)
Viral load at which infectiousness is half of the maximum	13,938 copies per mL	Fraser et al. (2007b)
Per-act maximum transmission probability (approximate)	0.002	Back-calculated from Fraser et al. (2007b) in Herbeck et al. (2014)
Relative risk of circumcision	0.53	Hughes et al. (2012a)
Relative risk of insertive anal intercourse	2.9	Derived from Patel et al. (2014) (see text)
Relative risk of receptive anal intercourse	17.3	Derived from Patel et al. (2014) (see text)

7. Set point viral load

Set point viral load (SPVL) in infected agents at model initialization is generated as a combination of viral (viral genotype) and environmental (a combination of undefined host and non-viral) factors. For infected agent *i* present at the start of the model, the viral contribution to SPVL is drawn from a normal distribution:

$$viral_{spvl,i} \sim N\left(\mu_{spvl,t_0}, \sigma^2_{viral,t_0}\right)$$

$\mu_{spvl,t_0} = 4.5$ $\log_{10}$ copies/mL

$\sigma^2_{viral,t_0} = h^2\, \sigma^2_{spvl,t_0}$,

where h^2 is the heritability coefficient, set here at 0.36, following Hollingsworth et al. (2010), and consistent with the Fraser et al. meta-analysis (2014), and σ^2_{spvl,t_0} is the variance of the distribution of SPVL in the initial population at model start. Note that this while the value of h^2 is set as a model input and employed to modulate the influence of viral genotype on the similarity in SPVL between transmission pairs, heritability is a population-level measure that can change over time and across populations.

For infections after model start, the viral component for newly infected agent *i* is:

$$viral_{spvl,i} = viral_{spvl,infector} + \epsilon$$

where ϵ is the assumed normally distributed stochastic mutational variance, $\epsilon \sim N(0,\ 1e-4)$.

The stochastic environmental contribution is normally distributed and is calculated similarly for the initial population and subsequent infections:

$$env_{spvl,i} \sim N(0, \sigma^2_{env})$$

$\sigma^2_{env} = (1 - h^2)\sigma^2_{spvl,t_0}$.

SPVL is then the sum of the viral and environmental contributions, constrained to a minimum value of 2 $\log_{10}$ copies/mL and a maximum value of 7 $\log_{10}$ copies/mL:

$$spvl_i = env_{spvl,i} + viral_{spvl,i}.$$

Table 7.1. Model parameters utilized in the assignment of set point viral load

Model parameter	**Value**	**Source(s) and notes**
Mean $\log_{10}$ SPVL at model initialization	4.5	Fraser et al. (2007a); Korenromp et al. (2009); (Herbeck et al., 2008)
Heritability of SPVL across transmissions (h^2)	0.36	Hollingsworth et al. (2010b)
Variance of $\log_{10}$ SPVL	0.8	Herbeck et al. (2012)
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.

8. Viral dynamics

Upon infection, viral load, *V*, grows exponentially at rate r_0 for the first 21 days according to the formula

$$V(t) = V_0 e^{r_0 t}$$

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) 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

$$V_{peak} = 4.639 + 0.495 * log_{10}(SPVL)$$

where the values of 4.639 and 0.495 are based on regression data given in Robb et al. (2016). 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:

$$V(t) = V_{peak}\left(\frac{V_{32}}{V_{peak}}\right)^{\frac{(t-21)}{11}}$$

where viral load at t=32 is a weighted geometric mean of V_{adj_peak} and SPVL:

$$V_{32} = SPVL^{0.714} * V_{peak}^{0.286}$$

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

$$V(t) = V_{32}\left(\frac{SPVL}{V_{32}}\right)^{\frac{(t-32)}{58}}$$

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

$$V(t) = SPVL * e^{0.14*\frac{t-90}{365}}$$

This trajectory continues until an agent initiates antiretroviral treatment or enters the AIDS stage, defined by CD4 less than 200 cells/mm^3. During the AIDS stage, the agent's viral load increases linearly by 1.004112-fold per day:

$$V(t) = 1.004112 * V(t-1)$$

Viral load in AIDS increases up to a maximum viral load of 6.38 $\log_{10}$ copies/mL.

Table 8.1. 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 et al. (2000)
r_0	1.19367006	Model-calibrated to replicate viral dynamics in Lindback et al. (2000)
Duration of exponential viral growth	21 days	Lindback et al. (2000)
Duration of phase 1 decay	11 days	Lindback et al. (2000)
Duration of phase 2 decay	58 days	Lindback et al. (2000)
Duration of acute infection	90 days	Fiebig et al. (2003)
Viral load progression rate, natural log	0.14	Geskus et al. (2007)
Maximum viral load in AIDS (CD4<200)	$2.4x10^6$ copies/mL = 6.38 $\log_{10}$ copies / mL	Piatak et al. (1993)

9. Disease progression

CD4 values determine the additional risk of death among infected agents. Values are categorized as CD4 ≥ 500 cells/mm^3, 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); Table 7.1). No agents are assigned a CD4 category of less than 200 cells/mm^3 upon initial infection.

Table 9.1. Probability of assignment to CD4 category stratified by set point viral load

Set point viral load ($\log_{10}$ copies/mL)	CD4 level (cells/mm^3)		
	≥ 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

We note that the two highest categories are included for the sake of completion, so that any individual who does evolve into this zone will have an associated CD4 value. However, these

persons are very rare in the model and die quickly, limiting the persistence of their viral genotype in the population.

In the absence of antiretroviral treatment, infected agents progress through CD4 categories probabilistically according to an exponential 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) and personal communication; Table 7.2).

Table 9.2. Mean time (in years) spent in each CD4 category stratified by set point viral load

Set point viral load (log_{10} copies/mL)	CD4 level (cells/mm^3)			
	≥ 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

10. Vital dynamics

10.1 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 (Centers for Disease Control and Prevention, 2015). 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.

10.2 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.

10.3 Exits

Age-specific annual mortality rates for US males ages 18-55 were obtained from the CDC WONDER database for the years 1999-2003 (Centers for Disease Control and Prevention, 2015). 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/mm^3 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/mm^3) is completed according to disease progression described in Section 7.

10.4 Aging

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

Table 10.1. 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 (Centers for Disease Control and Prevention, 2015)
Age-specific annual mortality rates	0.0011, 0.0012, 0.0013, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014, 0.0014,	CDC WONDER (Centers for Disease Control and Prevention, 2015)

	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	
Additional probability of death with CD4 > 500 cells/mm^3	0.0000112 per day	The values in CASCADE, 2011 (Writing Committee for the CASCADE Collaboration, 2011) are for men with mean age 30. Rates presented here therefore subtract 0.0014, the natural mortality rate for North American males aged 30 (Centers for Disease Control and Prevention, 2015), to estimate an excess death rate associated with this CD4 category.
Additional probability of death with CD4 350-500 cells/mm^3	0.0000148 per day	See note above
Additional probability of death with CD4 200-350 cells/mm^3	0.0000333 per day	See note above

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