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Special Article

Fighting the Public Health Burden of AIDS With the Human Pegivirus

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Highly active antiretroviral therapy has revolutionized the battle against human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). From its current global rollout, HIV/AIDS morbidity and mortality has been greatly reduced, yet there exists substantial interest in the development of new therapies to further mitigate the HIV/AIDS health burden and to inhibit any fallout from the development of antiretroviral drug resistance. One potential intervention is the human pegivirus (HPgV). HPgV is not known to cause disease, and most remarkably it is shown to delay the progression of HIV to AIDS. However, the health benefit of increasing HPgV prevalence in the community of HIV-infected men remains unknown at the public health level. We evaluated the utility of HPgV biovaccination for mitigating the HIV/AIDS health burden using mathematical models. Importantly, our work considers the potential concern that HPgV will, itself, evolve to become disease-causing by permitting mutant disease-causing HPgV strains to potentially arise during treatment. Our findings show that HPgV biovaccination rates of 12.5%–50% annually could prevent 4.2–23.6 AIDS incidences and 3.3–18.8 AIDS deaths, and could save 2.9–18.6 disability-adjusted life years per 1,000 people. Together, these findings indicate that HPgV biovaccination could be an effective therapy for reducing HIV/AIDS morbidity and mortality, and thus warrants further exploration.

acquired immune deficiency syndrome; biological therapy; *Flaviviridae*; GB virus C; hepatitis G virus; human immunodeficiency virus; human pegivirus; mathematical model

Abbreviations: AIDS, acquired immune deficiency syndrome; DALY, disability-adjusted life year; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HPgV, human pegivirus.

The human immunodeficiency virus (HIV) greatly threatens the welfare of human beings, with an astounding 55 million infections and 16 million attributable deaths over the last 3 decades (1). During this time, the United States has been one of the greatest funders of HIV research, yet it is still facing 40,000 new infections annually, which add to the already significant health burden caused by its 1.2 million HIV-infected citizens (2). Consequently, there is urgent need for new therapeutic options, especially given that only 37% of HIV-infected people benefit from highly active antiretroviral therapy (HAART) (2). For those on HAART, there is a profound increase in life expectancy (3). However, HAART does have drawbacks. HAART drugs can have serious side effects (4), and viral mutation can lead to drug resistance (5). Furthermore, HAART is also rather expensive—the treatment costs of $28,500 per patient annually (6) are more than half of the average household income in the United States (7). Fortunately, there continues to be significant progress towards universal access to HAART (8), and research continues to usher in new drug formulations and HIV therapies.

One potential HIV therapy is the human pegivirus (HPgV) (9). While HPgV is not as well-known as one of its closest genetic relatives, hepatitis C, it is similarly transmitted through infected blood and sexual routes, with male-to-male sex documented as the most effective mode of transmission (10). Furthermore, while hepatitis C can cause chronic liver damage, studies suggest that HPgV infection has a mutualistic relationship with humans (11). Towards this point, HPgV infection is associated with antiinflammatory properties that are considered generally beneficial (11). While some individuals can receive such benefits for decades due to persistent HPgV infection, most healthy individuals clear HPgV infection within 2 years (12, 13). Unfortunately, the mechanisms behind HPgV persistence and host immune modulation

remain poorly understood, in part due to the difficulty of studying HPgV in vitro (11). On the other hand, in vivo studies on HPgV have shed light on several important characteristics. For instance, once HPgV infection is cleared, and typically not before, HPgV surface envelope glycoprotein E2 antibodies develop, which temporarily inhibit HPgV reinfection (14). In addition, in vivo studies have shown that HPgV has relatively little impact on hepatitis C infection, given that HPgV does not influence hepatitis C viral load or the severity of liver disease (15, 16). While the aforementioned characteristics of HPgV are interesting, what truly makes HPgV remarkable is the clinical finding that it helps to mitigate the health burden of HIV (9, 17–22). Simply put, HPgV has a major impact on the progression from HIV to acquired immune deficiency syndrome (AIDS) (12, 19, 20, 23). These findings have led to a call to use HPgV biovaccination as a potential HIV therapy (9).

Before investing considerable time and resources into further experimental and clinical research on the utility of HPgV as a therapy option, it is first worthwhile to examine, theoretically, how effective such a strategy is likely to be. That is the goal of the research reported here. We used the findings of a meta-analysis on HPgV and HIV coinfection (19), as well as epidemiologic data on HIV and AIDS incidence for the largest HIV at-risk demographic in the United States, men who have sex with men, to construct a mathematical model to evaluate HPgV biovaccination as an HIV therapy at the population level. From this mathematical model, we evaluated the potential effectiveness of different HPgV biovaccination rates for reducing AIDS incidence and averting AIDS-related deaths.

METHODS

To evaluate HPgV biovaccination as an HIV therapy, we developed a mathematical model of HPgV and HIV coinfection to estimate the reduction in AIDS episodes (Web Figure 1, available at https://academic.oup.com/aje). To estimate the benefit of HPgV biovaccination with respect to HIV, we compared scenarios that consider HPgV biovaccination rates of 12.5%, 25%, and 50% per year relative with the current benefit from the uncontrolled HPgV transmission. For each scenario, the health benefit from HPgV biovaccination of HIV-infected individuals was characterized as the reduction in AIDS incidence, AIDS deaths averted, and saved disability-adjusted life years (DALYs) (24).

To provide further credibility towards the use of HPgV biovaccination as an HIV therapy, we also evaluated the potential spread of mutant strains of HPgV and the impact that this might have on predicted health outcomes. Specifically, we considered mutant strains of HPgV that cause mortality, possess an enhanced transmission rate, have slower or faster viral clearance rates, and have a reduced delay in the progression of HIV infection to AIDS.

Mathematical model

In the model, we considered a population divided into susceptible individuals (S), HIV-infected and untreated individuals (I), HIV-infected individuals who are treated with HAART (T), HIV-infected individuals who are treated with HAART and have progressed to AIDS (H), and HIV-infected individuals who have progressed to AIDS and are not receiving HAART (A). The population is further subdivided by HPgV infection status, which is positively indicated by a subscript g and a subscript g_p for individuals with persistent HPgV infection. The rate at which susceptible individuals acquire HPgV infection is given by the force of infection of HPgV:

$$\lambda_g = (1 - p)\beta_g \frac{(S_g + I_g + T_g + S_{g_p} + I_{g_p} + T_{g_p})}{N}, \quad (1)$$

where p is the proportion protected by prophylactics (the proportion of sexually active men who have sex with men that did not engage in condomless sex), β_g is the HPgV transmission rate, and N is the total population size of sexually active men who have sex with men.

The rate at which susceptible individuals acquire HIV infection is given by the force of infection of HIV:

$$\lambda_{HIV} = (1 - p)\beta_{HIV} \frac{(I + \alpha T + I_g + \alpha T_g + I_{g_p} + \alpha T_{g_p})}{N}, \quad (2)$$

where β_{HIV} is the HIV transmission rate, and α is the reduction in HIV transmission caused by HAART.

We assumed that the duration of HIV infection until diagnosis is $1/\epsilon$. The rate at which HIV infection progresses to AIDS for non-HPgV infected individuals is σ for the untreated and γ for those treated with HAART. Symbols with the subscript g denote the corresponding rates for HPgV infected individuals. We also consider a HPgV biovaccination rate ν, the efficacy of HPgV biovaccination f, the clearance of HPgV ψ, the persistence of HPgV ρ, and, for the model augmented by a mutant strain of HPgV (Web Appendix 1), a HPgV mortality rate d_m. Note, the clearance of HPgV is only considered for non-AIDS-diagnosed individuals, because individuals with AIDS are unlikely to clear any virus due to the nature of their syndrome. Additional parameter details, including references, are available in Table 1.

Parameter estimation

The model population size of men who have sex with men was estimated using data on the sexual preference of the sexually active male population in the United States (Table 1). To capture the spread of HIV among such men, the HIV transmission rate, β_{HIV}, was estimated using a least squares procedure with recent HIV surveillance data (Web Figure 2). Upon HIV infection, the rate of developing AIDS (on HAART) γ, where AIDS is defined by stage 3 HIV infection (25), was estimated using a standard approach (26) that makes use of the US life expectancy of 78.8 years (27), estimates that HIV infection reduces life expectancy on average by 6.8 years (28), and the AIDS mortality rate d_H (Web Appendix 2). The HPgV transmission rate was estimated from the HPgV prevalence in HIV-infected populations (13), together with the assumption that HPgV infection is close to its endemic equilibrium (Web Appendices 2 and 3). To

Table 1. Parameter Values, Distributions, and Sources Used in Model Predictions of the Health Benefit of Human Pegivirus Biovaccination on AIDS Morbidity and Mortality in the United States

Symbol	Parameter	Base	Distribution	Reference
p	Proportion protected by prophylactics[a]	0.6	U(0.5, 0.7)	(46)
β_{HIV}	HIV transmission rate	0.4063 $year^{-1}$	U(0.356, 0.457)	(25)
β_g	HPgV transmission rate	0.1807 $year^{-1}$	Triangular(0.1604, 0.1869, 0.1948)	–[b]
α	Reduction in HIV transmission caused by HAART	0.6		(47)
θ	Enhancement factor of mutant transmission rate		a. U(1, 2) b. U(1, 10) c. U(1, 50)	
β_M	Mutant HPgV transmission rate	$\theta\beta_g$		
$1/\epsilon$	Duration of HIV infection until diagnosis	5.25 years	Triangular(2, 4.14, 9.6)	(26)
ζ	Hazard ratio of the impact of HPgV coinfection on the progression to AIDS	0.88	Triangular(0.3, 0.84, 1.50)	–[b]
ζ_p	Hazard ratio of the impact of persistent HPgV coinfection on the progression to AIDS	0.41	Triangular(0.23, 0.31, 0.69)	–[b]
κ	Reduction factor of HPgV infection on AIDS mortality	0.22	Triangular(0, 0.08, 0.58)	(17)
ξ	Mutant HPgV mortality factor	0	0%, 0.1%, 1.0%, 10%	
d_m	Mutant strain of HPgV mortality rate	ξd		
$1/\mu$	Natural life expectancy	78.8 years		(27)
b	Male population birth rate	0.024 $year^{-1}$		(48)[b]
ν	HPgV biovaccination rate	0.025 $year^{-1}$	0.125, 0.25, 0.50	
f	Efficacy of HPgV biovaccination	0.25, 0.5, 0.75	U(0.25, 0.75)	
ψ	HPgV clearance rate	0.375 $year^{-1}$		–[b]
ρ	HPgV persistence rate	0.125 $year^{-1}$		–[b]
ϕ	Proportion of males that identify as homosexual or bisexual	0.035	U(0.033, 0.037)	(49)
M	Male population	111,508,222		(48)
N	Male persons that identify as homosexual or bisexual	ϕM		
	Proportion of HPgV infections leading to non-Hodgkin's lymphoma	0.0182		(29)
δ	HPgV antigenic drift rate	0.0084 $year^{-1}$		(37)
Rate of developing AIDS				
σ	Without viral suppression	0.1064 $year^{-1}$	Triangular(0.04, 0.10, 0.18)	(50, 51)
σ_g	Without viral suppression, coinfected with HPgV	$\zeta\sigma$		(50, 51)
σ_{g_p}	Without viral suppression, coinfected with persistent HPgV	$\zeta_p\sigma$		(50, 51)
γ	Receiving HAART	0.0384 $year^{-1}$	Exp(0.0384)	(26)
γ_g	With treatment, coinfected with HPgV	$\zeta\gamma$		
γ_{g_p}	With treatment, coinfected with persistent HPgV	$\zeta_p\gamma$		
AIDS mortality rate				
d	No treatment	0.5 $year^{-1}$	Exp(0.5)	(51)[b]
d_g	Coinfected with HPgV	κd		
d_H	Receiving HAART	0.02 $year^{-1}$	Exp(0.02)	(28)
d_{H_g}	Receiving HAART and coinfected with HPgV	κd^H		(17)

Table continues

Table 1. Continued

Symbol	Parameter	Base	Distribution	Reference
DALY weights				
D_{DT}	Non-Hodgkin's lymphoma (diagnosis and treatment)	0.55		(52)
D_R	Non-Hodgkin's lymphoma (remission)	0.19		(52)
D_I	HIV-infected individual (no treatment)	0.22		(24)
D_T	HIV-infected individual on HAART	0.053		(24)
D_{AIDS}	AIDS	0.55		(24)

Abbreviations: AIDS, acquired immune deficiency syndrome; DALY, disability adjusted life-year; HIV, human immunodeficiency virus; HPgV, human pegivirus; HAART, highly active antiretroviral therapy.

[a] Homosexual and bisexual men that did not engage in condomless sex.

[b] Details available in Web Appendix 3.

capture the benefits of HPgV and HIV coinfection on the duration from HIV infection to AIDS, data were obtained from a meta-analysis on HPgV and HIV coinfection (13). Specifically, the hazard ratios, when combined with the standard assumption of exponentially distributed waiting times in ordinary differential equation models, lead to the desired rates (Web Appendix 3).

Predicted health outcomes

To determine the health benefit of HPgV infection on death and disability due to the delayed progression from HIV to AIDS, we measured health outcomes in DALYs (24). We simulated the health benefits of HPgV infection over a 20-year period, discounting DALYs at the standard 3% annual rate. To determine the net DALYs saved, total DALYs lost without HPgV biovaccination were subtracted from scenarios with HPgV biovaccination rates of 12.5%, 25%, and 50%. Included in the calculation of DALYs is the slight increased risk of non-Hodgkin's lymphoma, which occurs in 1.82% of HPgV-infected individuals (29). Parameter values for the calculation of DALYs are available in Table 1. Additionally, because HPgV is associated with improved surrogate markers for HIV progression (30), we also estimated the impact of HPgV biovaccination on the average CD4+ counts occurring in the United States.

The benefits of HPgV infection

The considered benefits of HPgV infection on HIV-infected individuals are: 1) a delayed progression rates of developing AIDS (σ_g and γ_g), and 2) reduced AIDS mortality rates (d_g and d_{H_g}). For each benefit of HPgV infection, we estimated parameter distributions (Table 1, Web Appendix 3) based on available data, and then evaluated model predictions over 10,000 random parameter samples.

The risks of HPgV mutation

To evaluate the potential spread of mutant strains of HPgV and the impact that this might have on the utility of HPgV biovaccination as an HIV therapy, we use techniques from evolutionary invasion analysis (31). First, we constructed a model of HPgV and HIV coinfection (Web Appendix 1) for the resident strain of HPgV. From the model, we determined all equilibria (Web Appendix 2), identifying local stability conditions for the HPgV and HIV coendemic equilibria (Web Appendix 4). After this, the model was augmented to include both the transmission and antigenic drift to a mutant strain of HPgV (Web Appendix 1) that possesses novel traits. The novel traits considered for the mutant strain of HPgV are the ability to cause host mortality, an enhanced transmission rate (which is only considered for mutant HPgV strains), a reduced benefit for preventing AIDS, or some combination of these mutations (Table 1, Web Tables 1–3). For each scenario of these traits, we computed the proportion of 10,000 random mutations, as characterized by random parameter samples (Table 1), where the invasion number (a threshold indicating that a mutant strain would be able to increase when rare) indicated that the mutant strain would invade the population (Web Appendices 4 and 5). In addition, given the successful invasions by the mutant strain of HPgV, we also determined the proportion of cases where the mutant HPgV strain is the dominant HPgV strain, as indicated by the mutant reproductive number (the basic reproductive number for the mutant strain of HPgV) being greater than the basic reproductive number of the resident strain of HPgV ($R_m > R_0$) (Web Appendices 4 and 5). Furthermore, for each of these mutant strains of HPgV, we conducted the above-described simulations over a 20-year period as it attempted (and potentially succeeded) in spreading through the population, and we then calculated the AIDS incidence, number of AIDS deaths averted, saved DALYs, and the potential number of people dying from infection with the mutant HPgV strain.

Sensitivity analysis

To quantify the contribution of parameters to the variability of predicted model outcomes, we calculated first-order sensitivity indices (32). Specifically, a first-order sensitivity index for a parameter is an indication of how uncertainty in a particular parameter contributes to the variability of model outcomes. Details of the probability distributions used in the calculation of first-order sensitivity indices are available in Table 1.

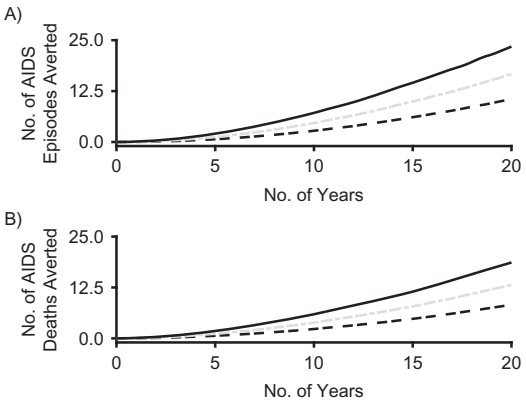

Figure 1. Reduction in AIDS episodes and averted AIDS deaths, from model predictions of the health benefit of human pegivirus biovaccination in the United States. A) Reduction in AIDS episodes for annual human pegivirus (HPgV) biovaccination rate of 12.5% (dashed line), 25% (dash-dotted line), and 50% (solid line); B) AIDS deaths averted per 1,000 people for annual HPgV biovaccination rate of 12.5% (dashed line), 25% (dash-dotted line), and 50% (solid line).

RESULTS

To determine the health benefit of HPgV biovaccination on AIDS morbidity and mortality, we simulated the transmission of both HPgV and HIV in addition to the subsequent progression of the HIV-infected individuals to AIDS. To evaluate HPgV biovaccination as an HIV therapy, we considered scenarios of low (12.5%), intermediate (25%), and high (50%) annual HPgV biovaccination rates, with efficacy rates of 25%, 50%, and 75%, over a 20-year time horizon. We gauged the risk of HPgV evolution by considering mutant strains with mortality rates of 0%, 0.1%, 1.0%, and 10% that of the AIDS mortality rate together with an enhanced transmission rate (Table 1).

In the absence of HPgV evolution, AIDS morbidity and mortality were significantly reduced for all HPgV biovaccination scenarios (Figure 1). Annual HPgV biovaccination rates of 12.5%–50% with an efficacy of 25% reduced AIDS incidence by 4.2–12.9 episodes per 1,000 people, averted 3.3–10.0 AIDS deaths per 1,000 people, and annually saved 2.9–9.1 DALYs per 1,000 people (Web Table 1). For an efficacy of 75%, the reduced AIDS incidence, averted AIDS deaths per 1,000 people, and annually saved DALYs per 1,000 people improved to 10.6–23.6 (Figure 1A), 8.4–18.8 (Figure 1B), and 7.7–18.6 respectively (Web Table 1).

Sensitivity analysis of model parameters showed that predictions of AIDS episodes were most sensitive to the rate of developing AIDS (while on HAART), and the rate of developing AIDS (without treatment), followed by initial HPgV prevalence (Table 2). Predictions of AIDS episodes were relatively insensitive to model parameters directly related to HPgV infection, with the HPgV transmission rate and clearance rate being the least influential (Table 2).

When mutant strains of HPgV were introduced, only those that cause very low mortality were typically able to invade unless they also had a greatly enhanced transmission rate (Table 3).

Table 2. First-Order Sensitivity Indices of Parameters[a] for a Model to Predict the Health Benefit of Human Pegivirus Biovaccination on AIDS Morbidity and Mortality in the United States

Parameter	Indices
p	0.0000
β_{HIV}	0.0000
β_g	0.0000
ϵ	0.0004
σ	0.0036
ζ	0.0000
γ	0.8925
κ	0.0001
d	0.0002
d_H	0.0001
ϕ	0.0003
Initial HPgV prevalence	0.0009
ζ_p	0.0001
f	0.0000
ρ	0.0001
ψ	0.0000
ν	0.0008

[a]Calculations based on sample sizes of 10,000 where $\nu \sim U[0, 0.75/365]$.

This result is further strengthened by the fact that the upper bound of the 95% quantile of the invasion number R_m^g is predominantly below the critical threshold of 1 when the enhancement in transmission is low (Figure 2). However, for mutant strains of HPgV with intermediate and high transmission rates, invasion was much more likely (Table 2, Figure 2). For the most

Table 3. Likelihood of Invasion and Mutant Strain Dominance for a Model to Predict the Health Benefit of Human Pegivirus Biovaccination on AIDS Morbidity and Mortality in the United States

Mutant Strain	$\theta \sim U(1, 2)$	$\theta \sim U(1, 10)$	$\theta \sim U(1, 50)$
Invasion condition ($R_m^g > 1$)			
Zero mortality ($0{\cdot}d$)	0.926	0.926	0.926
Low mortality ($0.001{\cdot}d$)	0.580	0.891	0.936
Intermediate mortality ($0.01{\cdot}d$)	0.549	0.645	0.667
High mortality ($0.1{\cdot}d$)	0.386	0.392	0.408
Strain dominance ($R_m > R_0$)			
Zero mortality ($0{\cdot}d$)	0.456	0.548	0.738
Low mortality ($0.001{\cdot}d$)	0.448	0.548	0.736
Intermediate mortality ($0.01{\cdot}d$)	0.354	0.522	0.712
High mortality ($0.1{\cdot}d$)	0.084	0.406	0.604

[a] Proportion of 10,000 simulations, given $\nu = 0$, where the invasion condition $R_m^g > 1$ and $R_m > R_0$ (given $R_m^g > 1$) for given mutant strain mortality and enhancement factor of mutant transmission rate.

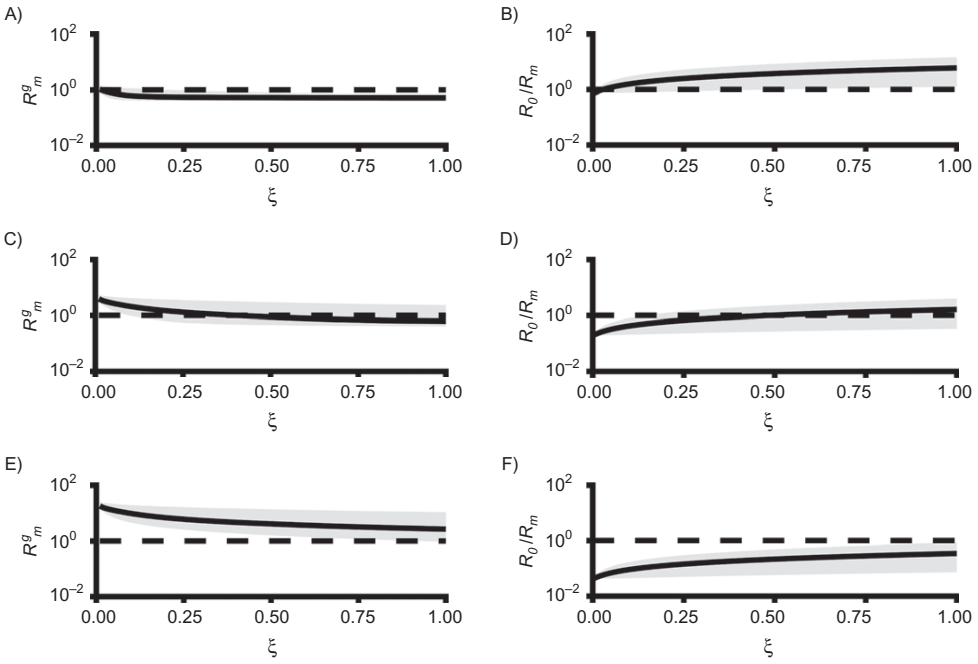

Figure 2. Invasion number (R_m^g) and ratio of human pegivirus reproductive numbers (R_0/R_m) versus the mutant mortality factor (ξ), from model predictions of the health benefit of human pegivirus biovaccination in the United States. The critical thresholds (dashed lines) for invasion, median values of the invasion number (solid lines), and 95% quantiles (gray region) for 10,000 random parameter samples given a mean mutant transmission rates of $\mathbb{E}[\theta] = 1.5$ (A), $\mathbb{E}[\theta] = 5.5$ (C), and $\mathbb{E}[\theta] = 25.5$ (E). The critical thresholds (dashed lines) for mutant strain dominance and the median ratio of reproductive numbers (solid lines) along with 95% quantiles (gray region) for 10,000 random parameter samples given a mean mutant transmission rates of $\mathbb{E}[\theta] = 1.5$ (B), $\mathbb{E}[\theta] = 5.5$ (D), and $\mathbb{E}[\theta] = 25.5$ (F).

potentially worrisome case, whereby the mutant strain causes a large mortality rate, only strains that also have a greatly enhanced transmission rate are able to spread (Figure 3).

Even when mutant, mortality-causing strains of HPgV spread, the use of HPgV biovaccination as an HIV therapy was still projected to have considerable utility. For example, under low and moderate mortality rates for the mutant strain, and with low to moderate enhanced transmission, HPgV biovaccination still reduced AIDS incidence by approximately 6.7–31.5 episodes per 1,000 people (Web Figures 3–5), averted 5.1–27.6 AIDS deaths per 1,000 people, and annually saved 4.3–26.0 DALYs per 1,000 people (Web Tables 2–7)—all while still not resulting in a substantial number of deaths from the mutant HPgV strain (Web Tables 2–7). Under more extreme parameter values, including very high HPgV mortality rates and very high transmission rates, HPgV biovaccination still provided great improvement in terms of AIDS incidence (Web Figures 3–5) and averted AIDS deaths at the expense of a considerable number of deaths due to mutant HPgV infection and its resultant impact on DALYs (Web Tables 8–10). Unsurprisingly, in the most extreme cases of both high mortality and high transmission, the number of deaths through HPgV infection greatly outnumber the AIDS deaths averted. However, this tends to require mutant HPgV death rates on the order of 10% of the AIDS death rate and a transmission rate enhancement of over 10 times that of the original benign strain (Figure 3).

Non-mortality-causing mutant strains of HPgV were typically able to invade through enhanced transmission; only 17.0% of the considered scenarios in which mutant strains of HPgV had enhanced transmission and modified viral clearance rate fell below the critical invasion threshold of $R_m^g = 1$ (Web Figure 6). This percentage drops below 1% when considering a diminished benefit of HPgV for delaying the progression to AIDS (Web Figure 7).

Model predictions showed that annual HPgV biovaccination rates of 12.5%–50%, with efficacies ranging from 25% to 75%, increased HPgV prevalence from 30.0% to 35.9%–88.5%. This result, coupled with the fact that HPgV is associated with improved surrogate markers for HIV progression (30), implies that the average CD4+ count occurring in the population of HIV-infected men who have sex with men would improve by 1%–3.1%, respectively (Web Table 11).

Last, Web Tables 3–10 also reveal the initially surprising outcome that the detrimental impact of HPgV evolution tended to be most extreme under the lowest biovaccination rates. This suggests that higher biovaccination rates better protect the population against such adverse evolution, but caution should be exercised with this interpretation. This outcome is due to the fact that greater biovaccination rates increase the intensity of competition experienced by any mutant HPgV genotype that arises. While this is likely an important factor, the model does not include the fact that the rate at which HPgV mutants appear will increase with the

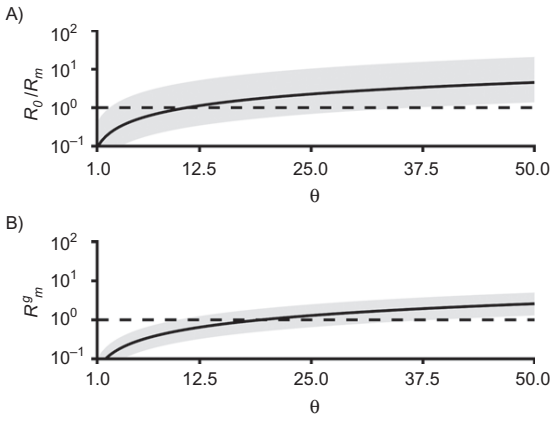

Figure 3. Invasion number (R_m^g) and ratio of human pegivirus reproductive numbers (R_0/R_m) versus the enhancement factor of mutant transmission rate (θ), from model predictions of the health benefit of human pegivirus biovaccination in the United States. A) The ratio of mutant and basic reproductive numbers for $\beta_m = \theta\beta_g$ and $1 \leq \theta \leq 50$, showing the critical threshold for the mutant human pegivirus (HPgV) strain to become the dominant HPgV strain (dashed line) and the median ratio of R_m/R_0 for 10,000 random parameter samples (solid line) with $\xi = 0.1$ and 95% quantiles (gray region). B) The invasion number for $\beta_m = \theta\beta_g$ and $1 \leq \theta \leq 50$, showing the critical threshold for successful invasion (dashed line) and the median of R_m^g for 10,000 random parameter samples (solid line) with $\xi = 0.1$ and 95% quantiles (gray region).

biovaccination rate, and thus as the prevalence of HPgV infection rises.

DISCUSSION

The analysis of our novel model of HPgV and HIV coinfection predicts that HPgV biovaccination substantially reduces AIDS morbidity and mortality among men who have sex with men in the United States. According to the model, rolling out HPgV biovaccination as an HIV therapy would achieve a reduction in AIDS incidence, avert AIDS deaths, and save DALYs. Furthermore, our model shows that while there are risks associated with using a live virus such as HPgV as an HIV therapy, a dramatic increase in disease transmissibility and mortality would need to occur in order to offset the benefits of HPgV biovaccination.

The magnitude of annual DALYs saved as a result of HPgV biovaccination is substantial and comparable to other HIV interventions, such as the scale-up of HAART treatment (33) and an improved quality of care (34). Our analysis was also conservative in that we focused on the impact of HPgV on AIDS episodes and AIDS mortality, and we did not account directly for the positive benefits of HPgV on other opportunistic infections, such as hepatitis C (35).

Although there are risks associated with the use of a live pathogen as a therapy, our results suggest that concern over the spread of disease-causing HPgV strains is perhaps less significant than might initially be anticipated for several reasons. First, our results show that it is only under the most extreme parameter values that the costs associated with mutant HPgV strains outweigh the benefits of using it as a therapy. Second, although we cannot rule out the possibility that dangerous mutants might arise and spread, there are sound theoretical reasons for expecting this to be unlikely. For instance, HPgV has presumably been circulating in the human population since speciation of the hominin (36), and evidence suggests it has almost no antigenic drift (37). Using it as a therapy would therefore effectively entail simply increasing the prevalence of an already naturally circulating benign virus. This type of intervention would therefore have adverse evolutionary consequences only if an increased prevalence of a wild-type pathogen would somehow lead to stronger selection for more transmissible, virulent strains. However, the majority of evolutionary epidemiologic theory and data shows that increased pathogen prevalence tends to produce weaker selection for increased transmission (38–41), and therefore such an intervention should forestall the spread of highly transmissible, virulent strains. Third, as far as can be discerned to date, HPgV coinfection can be viewed as a disease that enables HIV tolerance (42), as opposed to HIV resistance, and theory suggests that such interventions are less prone to resistance evolution on the part of HIV as well (43).

While we considered only HPgV and HIV transmission among men who have sex with men in the United States, our model would also benefit other HIV-infected demographic groups. For instance, studies illustrate a 85% reduced risk of mother-to-child HIV transmission with infant acquisition of HPgV (9, 44). Furthermore, our work is adaptable to describe other HPgV coinfections, and it is postulated that HPgV is beneficial in fighting other diseases, such as Ebola (45).

Necessarily, mathematical models of infectious diseases involve simplifications. For example, in our analysis, we did not account for transmission from AIDS-diagnosed individuals, the viral quasispecies nature of both HPgV and HIV, or triinfection with other diseases that are known to affect HPgV prevalence, such as hepatitis C. In addition, we accounted only for transmission of HPgV and HIV among men who have sex with men in the United States, and we did not take into account the likely health benefits of increasing HPgV prevalence among bisexual men's female partners. Furthermore, we did not evaluate the benefit of HPgV for other at-risk demographic groups, such drug injectors, sex workers, or other communities with high HIV prevalence, such as Sub-Saharan African populations. Because such at-risk demographics are highly studied, future models could account for these gaps using available data on HIV transmission and HPgV prevalence.

In summary, the use of HPgV infection as an HIV therapy for men who have sex with men infected with HIV could greatly reduce AIDS morbidity and mortality. Our findings show that HPgV biovaccination could effectively reduce AIDS episodes, avert AIDS deaths, and save DALYs, even in the face of mutant HPgV strains appearing. Thus, we suggest that the utility of HPgV biovaccination might be substantial and that further empirical research on this possibility appears to be a valuable direction for future study.

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