The Importance of Extended High Viremics in Models of HIV Spread in South Africa

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Abstract

Recent studies found a substantial fraction of 'extended high viremics' among HIV-1 subtype C, the most common subtype in southern Africa. Extended high viremics are HIV infected individuals who maintain a high viral load for a longer time period than usual after the initial infection. They are more infectious during this period, and their infection progresses to full-blown AIDS and death much faster than usual. This study investigates the impact of extended high viremics on the spread of the HIV epidemic in South Africa. We develop a simple deterministic compartmental model for HIV infection that includes extended high viremics. As the available data on extended high viremics are limited, we parameterize this model using only the fraction of extended high viremics among new infections and the reduced life-span of extended high viremics. We find that without extended high viremics, the HIV prevalence in South Africa would have remained close to its 1990 level, instead of increasing to the current epidemic levels. We also find that the greater the fraction of extended high viremics among susceptibles, the greater the steady-state HIV prevalence and the more sensitive the steady-state prevalence is to the HIV transmission probability. These results suggest that extended high viremics have an impact on the HIV epidemic in South Africa; justify the need for comprehensive epidemiological studies since the current data is limited; and suggest that future models of HIV for southern Africa should explicitly model extended high viremics.

Key Words: extended high viremics; HIV transmission; HIV epidemic; southern Africa; HIV; compartmental model

MSC: 92D30, 92B05

Abbreviations:

HIV – Human immunodeficiency syndrome

RNA - Ribonucleic acid

CHAVI - Center for HIV Vaccine Immunology

ART - Antiretroviral therapy

AIDS - Acquired immunodeficiency syndrome

MSM – Men who have sex with men

PrEP – Preexposure prophylaxis

IDU – Injection drug user

HAART – Highly active antiretroviral therapy

1 Introduction

The human immunodeficiency syndrome (HIV) epidemic in southern Africa experienced a rapid expansion throughout the last 20 years. From 1990 to 2009 the percentage of 15-49 year old people living with HIV in South Africa increased from 0.8% to 17.8% [1]. HIV-1 subtype C has become the dominant subtype in the epidemic in southern Africa [1,2] and accounted for 98% of all HIV infections throughout 2004-2007 [2] in this region.

In 2011, Novitsky et al. [3] examined the progression of ribonucleic acid (RNA) viral load after acute infection among 77 individuals in Botswana and South Africa infected with HIV-1 subtype C. They found that 34% of all participants maintained a viral load of at least 100 000 copies/ml throughout a period of 100-300 days after acute infection. Those individuals were named *extended high viremics* [3]. Extended high viremics showed a rapid decline in their CD4 cell counts, with a median time to reach 250 CD4 cells/μl of 363 days after seroconversion versus 1213 days for other study participants [3]. Findings of an unpublished study of the Center for HIV Vaccine Immunology (CHAVI) [4] show that 31% of 125 HIV-1 subtype C infected individuals had a steady-state concentration of 100 000 copies/ml or higher in their blood plasma. Taking the strong association between the risk of HIV transmission among heterosexuals and the level of HIV RNA viral load in blood and semen [5-8] as well as the course of the HIV epidemic in South Africa into account, these studies draw the conclusions that extended high viremics 'deserve attention' [4] and are likely to 'fuel and maintain' the epidemic [9]. However, Campbell et al. [10] found in a recent study among HIV-1 infected individuals in east and southern Africa similar fractions of extended high viremics among subtype C and non-C subtypes (24% vs. 32%), leading to the conclusion that extended high viremics might not explain the rapid expansion of the HIV epidemic in southern Africa.

For more than 20 years mathematical models have been used to study the HIV epidemic [11]. In particular, compartmental models have been widely used to model the spread of HIV in heterogeneous populations [12] and various aspects of transmission. For example, they have been used to conclude that heterosexual transmission accounts for the majority of HIV infections worldwide [1]. Various aspects of the heterosexual HIV epidemic in Africa have been studied by use of compartmental models: Bongaarts [13] projected in 1989, that the HIV prevalence

in a Central African population would rise from 0% in 1975 to 21% in 2000 and the mortality rate would double. To limit the spread of HIV, Armbruster and Lucas [14] studied the impact of an abstinent or safe-sex month on HIV transmission in three African countries. The impact of biomedical HIV prevention interventions such as male circumcision on heterosexual HIV transmission has been studied by Williams et al. [15] and UNAIDS/WHO/SACEMA [16]. Granich's et al. [17] findings suggest the HIV prevalence in South Africa could be reduced to less than 1% over 50 years using universal testing combined with immediate antiretroviral therapy (ART). Eaton et al. [18] provides a comprehensive literature review of about 12 mathematical models studying ART in terms of treatment as prevention. Given high levels of access and adherence, the models widely agree on the short term reduction of HIV but differ more on long term projections [18]. However, none of these studies stratified their HIV positive populations by extended high viremics.

Focusing on a second mode of HIV transmission, compartmental models have been used to study the HIV spread among men who have sex with men investigating the impact of sex-role [19,20] and prevention interventions such as testing [21], preexposure prophylaxis (PrEP) [22] and integrated prevention interventions [23]. Third, these models have been used to study the impact of prevention interventions [24,25] on HIV transmission among injection drug users (IDU's) and the cost-effectiveness of ART and highly active antiretroviral therapy (HAART) in IDU settings.

The fundamental assumption underlying compartmental models is homogeneous mixing [12], that all individuals in a compartment act similarly and that mixing between compartments is random. Selecting each new partner from the total population at random allows for a 'worst case' scenario of disease spread [28,29] with greatest magnitude. However, compartmental models have shown to be 'robust and predictive' [30] on a population level [31] and have been used extensively to study HIV transmission in southern Africa [14-18].

We use a deterministic compartmental model to study the impact of extended high viremics on the dynamics of the HIV-1 subtype C epidemic and viral transmission in South Africa. This is both the first model of HIV spread to incorporate extended high viremics and the first study looking at extended high viremics to use mathematical modeling to describe their impact. In addition it is a

model with relatively many conclusions, despite the available data on extended high viremics being quite limited.

The next section describes the compartmental model, the estimation of input parameters, and two measures to determine the impact of extended high viremics on the HIV epidemic in southern Africa in the past and the future. In Section 3 we examine how the HIV epidemic in South Africa from 1990-2010 would have been different without extended high viremics and evaluate the impact of different fractions of extended high viremics among susceptibles on HIV prevalence in the steady-state. In Section 4 we conclude with a discussion of the results and potential implications for both future research on extended high viremics and future models of HIV spread in southern Africa.

2 Methods

2.1 Compartmental Model

We develop a deterministic compartmental model to describe the sexual transmission of HIV-1 subtype C within the population of sexually active adults age 15-49. The model divides our population into twelve compartments by their infection status (susceptible and infected) and stage of infection, their ART status, and whether they become extended high viremics when infected. We assume that the propensity to be an extended high viremic is a property of the individual because there is no evidence that this property is transmitted through infection [3,32]. Fig. 1 illustrates the dynamics of this model. The compartments (and the state variables denoting the number of individuals in each) are listed in Table 1.

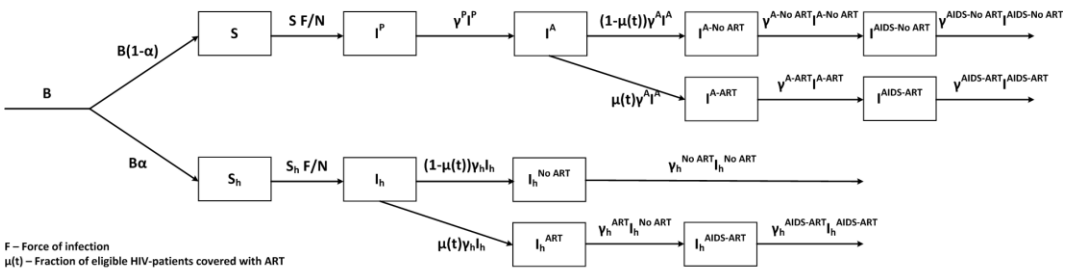

Fig. 1 Schematic illustration of the model showing the population of sexually active adults divided among twelve compartments and the annual flows among them.

Table 1: State variables of the compartmental model.

State variable	Description
Normals	
S	Susceptibles
I^P	Infected: primary infection period
I^A	Infected: asymptomatic infection period, not eligible for ART
$I^{A-No\ ART}$	Infected: asymptomatic infection period, eligible for ART, no treatment
$I^{A-\ ART}$	Infected: asymptomatic period, eligible for ART, treatment
$I^{AIDS-No\ ART}$	Infected: AIDS, no treatment
$I^{AIDS-ART}$	Infected: AIDS, treatment
Extended high viremics	
S_h	Susceptibles
I_h	Infected: not eligible for ART
$I_h^{No\ ART}$	Infected: eligible for ART, no treatment
I_h^{ART}	Infected: eligible for ART, treatment
$I_h^{AIDS-ART}$	Infected: AIDS, treatment

The inflow into the population is such that the net annual growth rate is g. A fraction α of the entering individuals B become susceptible extended high viremics. The force of infection F multiplied by the fraction of susceptibles, S/N and S_h/N, determines the number of new, normal and extended high viremic infections, respectively. After becoming eligible for ART, both normal infected and extended high viremics can receive treatment. Normal infected individuals leave the population at rates $\gamma_{I^{AIDS-No\ ART}} I^{AIDS-No\ ART}$ and $\gamma_h I_h$ and extended high viremic infected leave at rates $\gamma_{I_h^{AIDS-ART}}\ I_h^{AIDS-ART}$ and $\gamma_{I_h^{No\ ART}} I_h^{No\ ART}$. The corresponding nonlinear system of differential equations can be written as follows:

Normals

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (1-\alpha)B - F\frac{S}{N} \quad (1)$$

$$\frac{\mathrm{d}I^{P}}{\mathrm{d}t} = F\frac{S}{N} - \gamma_{I^{P}} I^{P} \quad (2)$$

$$\frac{\mathrm{d}I^{A}}{\mathrm{d}t} = \gamma_{I^{P}} I^{P} - \gamma_{I^{A}} I^{A} \quad (3)$$

$$\frac{\mathrm{d}I^{A-No\ ART}}{\mathrm{d}t} = (1-\mu(t))\gamma_{I^{A}} I^{A} - \gamma_{I^{A-No\ ART}} I^{A-No\ ART} \quad (4)$$

$$\frac{\mathrm{d}I^{A-\ ART}}{\mathrm{d}t} = \mu(t)\gamma_{I^{A}} I^{A} - \gamma_{I^{A-ART}} I^{A-ART} \quad (5)$$

$$\frac{\mathrm{d}I^{AIDS-No\ ART}}{\mathrm{d}t} = \gamma_{I^{A-No\ ART}} I^{A-No\ ART} - \gamma_{I^{AIDS-No\ ART}} I^{AIDS-No\ ART} \quad (6)$$

$$\frac{\mathrm{d}I^{AIDS-ART}}{\mathrm{d}t} = \gamma_{I^{A-ART}} I^{A-ART} - \gamma_{I^{AIDS-ART}} I^{AIDS-ART}, \quad (7)$$

Extended high viremics

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = \alpha B - F\frac{S_h}{N} \quad (8)$$

$$\frac{\mathrm{d}I_h}{\mathrm{d}t} = F\frac{S_h}{N} - \gamma_{I_h} I_h \quad (9)$$

$$\frac{\mathrm{d}I_h^{No\ ART}}{\mathrm{d}t} = (1-\mu(t))\gamma_{I_h} I_h - \gamma_{I_h^{No\ ART}} I_h^{No\ ART} \quad (10)$$

$$\frac{\mathrm{d}I_h^{ART}}{\mathrm{d}t} = \mu(t)\gamma_{I_h} I_h - \gamma_{I_h^{ART}} I_h^{ART} \quad (11)$$

$$\frac{\mathrm{d}\,I_h^{AIDS-ART}}{\mathrm{d}t} = \gamma_{I_h^{ART}} I_h^{ART} - \gamma_{\,I_h^{AIDS-ART}}\, I_h^{AIDS-ART} \quad (12)$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = gN, \quad (13)$$

where the total population is

$$N = S + S_h + I^{P} + I^{A} + I^{A-No\ ART} + I^{A-ART} + I^{AIDS-No\ ART} + I^{AIDS-ART} + I_h + I_h^{No\ ART} + I_h^{ART} + I_h^{AIDS-ART}; \quad (14)$$

the number of people entering the system is

$$B = gN + \gamma_{I^{AIDS-No\ ART}} I^{AIDS-No\ ART} + \gamma_{I^{AIDS-ART}} I^{AIDS-ART} + \gamma_{I_h^{No\ ART}} I_h^{No\ ART} + \gamma_{\,I_h^{AIDS-ART}}\, I_h^{AIDS-ART}; \quad (15)$$

the force of infection is

$$F(t) =$$

$$\beta(t)\left(c_P I^P + I^A + I^{A-No\ ART} + c_{ART}(I^{A-ART} + I_h^{ART}) + c_{AIDS} I^{AIDS-No\ ART} + c_{ART-AIDS}(I^{AIDS-ART} + I_h^{AIDS-ART}) + c_h(I_h + I_h^{No\ ART})\right); \quad (16)$$

and the overall contact rate is

$$\beta(t) = \beta_0 + \beta_v e^{-t/\beta_w}. \quad (17)$$

Here, c_P, c_{ART}, c_{AIDS}, $c_{ART-AIDS}$ and c_h are parameters characterizing the relative transmission probability in each infected compartment in comparison to the transmission probability of normal HIV infected individuals in the asymptomatic phase receiving no ART [7]. The parameters β_0, β_v and β_w characterize the exponential decay of $\beta(t)$ over time [15].

The fraction of eligible HIV-infected individuals receiving ART is

$$\mu(t) = \begin{cases} 0, & \text{for } t < 2004 \\ 0.09(t-2004), & \text{for } t \geq 2004 \end{cases} \quad (18)$$

This assumes that ART coverage has been increasing linearly since 2004 at a rate of 9 percentage points a year. This fits well the data on ART coverage in South Africa in [1]: the earliest number is that 55,000 were receiving ART in 2004 with this number rising steadily until 55% coverage was achieved in 2010.

2.2 Input Parameters

The input parameters and corresponding values are shown in Table 2.

Table 2: Input parameters

Parameter	Value	Source
Annual population growth rate *g*, %	1.1[a]	[33]
Fraction of extended high viremics among susceptibles *f*	0,0.24,0.34	[3], [7]
Fraction of eligible HIV-infected individuals covered with ART *μ(t)*, %		
Fig. 3, before 2004 (course of the epidemic)	0	[1]
Fig. 3, 2004-2010 (course of the epidemic)	9(*t*-2004)	[1]
Fig. 4, Table 4 (steady-state)	55	[1]
Per capita transition rate of normal infected individuals (Fig. 2) out of stage		

Parameter	Value	Source
Primary infection period γ_{I^P}, y^{-1}	1/0.25	[7]
Asymptomatic period, not eligible for ART γ_{I^A}, y^{-1}	1/7.52	[7,34]
Asymptomatic period, eligible for ART, no treatment $\gamma_{I^{A-No\ ART}}$, y^{-1}	1/2.5	[7,34]
Asymptomatic period, eligible for ART, treatment $\gamma_{I^{A-ART}}$, y^{-1}	1/26.31	[7,36]
AIDS, no treatment $\gamma_{I^{AIDS-No\ ART}}$, y^{-1}	1/0.75	[7]
AIDS, treatment $\gamma_{I^{AIDS-ART}}$, y^{-1}	1/0.75	[7]
Per capita transition rate of extended high viremics (Fig. 2) out of stage		
Infected, not eligible for ART γ_{I_h}, y^{-1}	1/1.25	[3,7]
Infected, eligible for ART, no treatment $\gamma_{I_h^{No\ ART}}$, y^{-1}	1/1.08	[3,7]
Infected, eligible for ART, treatment $\gamma_{I_h^{ART}}$, y^{-1}	1/5.38	[3,7]
AIDS, treatment $\gamma_{I_h^{AIDS-ART}}$, y^{-1}	1/0.75	[7]
Relative transmission probability (relative to transmission probability in asymptomatic period, no treatment for normals)		
In primary period c_P	26	[7]
In asymptomatic period, ART c_{ART}	0.04	[8]
In AIDS stage, no ART c_{AIDS}	7	[7]
In AIDS stage, ART $c_{ART-AIDS}$	0.28	
For extended high viremics, no ART c_h	26	[3,7]
Contact rate $\beta(t)$, y^{-1}		
Fig. 3[b] $\beta(t) = \beta_0 + \beta_v e^{-t/\beta_w}$		
Long-run contact rate β_0, y^{-1}	0.031	Calibrated
Scaling parameter β_v, y^{-1}	0.067	Calibrated
Time constant β_w, y	4.866	Calibrated

[a] Average of the annual growth rates from 2002 to 2010

[b] Assuming f=0.34 [3], the values for β_0, β_v and β_w give the best fit to the HIV prevalence in South Africa 1990-2009 [1]. The calibrated contact rate ranges from $0.098y^{-1}$ in 1990 to $0.032y^{-1}$ in 2010.

2.2.1 Transition rates

To derive the values for the transition rates out of the infected compartments for HIV-infected individuals, we focus on the sexually active life time of normal and extended high viremics after infection, stratified by stage of infection and ART

status. The rate at which a sexually active HIV infected individual leaves a specific compartment is the reciprocal of the duration an individual stays in the corresponding stage of infection. These durations, the corresponding viral load and the transmission probability per sexual act vary with the progression of the HIV infection [6,7], which is illustrated in Fig. 2. In our model, HIV infected individuals go through five stages of infection and for each we give in parentheses the parameter for the corresponding duration [7]: primary infection (d_P), asymptomatic period without ART ($d_{A\text{-}No\ ART}$) and with ART ($d_{A\text{-}ART}$), acquired immunodeficiency syndrome (AIDS) and sexual active (d_{AIDS}), and AIDS and not sexual active (d_0). The sexually active lifetime of an HIV infected individual is then the sum of all but the last of these durations, $d_P + d_{A\text{-}No\ ART} + d_{A\text{-}ART} + d_{AIDS}$.

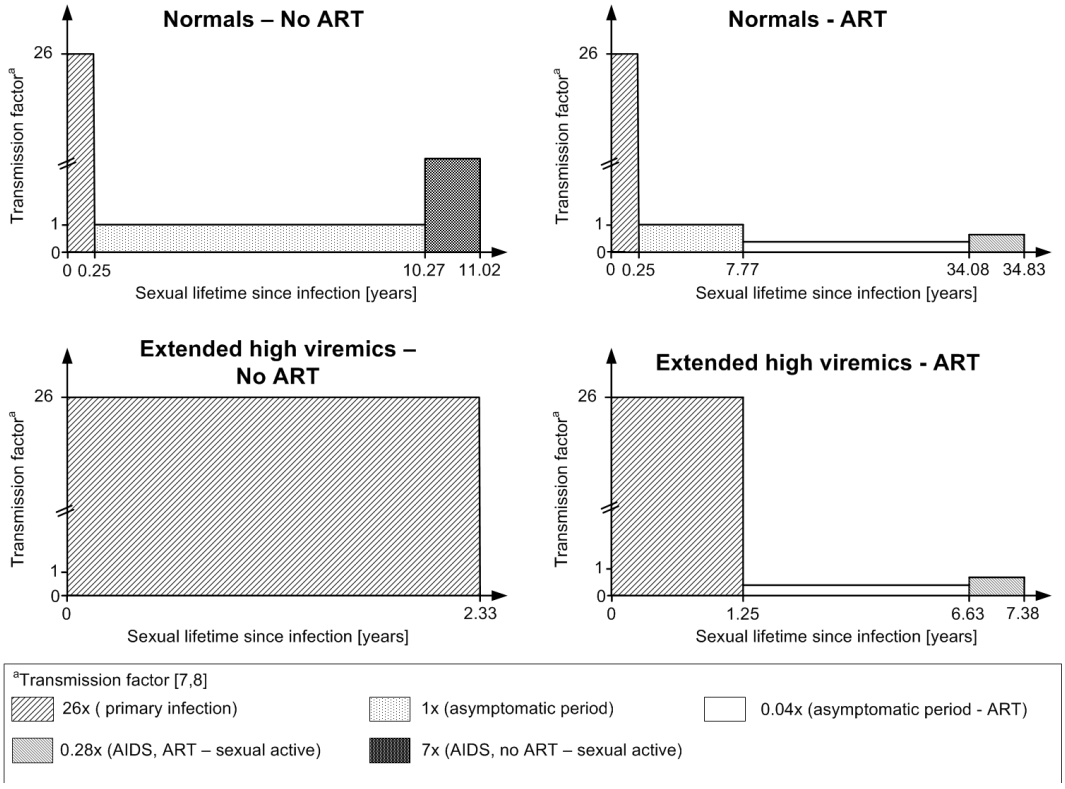

Fig. 2 The relative transmission rates over an infected individual's sexually-active lifetime.

Table 3 shows our estimates for the expected durations of the sexually active stages of HIV-infected normals and extended high viremics, both those who will and those who won't receive ART when they are eligible.

Table 3: Expected duration of sexually active stages of HIV infections in years.

Type HIV+	Sexual lifetime after infection	Stage of infection[a], y^{-1}				Source
		d_P	$d_{A\text{- No Art}}$	$d_{A\text{-ART}}$	d_{AIDS}	
Normals- No ART[a]	11.02	0.25	10.02	-	0.75	[7],[34]
Normals – ART	34.84	0.25	7.52	26.31	0.75	[7],[36]
Extended high viremics – No ART[b]	2.33	0.25	1.33	-	0.75	[3],[7]
Extended high viremics – ART	7.38	0.25	1	5.38	0.75	[3],[7]

[a] d_P-duration primary infection period; $d_{A\text{- No Art}}$-duration asymptomatic period without ART treatment; $d_{A\text{-ART}}$- duration asymptomatic period with ART treatment; d_{AIDS}-duration AIDS stage

[b] Normals: Duration asymptomatic period, not eligible for ART equals 0.75*10.02 y, i.e., γ_{I^A}=1/7.52 y^{-1} and duration asymptomatic period, eligible for ART, no treatment equals 0.25*10.02 *y*, i.e., $\gamma_{I^{A-No\ ART}}$ =1/ 2.5 y^{-1}

[c] Extended high viremics-No ART: Duration infection period, not eligible for ART equals d_P + 0.75* $d_{A\text{-No ART}}$, i.e., γ_{I_h}=1/1.25 y^{-1} and duration infection period, eligible for ART, no treatment equals 0.25* $d_{A\text{-No ART}}$ +d_{AIDS}, i.e., $\gamma_{I_h^{No\ ART}}$=1/1.08 y^{-1}

The values in the table are calculated as follows. Hollingsworth et al. [7] estimates that d_P, d_{AIDS}, and d_0 are three, nine, and ten months respectively. We assume for both normal infected and extended high viremics that the duration of the primary stage of infection, d_P, coincides with the time from infection until seroconversion. Glynn et al. [34] and Todd et al. [35] estimate that the age adjusted median survival time after seroconversion, i.e. $d_{A\text{-No ART}}$+d_{AIDS}+d_0 for individuals not receiving ART is 11.6 years. This allows us to calculate the estimates for the first row. We estimate the duration of $d_{A\text{-No ART}}$ for extended high viremics without ART by extrapolating from Novitsky et al. [3] which shows that the median time from seroconversion until a CD4 count of 250 cells/μl is around 363 days assuming a linear decline in the CD4 count from 700 cells/μl after seroconversion to 100 cells/μl at the beginning of AIDS for extended high viremics. For normal individuals receiving ART, Mills et al. [36] estimates that the life expectancy after initiation of ART, i.e. $d_{A\text{-ART}}$+ d_{AIDS}+$d_{0,}$ is 27.9 years. We assume that ART only extends the asymptotic period and the duration of primary

infection (d_P) and AIDS (d_{AIDS}) remain the same. Thus normal infected receive 26.32 years of treatment throughout the asymptomatic period ($d_{A\text{-}ART}$). To determine the length of the asymptomatic period before ART ($d_{A\text{-}No\ ART}$) we assume that when ART is available, it is initiated at the eligibility threshold before 2010 in South Africa of 250 CD4 cells/μl [3]. Again, we assume that without ART, the CD4 count decreases linearly within the asymptomatic period from 700 cells/μl after primary infection to 100 cells/μl at the beginning of AIDS. Thus the length of the asymptomatic period without ART ($d_{A\text{-}No\ ART}$) is for those who will receive treatment (700-250)/(700-100)=75% of the length of those who won't. Since the pre-ART viral load seems not to be correlated with the efficacy of ART [37], we assumed the efficacy of ART for extended high viremics to be the same as for normals. Specifically, we assume that the ratio of the sexual lifetimes of normals with and without ART was the same for extended high viremics. Thus, giving us the sexual lifetime of extended high viremics receiving ART as 7.38 years. Footnotes in Table 3 explain the relationship between the durations of $d_{A\text{-}ART}$ and $d_{A\text{-}No\ ART}$ and the durations of the corresponding stages shown in Fig. 2 and Table 1 respectively.

2.2.2 Transmission probability

The contact rate $\beta(t)$ denotes the annual transmission probability for normal infected individuals in the asymptomatic stage receiving no ART. Here, $\beta(t)$ aggregates a variety of parameters related to the annual transmission probability of HIV in a heterosexual population, e.g. the total number of sexual encounters per year and the transmission probability per sexual encounter, incorporating not only biomedical but also aspects of sexual behavior such as condom usage. We assume that the transmission probability varies with the stage of an HIV infection [5-7], whether an HIV infected individual receives ART [8], and whether it is an extended high viremic or a normal infected [3]. Fig. 2 shows not only the duration of the various periods of infected individual's sexually active life since infection but also their infectiousness relative to the asymptomatic period without ART. The relative transmission probability compared to the transmission probability of normal infected individuals in the asymptomatic stage is increased or decreased by factors c_P, c_{ART}, c_{AIDS}, $c_{ART-AIDS}$, and c_h. We now explain how those factors are derived.

For normal infected without ART we take the relative transmission probabilities from Hollingsworth et al. [7], i.e. c_P=26 and c_{AIDS}=7. For infected with ART we decrease the relative transmission rate in the asymptomatic period by 96% [8], c_{ART}=0.04. Granich et al. [17] and Armbruster and Lucas [14] assume that HIV infected individuals with ART in the AIDS stage do have the same relative transmission probability as infected with ART in the asymptomatic period. We set $c_{ART-AIDS}$= $c_{ART}c_{AIDS}$=0.28 implying a higher transmission probability than in the asymptomatic period with ART. Kigozi et al. [38] argues that the initiation of ART in the AIDS stage increases the likelihood of treatment failure compared to the initiation in the asymptomatic period. Since extended high viremics maintain a high viral load throughout their infection [3], we assume that they maintain the high transmission rate from the primary infection period throughout their sexually active lifetime, i.e., c_h=26.

2.2.3 Fraction α: Theorem and Proof

To parameterize the model, existing studies [3,4,10] have estimates of the fraction of extended high viremics among new infections, *f*, but do not provide estimates of the fraction α of individuals entering the (susceptible) sexually active population that are extended high viremics. We prove that these fractions are equal.

Theorem: Given the equations (1)-(16) defining our model, the fraction, α, of the (susceptible) entering individuals who are extended high viremics equals the fraction of extended high viremics among susceptibles, f.

Proof: The fraction of extended high viremics among susceptibles is

$$f = S_h/(S + S_h). \tag{19}$$

Since *f* is a constant parameter, when we differentiate with respect to *t*,

$$0 = \frac{\mathrm{d}S_h}{\mathrm{d}t}/(S + S_h) - (\frac{\mathrm{d}S}{\mathrm{d}t} + \frac{\mathrm{d}S_h}{\mathrm{d}t})S_h/(S + S_h)^2. \tag{20}$$

Rewriting this in terms of f,

$$0 = \frac{\mathrm{d}S_h}{\mathrm{d}t}\, f/S_h - f^2(\frac{\mathrm{d}S}{\mathrm{d}t} + \frac{\mathrm{d}S_h}{\mathrm{d}t})/S_h. \tag{21}$$

Substituting (1) and (3),

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (1-\alpha)B - F\frac{S}{N} \tag{22}$$

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = \alpha B - F\frac{S_h}{N}, \tag{23}$$

we obtain

$$0 = f/S_h \left(\alpha B - F\frac{S_h}{N} - f\left(B - (S+S_h)\frac{F}{N}\right)\right). \tag{24}$$

Since, $S+S_h=S_h/f$, this becomes

$$0 = f/S_h\ (\alpha - f)B, \tag{25}$$

proving that $\alpha = f$.

q.e.d.

2.3 Measuring the Impact of Extended High Viremics

To study the impact of extended high viremics we first investigate the course of the HIV epidemic in the past with and without extended high viremics. Then, to determine the future impact of extended high viremics we examine the effect on the long-term steady-state HIV prevalence. We conclude the section by describing analytically how the steady-states change for different HIV prevalences. We prove that the ratio of extended high viremics among infected individuals is independent of the prevalence.

2.3.1 Impact on the course of the epidemic

We study the impact of extended high viremics on the course of the HIV epidemic in South Africa from 1990 to 2010. We set the initial prevalence to the UNAIDS estimate of the prevalence in 1990. ART coverage in South Africa $\mu(t)$ has increased over this period [1]. We assume the coverage and efficacy of ART is the same for normal and extended high viremic infections. In particular we assume that the HIV status of infected individuals eligible for ART is known, i.e., infected leaving the compartments I^A or I_h receive ART with probability $\mu(t)$. We let the contact rate $\beta(t)$ decrease over time. This accounts for changes in the contact rate between 1990 and 2010 which are attributable to changes in sexual behavior [39]. Following Williams et al. [15], we let $\beta(t)$ be an exponential decay with three parameters which are chosen so that the model values for the prevalence from

1991 through 2009 minimize the least-squares difference to the UNAIDS estimates. Over time the contact rate $\beta(t)$ declines from initially $\beta_0 + \beta_v$ to the long run contact rate β_0 with a "decay time" of β_w years. We assumed the fraction of extended high viremics among susceptibles *f* to be 34% [3]. Keeping these parameters, we then calculated for comparison the epidemic trajectory with no extended high viremics, *f*=0. We show the results in Fig. 3.

2.3.2 Impact on the steady-state of the epidemic

Considering different constant choices for the contact rate β, we investigate the impact of extended high viremics on the steady-state prevalence of the HIV epidemic. The steady-state contact rate β corresponds to the long run contact rate β_0 in the exponential decay function of $\beta(t)$ over the course of the epidemic, i.e., in the steady-state we assume the transmission probability to be constant in the asymptomatic period without ART. To calculate the steady-state prevalence in Fig. 4 and Table 4, we solve the following set of steady-state equations.

In the steady-state we define the prevalence *p*, the fraction of extended high viremics among susceptibles, *f*, and the fraction of extended high viremics among infected, *x*, as follows:

$$p = (I^P + I^A + I^{A-No\ ART} + I^{A-ART} + I^{AIDS-No\ ART} + I^{AIDS-ART} + I_h + I_h^{No\ ART} + I_h^{ART} + I_h^{AIDS-ART})/N \quad (26)$$

$$f = S_h/(S + S_h) \quad (27)$$

$$x = (I_h + I_h^{No\ ART} + I_h^{ART} + I_h^{AIDS-ART})/(I^P + I^A + I^{A-No\ ART} + I^{A-ART} + I^{AIDS-No\ ART} + I^{AIDS-ART} + I_h + I_h^{No\ ART} + I_h^{ART} + I_h^{AIDS-ART}). \quad (28)$$

Next, we can define the growth rate for each compartment in the steady state by

Normals

$$\frac{dS}{dt} = gS \quad (29)$$

$$\frac{dI^P}{dt} = gI^P \quad (30)$$

$$\frac{dI^A}{dt} = gI^A \quad (31)$$

$$\frac{dI^{A-No\ ART}}{dt} = gI^{A-No\ ART} \quad (32)$$

$$\frac{\mathrm{d}I^{A-\,ART}}{\mathrm{d}t} = \; gI^{A-ART} \tag{33}$$

$$\frac{\mathrm{d}I^{AIDS-No\;ART}}{\mathrm{d}t} = gI^{AIDS-No\;ART} \tag{34}$$

$$\frac{\mathrm{d}I^{AIDS-ART}}{\mathrm{d}t} = gI^{AIDS-ART}, \tag{35}$$

Extended high viremics

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = gS_h \tag{36}$$

$$\frac{\mathrm{d}I_h}{\mathrm{d}t} = \; gI_h \tag{37}$$

$$\frac{\mathrm{d}I_h^{No\;ART}}{\mathrm{d}t} = \mathrm{g}I_h^{No\;ART} \tag{38}$$

$$\frac{\mathrm{d}I_h^{ART}}{\mathrm{d}t} = \; gI_h^{ART} \tag{39}$$

$$\frac{\mathrm{d}I_h^{AIDS-ART}}{\mathrm{d}t} = \; gI_h^{AIDS-ART} \tag{40}$$

We also add equations (1)-(16) assuming constant β as well as a steady-state ART coverage of μ=55%. We then solve this system of equations after substituting N=1 and values for p, g, and f. We obtain values for x, S, I^P, I^A, $I^{A-No\;ART}$, I^{A-ART}, $I^{AIDS-No\;ART}$, $I^{AIDS-ART}$, S_h, I_h, $I_h^{No\;ART}$, I_h^{ART}, $I_h^{AIDS-ART}$, α, β, F, $\frac{\mathrm{d}S}{\mathrm{d}t}$, $\frac{\mathrm{d}I^P}{\mathrm{d}t}$, $\frac{\mathrm{d}I^A}{\mathrm{d}t}$, $\frac{\mathrm{d}I^{A-No\;ART}}{\mathrm{d}t}$, $\frac{\mathrm{d}I^{AIDS-ART}}{\mathrm{d}t}$, $\frac{\mathrm{d}S_h}{\mathrm{d}t}$, $\frac{\mathrm{d}I_h}{\mathrm{d}t}$, $\frac{\mathrm{d}I_h^{No\;ART}}{\mathrm{d}t}$, $\frac{\mathrm{d}I_h^{ART}}{\mathrm{d}t}$, $\frac{\mathrm{d}I_h^{AIDS-ART}}{\mathrm{d}t}$ and B.

2.3.3 Description of steady-states: Theorem and Proof

Theorem: Suppose the current state is a steady-state (it satisfies equations 26-40) with prevalence p using contact rate β. Then a state with susceptible compartments S'=S(1-p')/(1-p) and S_h'=S_h(1-p')/(1-p) and infected compartments I_k'=I_k p'/p is a steady-state with prevalence p' using contact rate β'= β(1-p)/(1-p'). This implies that the fraction of extended high viremics among infected individuals, x, is independent of the steady-state prevalence p.[1]

Proof: Let w and w_h be the rate of new infections among normal and extended high viremics, respectively and let c_k be the relative transmission probability of

[1] We thank a reviewer for suggesting that this can be proven.

infected individuals in compartment I_k. Then $S/N=(1-f)(1-p)$; $S_h/N=f(1-p)$; the force of infection is $F = \beta \sum_k c_k I_k$; $w=F(1-p)(1-f)$; and $w_h=F(1-p)f$.

The outflows from the infected compartments are proportional to the compartment sizes. Thus to verify that the infected compartments are in steady-state we only need to check that the inflows, specifically w and w_h are also scaled by a factor of p'/p in the new state. Note that

$w'=F'(1-p')(1-f)$

$= \beta(1-p)/(1-p')(\sum_k c_k I_k\ p'/p)\ (1-p')(1-f)$

$=w\ p'/p,$

and similarly for w_h'.

We now turn to the susceptible compartments and show that whenever the infected compartments are in steady-state, then the susceptible compartments are also. Let d be the total rate of deaths from the infected compartments. Then

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (d + gN)(1 - f) - F\frac{S}{N} = (d + gN - F(1 - p))(1 - f) \text{ and} \qquad (41)$$

$$\frac{\mathrm{d}S_h}{\mathrm{d}t} = (d + gN)f - F\frac{S_h}{N} = \big(d + gN - F(1 - p)\big)f. \qquad (42)$$

Since the infected compartments are in steady-state, then the total inflow $w+w_h=F(1-p)$ equals the deaths in the infected compartments plus population growth, $d+g(Np)$. In that case, $d+gN-F(1-p)=gN(1-p)$. Substituting this into (41)-(42), we obtain $\frac{\mathrm{d}S}{\mathrm{d}t} = gS$ and $\frac{\mathrm{d}S_h}{\mathrm{d}t} = gS_h$, proving that the compartments are in steady-state.

q.e.d.

3 Results

Impact on the course of the epidemic (Fig. 3). Without extended high viremics (f=0), the HIV prevalence remains close to its 1990 level throughout the observation period, given the same input parameters and calibrated exponential decay of contact rate $\beta(t)$. With extended high viremics, f=0.34, the HIV prevalence will in the future decline further until it vanishes in the steady-state (examine Fig. 4 with the calibrated long-run contact rate β_0 being 0.031).

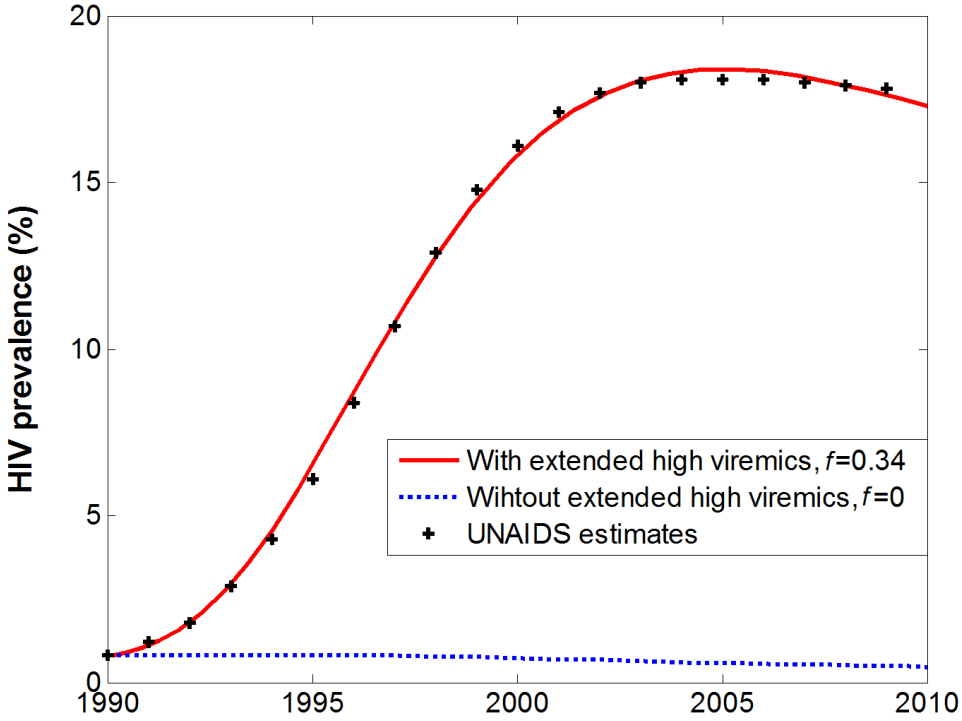

Fig. 3 Impact of extended high viremics on the course of the HIV epidemic in South Africa during 1990-2010. Assuming the observed fraction of extended high viremics among susceptibles f=0.34 [3], the model (solid red line) was fitted to estimates of HIV prevalence in South Africa 1990-2009 [1] (black data points). The dashed blue line shows the course of the HIV epidemic without extended high viremics (f=0), given the same values for all the other parameters.

Impact on the steady-state of the epidemic. Given a constant contact rate β, the steady-state prevalence depends on *f*, the fraction of extended high viremics among susceptibles (Fig. 4). Here, the greater the value of *f*, the greater is the steady-state prevalence and the rate at which it increases with respect to the constant contact rate β.

Table 4 shows the distribution of the population among compartments for different steady-state prevalences, with the fraction of extended high viremics among new infections, *f*, at 34%. It shows that the fraction of extended high viremics among HIV infected individuals is 11.5% and that the HIV prevalence among 'normal' individuals is about 3-4 times higher than among extended high viremics.

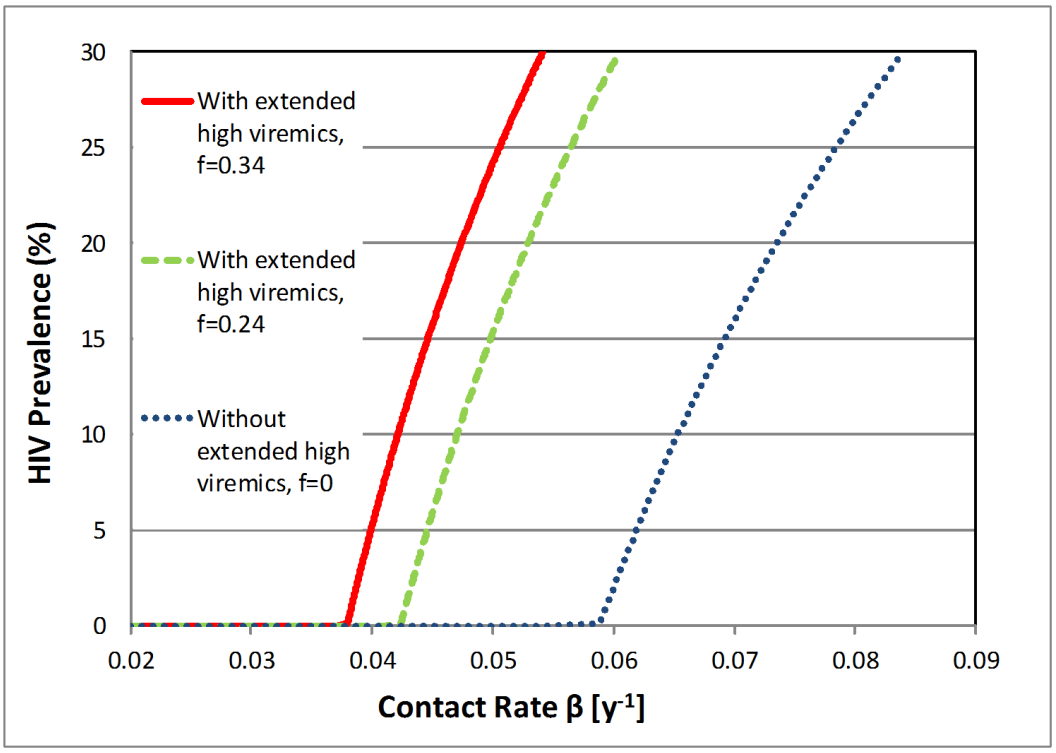

Fig. 4 Impact of extended high viremics on the steady-state HIV prevalence for different contact rates β. The blue dotted line shows the case without extended high viremics (*f*=0); the green dashed line the case of *f*=24% extended high viremics among susceptibles [10]; and the red solid line the case of *f*=34% extended high viremics among susceptibles [3].

Table 4: Population Breakdown with Steady-State Prevalence.

	HIV-	HIV+	HIV Prevalence
Fraction of extended high viremics *f*=0.34, steady-state prevalence is 5%			
Normals	62.7%	4.4%	6.6%
Extended High Viremics	32.3%	0.6%	1.8%
Fraction Extended High Viremics	34.0%	11.5%	-
Fraction of extended high viremics *f*=0.34, steady-state prevalence is 17.8%			
Normals	54.3%	15.7%	22.5%
Extended High Viremics	27.9%	2.1%	6.9%
Fraction Extended High Viremics	34.0%	11.5%	-

4 Discussion

From 1990 to 2009, South Africa experienced an estimated 3 400 000 AIDS deaths and 8 900 000 new HIV infections [1]. We assumed that 34% of the susceptibles were extended high viremics [3]. If instead, there had been no extended high viremics, then the HIV epidemic would have taken a much less tragic course. The results imply that extended high viremics do have a significant impact on the rapid expansion of the HIV epidemic. This coincides with the conclusion of a study in Botswana and South Africa that extended high viremics are likely to 'fuel' the epidemic [3].

The greater the fraction of extended high viremics among susceptibles, the greater is the steady-state HIV prevalence, given the same risk of HIV transmission. In addition to sexual behavior [40], the risk of HIV transmission is also associated with the level of HIV RNA viral load [5-8], which is high among extended high viremics [3,4,10]. Hence, our model strongly suggests that given the same sexual behavior, the steady-state prevalence of the HIV epidemic depends on the number of extended high viremics. This might explain why in some settings, e.g. settings with high risk sexual behavior and a large fraction of extended high viremics, the HIV epidemic experiences a more rapid expansion and a greater steady-state prevalence than in other settings, e.g. settings with high risk sexual behavior and a small fraction of extended high viremics. In addition, the sensitivity of the steady-state prevalence on the contact rate for populations

with large fractions of extended high viremics implies that prevention efforts that reduce the contact rate are more effective in such populations.

We fitted our model to the UNAIDS estimates of prevalence in South Africa from 1990-2010 [1] by calibrating the contact rate $\beta(t)$, i.e. the transmission probability per year of normal infected individuals in the asymptomatic stage being not eligible for ART. Assuming at least one partnership, Sanders et al. [41] estimated the ranges for the annual transmission probability of an HIV infected male and female in the asymptomatic stage to be [0.015,0.12] and [0.005,0.04], respectively. With the equal split of males and females in our study population [42] this could be translated into a combined range of [0.01,0.08], which aligns with our findings. The sensitivity of the prevalence to the constant contact rate β in the steady-state might not be a precise representation of the HIV epidemic dynamics in reality, however it is valid enough for us to draw the conclusion based upon the findings shown in Fig. 4, that the steady-state prevalence for the same contact rate β increases with the fraction of extended high viremics among susceptibles.

The results shown above rely heavily on estimates based on limited data. To the best of our knowledge, we found two published estimates [3,10] and one unpublished estimate [4] of the fraction of extended high viremics among susceptibles, *f*. Sample sizes were *n*=77 [3], *n*=44 [10], and *n*=125 [4]. For the median time to reach a CD4 cell count of 250 CD4 cells/μl we were only able to find one estimate [3]. Since these studies have small, non-random 'convenience' samples, they might not accurately represent the overall population in southern Africa and thus might bias our results. ART coverage varies regionally, and the efficacy of ART for extended high viremics is unknown and may differ from our assumption of being equal to the efficacy for normal HIV infected individuals. Additionally, we assume that the HIV status is known once an infected individual is eligible for ART. Considering the shorter time span of the CD4 cell count decline from seroconversion to the ART initiation threshold (1 year for extended high viremics compared to 7.52 years for normal infected), extended high viremics might be less likely to be tested and identified and therefore less likely to receive ART. By assuming that ART is as effective and ART coverage as large for extended high viremics as for normal infections, we consider the case where extended high viremics are least infectious.

To model heterosexual HIV transmission probability by stage of infection, we use the transmission probability estimates of Hollingsworth et al [7], which are considered to be the 'best available estimates' [42]. Alternate assumptions about relative transmission probabilities estimates and different durations by infection stage would lead to changes in relative transmission rates, the overall force of infection F, and transition rates, ultimately affecting our results. However, these changes would apply to both normal infected and extended high viremics, almost equally.

One consequence of the limited data about extended high viremics is our decision to use a simple model. While model simplicity is valuable and lends itself to easy analysis, it may also be a limitation if it does not accurately reflect the process of HIV transmission. More detailed models may for example take into account various sources of heterogeneity such as the fraction of undiagnosed, different levels of ART efficacy, and the structure of the sexual network [43,44]. However, since we do not seek to make quantitative predictions but merely determine the magnitude of the effect extended high viremics have, a minimal model such as ours suffices [12,30]. More complex models will be appropriate when we seek to make more quantitative predictions and have the necessary data to parameterize such models.

Our model studies the impact of extended high viremics on the transmission dynamics of HIV-1 subtype C, specifically the HIV epidemic in South Africa. The importance of the results shown justifies the need for reliable estimates about extended high viremics. We also recommend incorporating testing for extended high viremics among HIV+ participants in studies of sexual behavior. This would allow us to determine whether extended high viremics differ in their socioeconomic background or sexual behavior from other infected individuals. Additionally, testing for extended high viremics should be also incorporated into HIV prevention trials to evaluate the efficacy of ART in extended high viremics. This information is necessary to obtain a holistic understanding of the impact of extended high viremics in southern Africa. Ultimately, this could be seen as a starting point for the development of public health interventions targeting extended high viremics to reduce HIV transmission [9]. Increased and more frequent testing could potentially identify extended high viremics in a very early stage of their infection. Given the efficacy of ART in

extended high viremics, this could both improve their health status and reduce HIV transmission. Additionally, future models of the HIV-1 subtype C epidemic (e.g., models of HIV spread in southern Africa) should include extended high viremics as a separate subgroup among susceptibles and HIV infected individuals. Our results suggest that using only one homogeneous group of HIV infected individuals would not accurately reflect the dynamics of the HIV-1 subtype C epidemic and viral transmission in southern Africa. Then, when more data about extended high viremics is available, we can use this to add additional detail to our models.

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