Modelling the dynamics of population viral load measures under HIV treatment as prevention

Appendix

1. Model equations

In this section we describe the model used to investigate the behavior of population level VL measures during an HIV epidemic and all sensitivity analyses. The model is a simplified version of the risk structured model from [1, 2] which is extended to include undiagnosed population. Heterogeneity in sexual behavior is accounted for in the model implicitly by allowing the rate of HIV transmission depend on HIV prevalence as in Ref. [3]. The diagram of the model is shown in Figure 1 in the main text.

The model assumes that a population of size N is stratified according to HIV status into susceptible (S), undiagnosed infected (I_k), diagnosed but not on treatment (D_k) and treated (A_k) individuals. HIV infected individuals are stratified according to infection stage $k = 1, 2, 3, 4$ into primary infection ($k = 1$), chronic infection ($k = 2$), and AIDS ($k = 3, 4$). The two AIDS stages differ in infectivity which we assume to be zero in the latter stage due to severe illness and the cessation of sexual activity.

The model is described by a set of 13 ordinary differential equations as follows:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \beta N_0 - \mu S - JS, \tag{1}$$

$$\frac{\mathrm{d}I_1}{\mathrm{d}t} = JS - (\mu + \rho_1 + \theta_1)I_1, \tag{2}$$

$$\frac{\mathrm{d}I_k}{\mathrm{d}t} = \rho_{k-1}I_{k-1} - (\mu + \rho_k + \theta_k)I_k, \tag{3}$$

$$\frac{\mathrm{d}D_1}{\mathrm{d}t} = \theta_1 I_1 - (\mu + \rho_1 + \tau)D_1 + \phi A_1, \tag{4}$$

$$\frac{\mathrm{d}D_k}{\mathrm{d}t} = \theta_k I_k + \rho_{k-1}D_{k-1} - (\mu + \rho_k + \tau)D_k + \phi A_k, \tag{5}$$

$$\frac{\mathrm{d}A_1}{\mathrm{d}t} = \tau D_1 - (\mu + \sigma_1 + \phi)A_1, \tag{6}$$

$$\frac{\mathrm{d}A_k}{\mathrm{d}t} = \tau D_k + \sigma_{k-1}A_{k-1} - (\mu + \sigma_k + \phi)A_k, \tag{7}$$

where $k = 2, 3, 4$.

In Eqs. (1)-(7) J is the force of infection

$$J = \frac{\lambda}{N}\sum_{k=1}^{4}(h_k I_k + h_k D_k + \epsilon A_k), \tag{8}$$

where ϵ is infectivity of individuals on ART, h_k is infectivity of untreated individuals in stage $k = 1, 2, 3, 4$ of infection. By taking h_k equal both for diagnosed individuals who are not on treatment and individuals unaware of their infection we assume that diagnosis does not change infectivity. The parameter λ is HIV transmission rate which is calculated according to the expression simplified from Ref. [3]

$$\lambda = \lambda_0 \exp(-\alpha \text{HIV prevalence}), \tag{9}$$

where α is 'location' parameter of the epidemic and λ_0 is transmission rate at zero prevalence. In this expression the prevalence was computed as $\sum_{k=1}^{4}(I_k + D_k + A_k)/N$. Parameter α describes how quickly the transmission rate decays for a given level of prevalence. Lower values of α correspond to epidemics with more pronounced peaks in HIV prevalence, while higher values of α produce epidemics where HIV prevalence increases and stays rather constant.

2. Testing, diagnosis and treatment uptakes

We modelled the rollout of a test-and-treat strategy assuming that testing and diagnosis rate in chronic stage, $\theta_2(t)$, is time-dependent and scales up with time. This was done by writing $\theta_2(t) = \theta_2^{max} c(t)$, where θ_2^{max} is the maximal diagnosis rate. The time-dependent rollout function $c(t)$ is the solution of the logistic equation

$$\frac{\mathrm{d}c(t)}{\mathrm{d}t} = rc(t)\left[1 - c(t)\right]. \tag{10}$$

Here r governs the speed of the scale up of $\theta_2(t)$, and $c(0)$ determines the initial rollout. In the model, testing and diagnosis of individuals in chronic stage become available since the beginning of an epidemic at rate $\theta_2^{max} c(0)$, and they start to scale up 5 years later. This is done by shifting the value of $c(t)$ by the time of the beginning of the scale up. We adjusted the values of r and $c(0)$ so that the average time to diagnosis in chronic stage (given by the inverse of $1/\theta_2(t)$) is 15 years for the first five years of the epidemic in both WE and SSA scenarios. This then shortens to $1/\theta_2^{max} = 2.6$ years for WE and $1/\theta_2^{max} = 7$ years for SSA within the next 45 years. Diagnosis rates in primary and AIDS stages (θ_1, θ_3 and θ_4) were fixed during all analyses. Diagnosis rates in chronic stage and the corresponding times to diagnosis for SSA and WE baseline scenarios are shown in Figure 1.

The scale up of treatment uptake rate, $\tau(t)$, was modelled similarly by writing $\tau(t) = \tau^{max} c(t)$, where τ^{max} is the maximal treatment uptake rate and $c(t)$ is the solution of Eq. (10) shifted by the starting year of the scale-up. We assumed that ART becomes available 15 years after the beginning of the epidemic and starts to scale up at year 20.

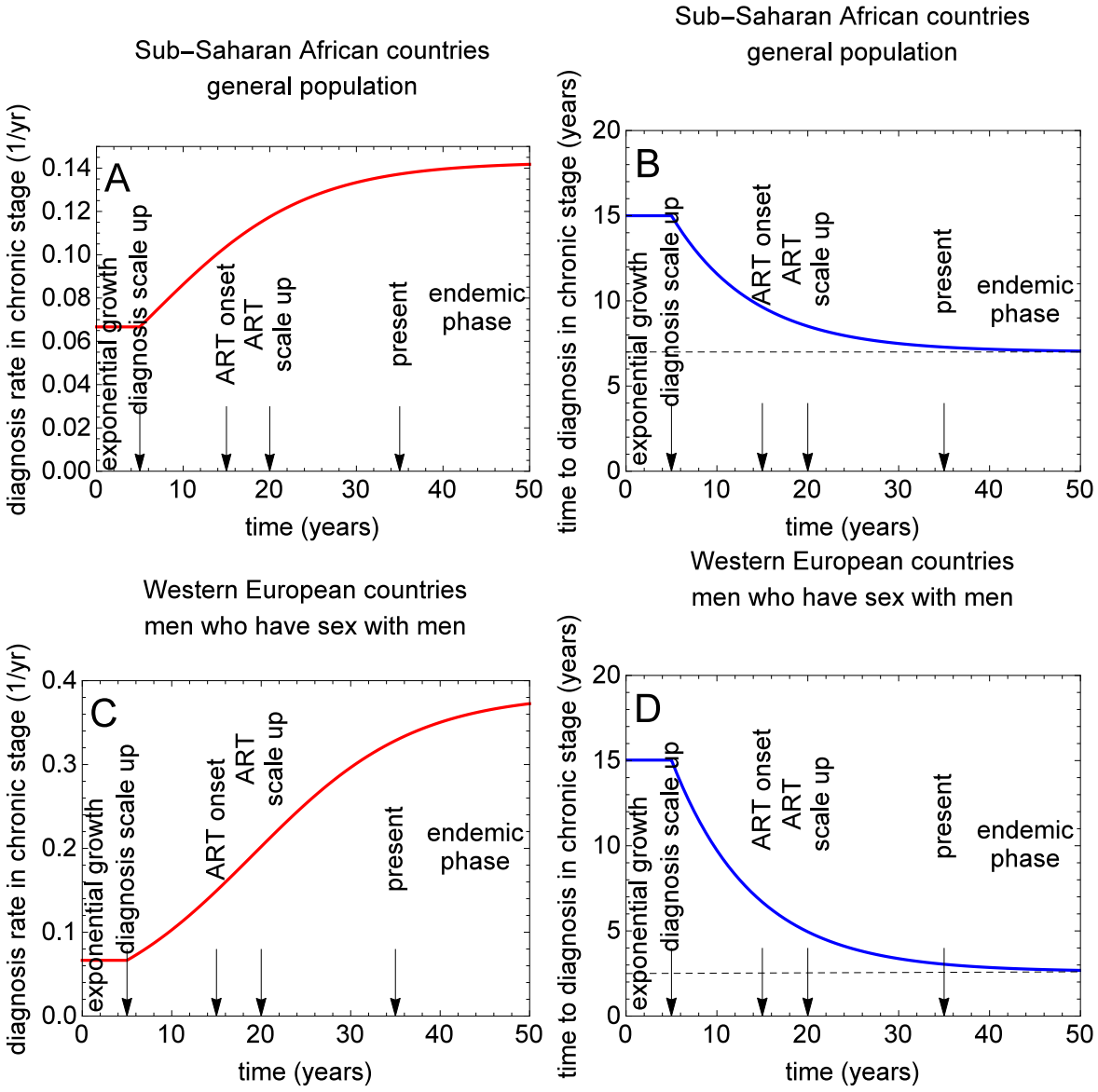

Figure 1: **Baseline diagnosis rates and time to diagnosis in chronic stage.**

We adjusted r and $c(0)$ so that annual treatment uptake rate reaches its maximum, τ^{max}, 20 years later. In Figure 2 we show the default annual treatment uptake rate, $\tau(t)$, and the corresponding annual treatment uptake percentage, $\bar{\tau}(t)$. Note that these parameters are the same both for WE and SSA but treatment coverage computed as the percentage of people on ART with respect to all infected population is different (compare Figure 2 A and B).

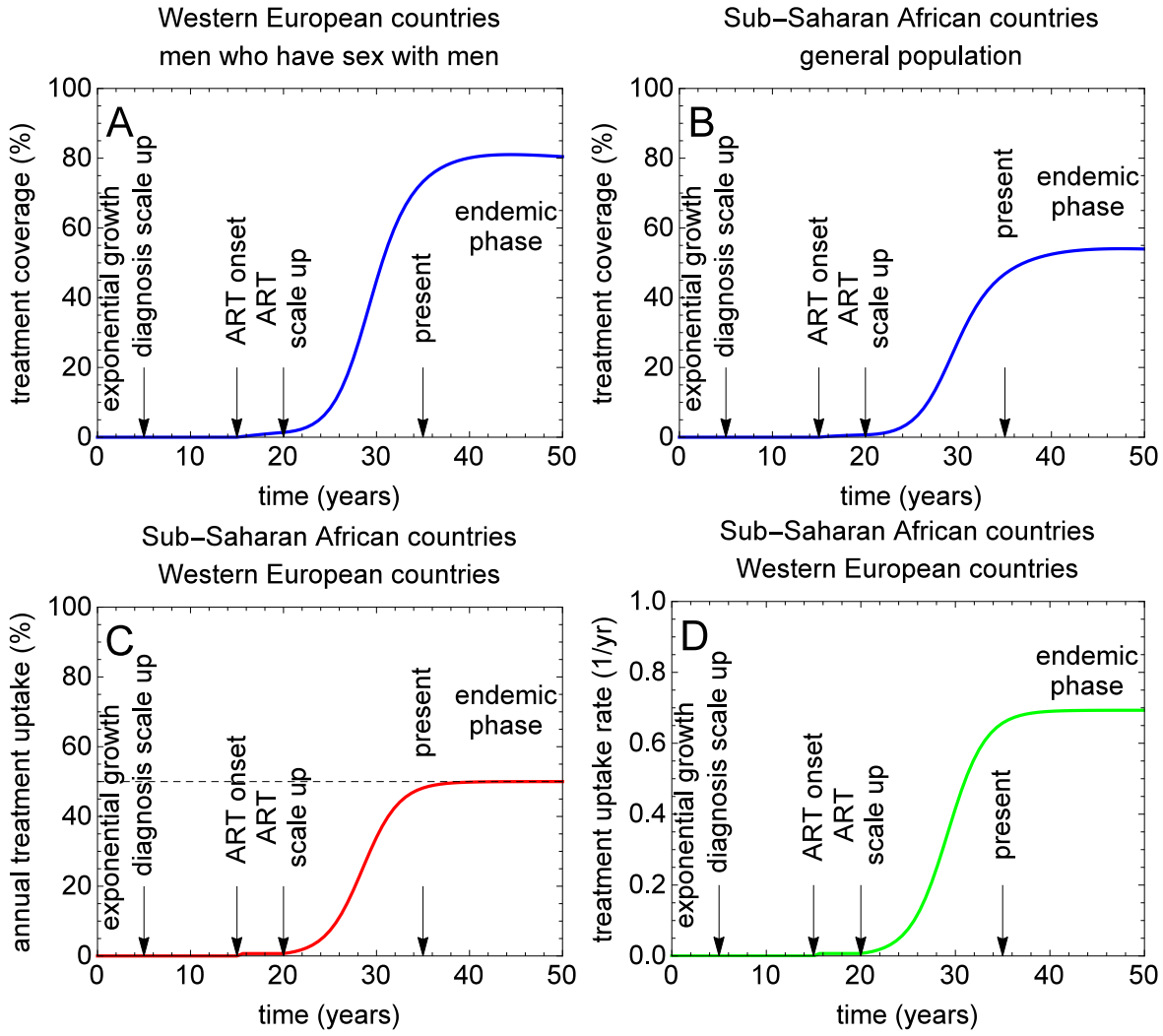

Figure 2: **Baseline annual treatment uptake rate, annual treatment uptake percentage and treatment coverage.**

3. Model calibration, parameter estimates and dynamics

Estimates for the rates of transition between infection stages for untreated [1, 4, 5, 6] and treated [1, 5, 7] individuals, as well as for the infectivities of untreated [1, 6, 8], and

treated [1, 3] individuals were extracted from published literature. The ratio of primary to chronic infectivity for untreated population was around 5.2 following [8]. Infectivity of individuals under treatment in any stage was 1% [3]. Bellan and colleagues [8] show that on a log-log scale there is a linear relationship between VL and infectivity. In our analysis, we relied on estimates of transmission rates from transmission studies (e.g. [6, 8]), and VLs were used only in the computation of aggregate VL measures.

The initial population size was set to 1 million individuals out of which 1% were undiagnosed in primary stage of infection and the rest were susceptible.

For the model calibration we adjusted transmission rates [3] to produce steady-state prevalence of 30% for SSA and 10% for WE before ART that decreased to about 22% and 6% at annual ART uptake of 50%. These levels are representative of Southern Africa ([9, 10] and references therein) and of MSM population in the Netherlands [11]. The basic reproduction number in the beginning of the epidemic was 2.72 for SSA and 4.07 for WE, which is in line with their estimates for South Africa and the Netherlands (see [1], supplementary material).

The summary of the parameters of the model is given in Table 1, where we also indicate their estimates used in the analysis.

3. Model dynamics

The time-dependent dynamics of the number of individuals in different subgroups is shown in Figure 3 (the WE scenario, results for the SSA scenario are qualitatively similar). In the beginning of the epidemic there are more undiagnosed individuals with chronic infection than with AIDS just because it takes time to develop AIDS (8.3 years). However, among the diagnosed population initially there are more people with AIDS than people with chronic infection. This is because the former develop symptoms and get diagnosed much quicker (1 month) than the latter for whom it takes up to 6.5 years on average before ART. As time goes on, more and more chronically infected individuals get diagnosed but these individuals do not progress to AIDS as quickly (without ART progression to AIDS still takes 8.3 years independently of diagnosis). At the same time people who were already diagnosed in AIDS stage die from disease related mortality quite fast (after about 1.3 years). This leads to a faster growth of the chronic diagnosed population than of the AIDS diagnosed population. Since VL in AIDS patients is much higher than VL during chronic infection (Table 2 in main text), before ART the contribution of AIDS patients to CVL decreases during the course of the epidemic, and the contribution of chronic infections increases, with the overall CVL decreasing.

Table 1: Description of the parameters of the model and their baseline values.

Notation	Baseline value, unit	Description	Source
N_0	1000000	Initial population size (constant)	—
β	$1/50$ yr^{-1}	Rate of recruitment to sexually active population	—
μ	$1/50$ yr^{-1}	Rate of leaving sexually active population	—
ρ_k, $k = 1, 2, 3$	$\rho_1 = 1/0.271$ yr^{-1} $\rho_2 = 1/8.31$ yr^{-1} $\rho_3 = 1/1.184$ yr^{-1}	Rate of transition from stage k to stage $k+1$ for untreated individuals	[1, 4, 5, 6]
ρ_4	$\rho_4 = 1/1.316$ yr^{-1}	Disease related mortality for untreated individuals	
σ_k, $k = 1, 2, 3$	$\sigma_1 = 1/8.21$ yr^{-1} $\sigma_2 = 1/54.0$ yr^{-1} $\sigma_3 = 1/2.463$ yr^{-1}	Rate of transition from stage k to stage $k+1$ for treated individuals	[1, 5, 7]
σ_4	$\sigma_4 = 1/2.737$ yr^{-1}	Disease related mortality for treated individuals	
h_k, $k = 1, 2, 3, 4$	$h_1 = 0.62$ $h_2 = 0.12$ $h_3 = 0.642$ $h_4 = 0.0$	Infectivity of untreated individuals in stage k of infection	[8] [1, 6]
ϵ	0.01	Infectivity of treated individuals	[1, 3]
λ	see Eq. (9), yr^{-1}	Transmission rate	Simplified from [3]
$\bar{\phi}$	5% (WE), 20% (SSA) 5–25% (sens. anal.)	Annual dropout percentage	[10]
ϕ	$-\ln[1 - \bar{\phi}/100\%]$ yr^{-1}	Annual dropout rate	

Notation	Baseline value, unit	Description	Source
λ_0	2.46239 yr^{-1} (WE)	Transmission rate in the beginning of HIV epidemic (at 0 prevalence)	Adjusted so that $R_0 = 4.065$ ([1], suppl. mat.)
	1.64647 yr^{-1} (SSA)		Adjusted so that $R_0 = 2.728$ ([1], suppl. mat.)
α	12.8 (WE)	Location parameter	Adjusted so that steady state prevalence before ART is 10% [11]
	2.14 (SSA)		Adjusted so that steady state prevalence before ART is 30% [9, 10]
$\tau(t)$	$\tau^{max}c(t)$ yr^{-1}	Annual treatment uptake rate	[3]
$\bar{\tau}(t)$	$(1-\exp[-\tau(t)])100\%$	Annual treatment uptake percentage	
$\bar{\tau}^{max}$	50% (default)	Maximal annual treatment uptake	[12]
	0–100% (sens. anal.)	percentage	
τ^{max}	$-\ln[1 - \bar{\tau}^{max}/100\%]$ yr^{-1}	Maximal annual treatment uptake rate	
θ_1	0 yr^{-1}	Diagnosis rate in primary phase	[13]
$1/\theta_{3,4}$	1/12 yr	Time to diagnosis in AIDS stage	[13]
$\theta_2(t)$	$\theta_2^{max}c(t)$ yr^{-1}	Testing and diagnosis rate in chronic stage	[3]
$1/\theta_2(t)$	$1/[\theta_2^{max}c(t)]$ yr	Time to testing and diagnosis in chronic stage	[3]
$1/\theta_2^{max}$	2.6 (WE), 7 (SSA) yr	Minimal time to diagnosis in chronic stage	[13, 14]

Notation	Baseline value, unit	Description	Source
$c(t)$	Eq. (10)	Function describing the rollout of testing and diagnosis/treatment uptake rates	[3]; Adjusted so that annual treatment uptake reaches 50% within 20 years and time to diagnosis in chronic stage decreases from 15 to 2.6 years (WE) and to 7 years (SSA)
r	$1/9$ yr^{-1}	Speed of the rollout of testing and diagnosis	
	$1/2$ yr^{-1}	Speed of the rollout of treatment	
$c(0)$	2.6/15 (WE), 7/15 (SSA)	Initial rollout for testing and diagnosis	
	0.01	Initial rollout for treatment	

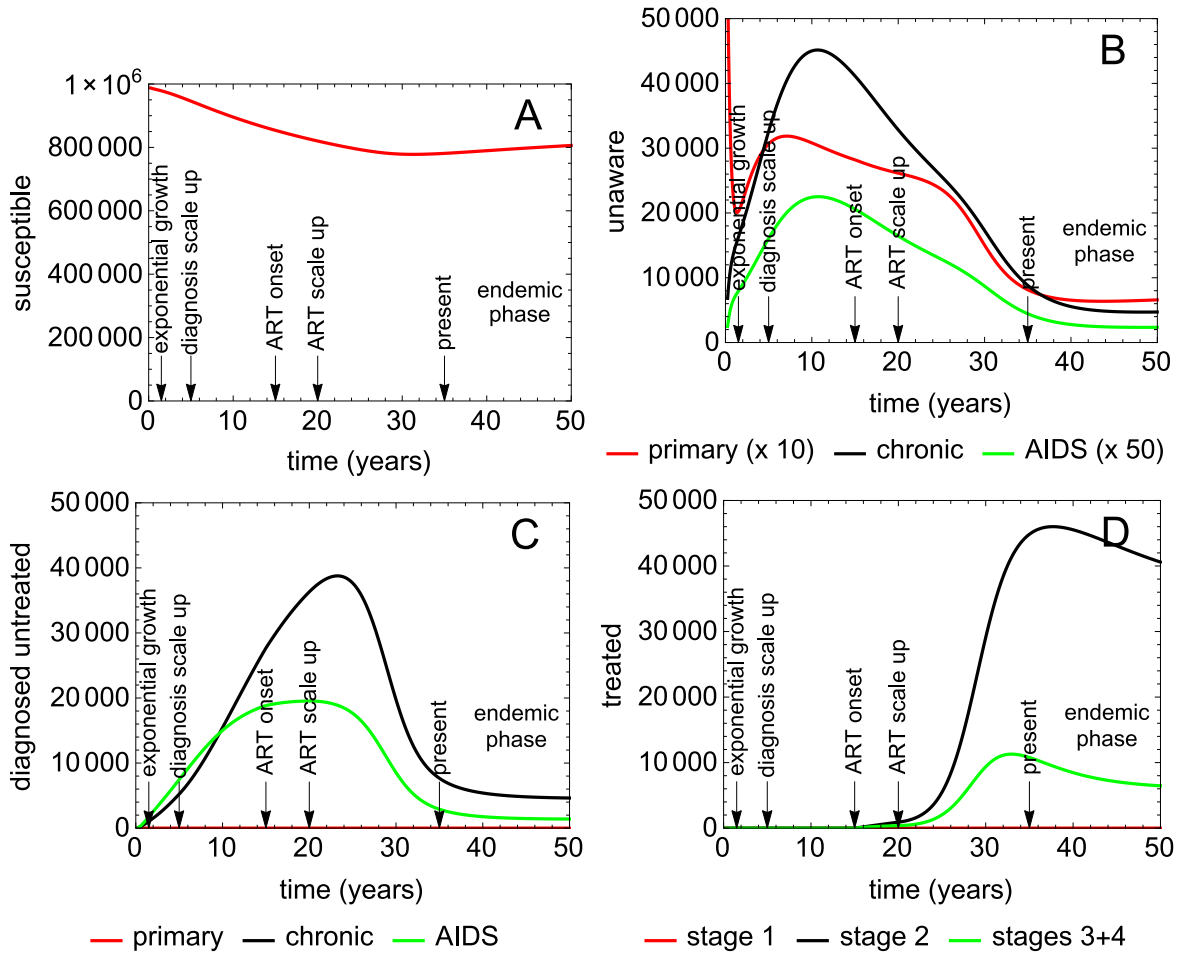

Figure 3: **Time-dependent dynamics of the number of individuals in different subgroups.** Results are shown only for the WE scenario. Results for the SSA scenario are qualitatively similar.

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