Prospects of elimination of HIV with test-and-treat strategy

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Recently, there has been much debate about the prospects of eliminating HIV from high endemic countries by a test-and-treat strategy. This strategy entails regular HIV testing in the entire population and starting antiretroviral treatment immediately in all who are found to be HIV infected. We present the concept of the elimination threshold and investigate under what conditions of treatment uptake and dropout elimination of HIV is feasible. We used a deterministic model incorporating an accurate description of disease progression and variable infectivity. We derived explicit expressions for the basic reproduction number and the elimination threshold. Using estimates of exponential growth rates of HIV during the initial phase of epidemics, we investigated for which populations elimination is within reach. The concept of the elimination threshold allows an assessment of the prospects of elimination of HIV from information in the early phase of the epidemic. The relative elimination threshold quantifies prospects of elimination independently of the details of the transmission dynamics. Elimination of HIV by test-and-treat is only feasible for populations with very low reproduction numbers or if the reproduction number is lowered significantly as a result of additional interventions. Allowing low infectiousness during primary infection, the likelihood of elimination becomes somewhat higher. The elimination threshold is a powerful tool for assessing prospects of elimination from available data on epidemic growth rates of HIV. Empirical estimates of the epidemic growth rate from phylogenetic studies were used to assess the potential for elimination in specific populations.

HIV elimination | mathematical model | primary HIV infection | treatment coverage

Mathematical modeling has played a key role in the discussion of the impact of treatment as prevention strategies, highlighted by the paper by Granich et al. (2), and followed up by others (11–14). These models all set out to assess the impact of treatment on population prevalence and incidence using simulations with parameter values estimated from various data sources. Although this approach is useful to compare quantitatively various intervention strategies or for cost-effectiveness analyses (14), it does not allow the answer to a more generic question, namely, under what conditions upon transmission rates is elimination possible at all (15)? To address the latter question an analytic approach is required.

We developed a modeling approach that allows assessment of the prospects of elimination given that some information is available on the initial phase of the epidemic. We generalized the model by Granich to allow for a more flexible description of the natural history of infection. We defined elimination as a threshold phenomenon and related the elimination threshold to the basic reproduction number $R_0$. We showed how basic reproduction number and exponential growth rate are related given our knowledge on disease progression and transmission. We investigated how the feasibility of elimination depends on the distribution of infectivity during the infectious period. Finally, we used published estimates of epidemic growth rates from incidence data or genetic sequence data to judge the prospects of elimination thresholds in specific populations.

Methods

Model Formulation. Our model is a direct generalization of the model in ref. 2 in that it allows for an arbitrary number of stages of infection with variable duration (Fig. 1 and SI Appendix). The model describes progression through $n$ stages of infection, background mortality, additional mortality from HIV infection, and the uptake and dropping out of treatment. We formulated the model as a system of differential equations as follows:

$$\frac{ds}{dt} = \beta - \lambda s - \mu s,$$

$$\frac{dI_1}{dt} = \lambda s - \mu I_1 - \rho_{1I_1} - \sigma_1I_1 + \phi \theta_1,$$

$$\frac{dI_2}{dt} = \rho_{1I_1}I_1 - \mu I_2 - \rho_{2I_2} - \sigma_2I_2 + \phi \theta_2,$$

$$\frac{dA_1}{dt} = \sigma_1I_1 - \mu A_1 - \rho_{\Lambda A_1} + \phi \theta_3,$$

$$\frac{dA_2}{dt} = \sigma_2I_2 - \mu A_2 - \rho_{\Lambda A_2} - \sigma_3A_2 - \mu A_2 + \phi \theta_4.$$
infection of stage $k$ (for $k = 1, 2, \ldots, n$) in case of treatment failure. The force of infection is determined by $j$, which is defined as

$$j = \sum_{k=1}^{n} h_k i_k + e a_k.$$ 

Here, parameter $e$ quantifies the reduced infectivity for an individual on ART, whereas the $h_k$ describe the infectivity in stage $k$ of the infection. The $r_k$ and the $a_k$ denote transition rates from stage $k$ to stage $k+1$ for untreated and treated individuals, respectively. The parameter $e$ represents the rate of moving from the untreated to the treated population, i.e., a combination of screening and treatment uptake. The parameter $\phi$ is the rate of moving from the treated back to the untreated population, i.e., the rate of dropping out of treatment. Finally, $\rho$ denotes the recruitment into the population and $\mu$ the background mortality rate. A key parameter is $\lambda$, the transmission rate between susceptible and infected individuals. A summary of parameters and their default values are given in SI Appendix, Table S2. The model used by Granich is obtained from the above formulation by setting $n = 4$ and by assuming that $r_k = \rho$ and $a_k = e$ for all $k$ (SI Appendix). Also, Granich’s model was formulated in terms of numbers and took varying population size into account, which we avoid by using population proportions. Finally, Granich’s model included a prevalence-dependent exponential term in the transmission parameter that served to capture density dependence and saturation effects for high prevalence. Density dependence does not play a role near threshold, so we simplified the model in that respect.

We then analyzed the threshold behavior of the model using theory described in refs. 16, 17. We showed that the threshold can be computed explicitly as a function of the model parameters for arbitrary values of $n$. We analyzed the threshold as a function of treatment-related parameters. In the absence of treatment, the threshold quantity is simply the basic reproduction number $R_0$, whereas in the presence of treatment it defines the elimination threshold quantity $R_*$. We parametrized the model for the case $n = 4$, because for this choice good estimates were available from literature on duration of stages and transmission rates per stage. We finally used the model to investigate how the elimination threshold depends on intervention parameters and how infectivity during primary infection impacts on possible intervention success. For details of the analysis we refer the reader to SI Appendix.

**Natural History of Infection.** To parametrize the model we made use of investigations into progression rates from infection to death (18, 19) and estimates of the duration of stages with high and low infectivity, i.e., (the time-varying) potential for transmission given contact (20). Following Hollingsworth and colleagues we distinguished four stages of infection with varying duration and transmission rates, where the last two stages together defined the symptomatic AIDS stage. The AIDS stage is subdivided into an infectious and a noninfectious period (due to severe illness leading to cessation of sexual activity). The durations of the primary infection and the asymptomatic chronic stage were chosen based on estimated disease progression by CD4+ counts as estimated by the Concerted Action on Sero-Conversion to AIDS and Death in Europe (CASCADE) collaboration; these durations then determined the values of the progression rates between stages. Furthermore, we determined transmission rates for the different infectious stages from ref 20 (Fig. 2 A and B). We assumed that disease progression is comparable across populations, i.e., that the same transition rates and infectivities can be used for different populations. The assumptions on progression rates were based on: the CASCADE study showing that progression did not differ by risk group, and only depended on the age at infection; a cohort study in Uganda, reporting progression rates in a sub-Saharan African population not to differ significantly from those in industrialized countries (21); and a metaanalysis (22), confirming the similarity in progression between those populations. Reliable estimates of per-contact transmission probabilities are only available for heterosexual couples. However, infectivity may be higher for unprotected anal intercourse, the main transmission route in men who have sex with men. We performed sensitivity analyses to investigate this possibility and other uncertainties (SI Appendix).

In the model the stages of the population under treatment have no biological interpretation. They were chosen such that the survival probability has a distribution function that agrees with CASCADE data from the time period after introduction of ART. We made the additional assumption that individuals dropping out of treatment move into the corresponding non-treatment stage of infection. Therefore, for individuals under treatment the proportion of time spent in each stage is similar to that without treatment, but the absolute duration is longer as it is adjusted to the prolonged survival under treatment. With these assumptions we estimated the transition rates for individuals on treatment (for details see SI Appendix).

**Basic Reproduction Number and Exponential Growth Rate.** The transmission parameter $\lambda$ describes the speed of transmission between individuals and therefore determines the basic reproduction number $R_0$. There are general methods for estimating $R_0$ directly (23), but for HIV many of the assumptions...
usually made in estimation procedures are not fulfilled. On the other hand, estimates of incidence and/or exponential growth rates at the beginning of the HIV epidemic are more readily available and allow a more direct estimate of $R_0$. Therefore, we made use of the following relationship between the basic reproduction number and the exponential growth rate:

$$\frac{1}{R_0} = \int_0^\infty e^{-\lambda t} g(t) \, dt. \quad [1]$$

Here, $g(t)$ denotes the generation time distribution, i.e., the probability density for the interval between the time of infection of an index and its secondary cases. The generation time distribution can be computed in terms of the parameters describing the progression through stages of infection and the transmission rates per stage (Fig. 2C). This means that if we can estimate the exponential growth rate $\lambda$ from data, the above formula gives us an estimate of $R_0$ and therefore for $\lambda$. Once an estimate for $\lambda$ is obtained, we have a formula for the elimination threshold depending on parameters $\lambda$ and $\psi$, which are determined by the program specifications, i.e., screening and treatment uptake and dropping out of treatment (SI Appendix). We plotted our results in terms of annual treatment uptake and annual dropout rate. To translate those results into results on coverage of treatment, we plotted the coverage as a function of annual treatment uptake for various values of the dropout rate. To do this, we assumed that coverage is at steady state with a constant force of infection.

So far, we have assumed that all underlying complexity of transmission patterns (i.e., heterogeneity in risk groups and contact patterns) can be subsumed under one parameter $\lambda$ that links infectivity and exponential growth rate. To translate this assumption into a statement on elimination, we then start by assuming that these underlying transmission patterns have not substantially changed in between the onset of the epidemic (from when we derive an estimate of $\lambda$) and the elimination phase. In other words, we assumed that risk behavior patterns and main risk groups have remained stable over the time of the epidemic. We then assessed elimination prospects with respect to the estimated survival, i.e., the probability to still be alive, to-
the transmission potential of HIV in a population under treatment with given treatment parameters, relative to the transmission potential of the untreated population. In other words, $R_f$ describes the relative transmission potential in a treated population compared with the untreated population assuming that all is equal except the availability of treatment. $R_f$ is always below 1 and is plotted in Fig. 4B as a function of annual treatment uptake and dropout rate, respectively, whereas the respective other parameter is kept constant. If an estimate of the exponential growth rate or of $R_0$ is available, the required annual treatment uptake needed for elimination given a certain dropout rate can be found at the intersection of $R_f$ with the constant level $1/R_0$. Fig. 4C then shows how coverage depends on annual treatment uptake for different dropout rates.

We investigated how the elimination threshold quantity $R_e$ changes with decreasing infectivity of primary infection (Fig. 5). The results shown here are computed for an exponential growth rate of 0.273/y as reported by Walker et al. (36) for sub-Saharan African countries and a 5% dropout rate per year. If infectivity is set at its baseline values (Fig. 2B), we found that annual treatment uptake of more than 70% is needed for elimination which corresponds to a coverage above 85%. Lower values of treatment uptake suffice when infectivity is shifted to later stages of infection.

**Elimination Thresholds Estimated from Exponential Growth Rates.** For some studies we found a discrepancy between the estimates for $r$ and $R_0$ (SI Appendix, Table S4) according to our disease progression model. In those studies, the estimated values of $R_0$ are higher than would be expected from the reported exponential growth rate, possibly due to effects of underlying contact patterns. Interesting are the results reported in ref. 33, where exponential growth rates were estimated from genetic data for two HIV-1 subtypes. The two subtypes differed in their growth rates. If an infectious duration of 3 y was taken to compute the basic reproduction number, the estimates were similar to ours (SI Appendix, Table S4). Adopting a duration of infection of 10 y, the resulting estimates were much higher and inconsistent with ours. The underlying assumption in ref. 33 was that the probability of transmission did not change during the infectious period. When using reported exponential growth rates and model-derived values of $R_0$ as a basis for comparison, we found that the values for $R_0$ all lie within the range of 2.0 and 4.5 regardless of geographical location, population, and methodology of the study. Elimination thresholds separate the parameter space defined by annual treatment uptake and dropout rates into the regions above the curves where elimination is possible, and below the curves, where elimination is not possible (Fig. 4A). With increasing $R_0$, the conditions for elimination become more stringent. For the $R_0$ values from SI Appendix, Table S1, elimination is possible for populations with $R_0$ slightly above 2.0, increasingly difficult as $R_0$ values approach 3.0, and impossible for populations with $R_0 > 3.0$. However, even for the population with the lowest estimate of $r$ (36), annual treatment uptake of more than 65% is required at a dropout rate of 5% corresponding to a coverage of more than 85%. If transmission probability under treatment is lower than our baseline value of 0.01 the elimination thresholds become more favorable (SI Appendix, Fig. S5). Lowering the reproduction rate by additional interventions shifts the thresholds downward; we computed the additional effort required (in terms

**Fig. 4.** (A) Elimination threshold $R_e$ as a function of annual treatment uptake and dropout rate for a population with an epidemic growth rate $r$ of 0.273/y. (B) Relative threshold quantity $R_f$ as a function of annual treatment uptake (blue) and dropout rate (red). The respective other parameter is kept constant: the blue curve assumes a dropout rate of 5%; the red curve assumes annual treatment uptake of 80%. Horizontal lines show where the elimination threshold is reached for different values of the exponential growth rate. The uppermost line denotes the threshold for $r = 0.273$, the lines below for multiples of that value. (C) Relationship between annual treatment uptake and the coverage at a steady state for different values of the dropout rate.

**Fig. 5.** Impact of distribution of infectivity during the infectious period on the elimination threshold. The infectivity distribution from Fig. 2B leads to the upper red curve. Then infectivity is shifted stepwise from primary to chronic infection while retaining a constant total infectivity (coloring of curves shifting from red to green). With infectivity shifting to later stages of infection the required annual treatment uptake for elimination (dots) decreases. The epidemic growth rate is again set to 0.273/y and dropout rate is assumed to be 5% per year.
of lowering the transmission rate) to reach elimination for a given treatment rate and dropout rate (SI Appendix, Fig. 5f).

**Heterogeneous Populations.** For the type of contact pattern considered here, namely proportionate mixing among different subgroups of the population with differing contact rates, the heterogeneity in contact rates does not impact on the above analysis. In other words, the relationship between basic reproduction number and elimination threshold is not affected by heterogeneity. This result holds for heterogeneity in contact rates between individuals and certain forms of mixing. It does not carry over to situations where there is heterogeneity in how contacts are spaced in time, for example if there are long-term monogamous partnerships or if high risk occurs in episodic bursts (37, 38).

If there are differential changes in levels of risk between different risk groups, the relationship between the basic reproduction number and the elimination threshold changes. We used data from men who have sex with men (MSM) in the United Kingdom (39) as a basis for considering an example of a population where 80% have a low partner change rate (defined to be one new partner per year) and the remaining 20% have a higher rate (five new partners per year). We assumed an epidemic growth rate of 0.273 as in ref. 36, which corresponds to an $R_0$ of around 2. If intervention succeeds in lowering the partner change rate of the 20% high-risk population, elimination will become more feasible, even if 80% of the population does not change their behavior. If the basic reproduction number is around 2 at the onset of the epidemic, a reduction of 50% in the partner change rate of the high-risk group brings elimination within reach (Fig. 6b). If the basic reproduction number is around 3, as is estimated for MSM populations in Western countries, more effort is needed in reducing risk levels in the high-risk group (SI Appendix, Fig. S7). This reflects the fact that the basic reproduction number is largely determined by small high-risk subgroups in the population. Note that we assume here that estimates of $R_0$ from data—such as genetic sequence data—already implicitly incorporated heterogeneity in contact rates.

If there is heterogeneity between different strains or subtypes of the virus with respect to transmission probability and progression rates, the analysis can be made strain-specific. The overall basic reproduction number is then determined by the strain or subtype with the highest reproduction number.

**Discussion**

We designed a model reminiscent of Granich’s model, but better suited to describe the natural history and variable infectivity of HIV infection, to analyze the elimination threshold and its dependence on treatment-related variables (annual treatment uptake, dropping out of treatment, and reduction of infectiousness in treated persons) and transmission rate. The transmission parameter was estimated from exponential growth rates extracted from the literature. Assuming that exponential growth rates characterize the risk potential of a population, we assessed whether or not elimination is feasible in a population with a given growth rate. We found that elimination is only feasible in populations with very low basic reproduction number (around 2.0) and high annual treatment uptake, or if additional interventions substantially reduce the reproduction number.

In our modeling approach, basic reproduction number and elimination threshold both depend linearly on the transmission parameter, suggesting that both quantities are related to underlying contact patterns in the same way. This is confirmed by analysis of a model with different sexual activity levels and proportionate mixing. Further generalization of contact heterogeneity is possible along the same lines; however, for more general mixing patterns thresholds can only be computed numerically. Therefore, the ratio of basic reproduction number and elimination threshold is independent of transmission patterns. Moreover, the relationship between $R_0$ and exponential growth rate is independent of the underlying model structure and solely reflects the distribution of infectivity over the infectious period. Our only assumption regarding contact patterns is that the rate of encountering new susceptible partners is time homogeneous. This may be violated for populations where a majority of individuals are in long-lasting monogamous partnerships or for so-called episodic risk (37). Including heterogeneity with respect to timing of contacts is more difficult and will be the subject of future research where we plan to combine our approach with models taking partnership duration into account as in refs. 40 or 41.

Our analysis—conducted for a model with four stages of infection and parameter values comparable to those in ref. 2—extends the analysis of Hollingsworth et al. by taking varying infectivity into account. Incorporating these more realistic assumptions hugely influenced the results on feasibility of elimination. Our results demonstrated that assuming a uniform distribution of infectivity as in ref. 2 leads to much more optimistic expectations on the prospects of elimination. There is a debate on whether the estimates used in our model and originally reported by Hollingsworth exaggerate the infectivity of primary infection (14, 42), but we are reliant upon them in the absence of better alternatives. A further limitation is that these estimates were obtained from heterosexual couples and may therefore not be applicable for MSM or other risk populations. However, they represent the only relevant information available at this point. Assuming that Hollingsworth’s estimates correctly quantify the infectivity of primary infection, we conclude that in populations with a basic reproduction number $>3$ elimination is not feasible unless additional other interventions succeed in vastly reducing transmission or if substantial reduction of risk behavior has already occurred in the highest risk groups. If the basic reproduction number is 2.62, as computed on the basis of the reported epidemic doubling time in South Africa (2), elimination will be very hard to achieve taking into account the high annual treatment uptake of at least 80% and low dropout rate needed, which correspond to a coverage of more than 90%. In comparison, the World Health Organization estimates that by late 2010 in Africa
49% (confidence interval 46–52%) of people eligible for treatment were receiving ART (43).

A requirement for the application of the modeling approach is the availability of information on the exponential growth rate of the epidemic in its initial phase. The rationale of this approach can be compared with the concept of the critical vaccination coverage for vaccine-preventable diseases, where information from prevaccination epidemiology is used to determine the vaccination coverage needed for elimination of a disease in the future. We suggest the use of HIV sequence data to estimate early growth rates of the epidemic in specific populations. Some such estimates are available from coalescent analysis and may become more reliable if demographic processes of the host population are also taken into account. We expect that rapid development of sequencing methods and mathematical tools to use sequence data to gain insight into infection dynamics will become more important for public health in the future (45).

There are various directions in which the modeling approach laid out here can be extended. Various other types of population heterogeneity can be taken into account, such as age dependency and specific transmission risk groups. Also, if there is evidence for differences in transmission potential between different HIV subtypes, the model could be applied to those subtypes separately if estimates for exponential growth rates can be obtained. Such extensions would be useful for analyzing situations where treatment coverage is heterogeneously distributed or where treatment is targeted to specific population subgroups or HIV subtypes. The main conclusions from the work presented here are that elimination as a threshold phenomenon can be studied using information from the beginning of the epidemic, and that information from phylogenetic analyses may be helpful for assessing the prospects of elimination. More research is needed to derive quantitative predictions that can be used for the design of effective and cost-effective intervention strategies.

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Supplementary Information
Prospects of elimination of HIV by test and treat strategy

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This document describes the details of the mathematical model and analysis for the derivation of the elimination threshold. The underlying rationale of relating the basic reproduction number $R_0$ to efforts needed for elimination are analogous to arguments used for vaccine preventable infectious diseases, where the basic reproduction number determines a critical vaccination coverage needed for elimination of the disease [1].

1 The model

We used ideas put forward in figure 2 of [2], but generalized the model to include a series of $n$ infectious compartments of varying durations. Our model is described by the following system of differential equations

$$
\begin{align*}
\frac{dS}{dt} &= \beta N - \lambda_0 SJ - \mu S \\
\frac{dI_1}{dt} &= \lambda_0 SJ - \mu I_1 - \rho_1 I_1 - \tau I_1 + \phi A_1 \\
\frac{dI_k}{dt} &= \rho_{k-1} I_{k-1} - \mu I_k - \rho_k I_k - \tau I_k + \phi A_k \\
\frac{dA_1}{dt} &= \tau I_1 - \mu A_1 - \sigma_1 A_1 - \phi A_1 \\
\frac{dA_k}{dt} &= \tau I_k + \sigma_{k-1} A_{k-1} - \sigma_k A_k - \mu A_k - \phi A_k
\end{align*}
$$

with $k = 2, \ldots, n$. Here $S$ denotes the susceptible population, $I_k$ infected untreated persons in stage $k$ of the infection, and $A_k$ infected persons under ART in stage $k$ of infection. $\beta$ is a birth rate, $\mu$ the rate of background mortality, $\rho_k$ the rate of progression from stage $k$ to stage $k+1$ for untreated individuals, $\sigma_k$ is the progression rate for treated individuals, and $\lambda_0$ is the transmission rate parameter. The parameter $\tau$ describes the rate of taking up treatment, and $\phi$ the rate of dropping out of treatment. The rates $\rho_n$ and $\sigma_n$ describe disease related mortality in the last stage of infection.

The force of infection is determined by

$$J = \sum_{k=1}^{n} (h_k I_k + \epsilon A_k)$$

where the $h_k$ describe the infectiousness of stage $k$ and $\epsilon$ quantifies the reduced infectiousness due to antiretroviral treatment.
We standardized the model equations by dividing by the population size and introducing a scaled parameter

$$\lambda = N\lambda_0.$$ 

The scaled variables $s, i_k, \text{ and } a_k$ were defined as $s = S/N, i_k = I_k/N$ and $a_k = A_k/N$. We get

$$\frac{ds}{dt} = \beta - \lambda sj - \mu s$$

$$\frac{di_1}{dt} = \lambda sj - \mu i_1 - \rho i_1 - \tau i_1 + \phi a_1$$

$$\frac{di_k}{dt} = \rho_{k-1}i_{k-1} - \mu i_k - \rho_i i_k - \tau i_k + \phi a_k$$

$$\frac{da_1}{dt} = \tau i_1 - \mu a_1 - \sigma_1 a_1 - \phi a_1$$

$$\frac{da_k}{dt} = \tau i_k + \sigma_{k-1}a_{k-1} - \sigma k a_k - \mu a_k - \phi a_k$$

with $k = 2, ..., n$ and the force of infection determined by

$$j = \sum_{k=1}^{n} (h_k i_k + \epsilon a_k)$$

A flow scheme of the model is shown in figure 1.

![Figure 1: Flow scheme of the model](image-url)
For this model the basic reproduction number in the situation without treatment was computed as

$$R_0 = \lambda \left( \sum_{k=1}^{n} h_k \prod_{s=1}^{k} \frac{\rho_{s-1}}{\rho_s + \mu} \right) \quad (1)$$

with $\rho_0 = 1$. We denoted the total infectiousness over the entire infectious period by

$$H = \left( \sum_{k=1}^{n} h_k \prod_{s=1}^{k} \frac{\rho_{s-1}}{\rho_s + \mu} \right),$$

then $R_0 = \lambda H$. The basic reproduction number gives us a relationship between the transmission parameter $\lambda$ and the exponential growth rate $r$ as detailed in section 5.

The Granich model [2] is recovered by setting $n = 4$ and assuming that $\rho_k = \rho$ and $\sigma_k = \sigma$ for all $k$. We ignored here the complexities of the Granich model that have to do with density dependence of the transmission parameter, since here we were only interested in the thresholds of the system and not in its transient behaviour.

### 2 The elimination threshold

We assumed that without treatment the reproduction number is larger than 1. Therefore, the infection will reach an endemic equilibrium for $t \rightarrow \infty$. As our model is a variant of the SIR model, this follows from standard theory [3]. In the presence of treatment the existence of the endemic steady state depends on the values of the parameters $\tau$ and $\phi$. The elimination threshold is defined as the level of treatment above which the infection can no longer persist in endemic steady state. It can be derived from the reproduction number in the presence of treatment, which we will denote by $R_e$. We refer to $R_e$ as the elimination threshold quantity. Elimination will occur if $R_e < 1$. Therefore $R_e = 1$ defines the elimination threshold.

To compute $R_e$, we used the methods introduced in [4, 5] to decompose the next generation matrix into a product of a matrix $T$ describing transmission and the inverse of a matrix $\Sigma$ describing all transitions. In our case these matrices have the dimension $2n \times 2n$, where $n$ is the number of infection stages. The transmis-
The transmission matrix $T$ is given by
\[
T = \lambda \begin{pmatrix}
h_1 & \epsilon & h_2 & \epsilon & \ldots & h_n & \epsilon \\
0 & 0 & 0 & 0 & \ldots & 0 & 0 \\
& \ldots & \ddots & \ldots & \ddots & \ldots & \ddots \\
0 & 0 & 0 & 0 & \ldots & 0 & 0
\end{pmatrix}
\]
and $\Sigma$ is composed from submatrices $\Sigma_{1k}$ and $\Sigma_{2k}$ as
\[
\Sigma = \begin{pmatrix}
\Sigma_{11} & 0 & 0 & 0 & \ldots & 0 \\
\Sigma_{21} & \Sigma_{12} & 0 & 0 & \ldots & 0 \\
0 & \Sigma_{22} & \Sigma_{13} & 0 & \ldots & 0 \\
0 & 0 & \Sigma_{23} & \Sigma_{14} & \ldots & 0 \\
& \ddots & \ddots & \ddots & \ddots & \ddots \\
0 & 0 & 0 & \ldots & 0 & \Sigma_{1,n-1} \\
0 & 0 & 0 & \ldots & 0 & \Sigma_{2,n-1} & \Sigma_{1n}
\end{pmatrix}
\]
with
\[
\Sigma_{1k} = \begin{pmatrix}-\mu - \rho_k - \tau & \phi \\
\tau & -\mu - \phi - \sigma_k
\end{pmatrix}
\]
and $\Sigma_{2k} = \begin{pmatrix}\rho_k & 0 \\
0 & \sigma_k
\end{pmatrix}$

The matrix $\Sigma$ contains $n$ blocks of $\Sigma_1$ and $n-1$ blocks of $\Sigma_2$. Now we can define $R_e$ as the largest eigenvalues of $K = -T\Sigma^{-1}$. The matrix $K$ has rank 1 and therefore $n-1$ eigenvalues equal zero, there is only one non-zero eigenvalue. This eigenvalue can be computed explicitly as a function of the parameters for arbitrary $n$, however the expressions become large for large $n$. It is reassuring that for $\tau = 0$ this eigenvalue equals the basic reproduction number as defined above. We investigated how $R_e$ depends on various parameters and under what conditions $R_e < 1$. For $n = 1$ the elimination threshold quantity is given by
\[
R_e = \lambda \frac{\epsilon \tau + h_1(\mu + \phi + \sigma_1)}{\mu(\mu + \phi + \tau + \rho_1 + \sigma_1) + \phi \rho_1 + \sigma_1(\tau + \rho_1)}
\]
For larger $n$ the expression becomes long and does not convey any insight, so we do not report it here.

As both $R_0$ and $R_e$ depend linearly on $\lambda$ we also considered the ratio of the two
quantities

\[ R_f = \frac{R_e}{R_0} \]

It is clear that \( R_f \leq 1 \) for all values of \( \tau \) and \( \phi \). Furthermore, \( R_f \) is independent of the details of the transmission process, but only depends on parameters specifying disease progression and infectivity. Therefore, \( R_f \) is independent of the population under consideration and is only determined by infection related parameters.

3 Natural history

Transitions between disease stages are described by transition rates \( \rho_k \) and \( \sigma_k \) for the untreated and treated populations, respectively. We denote by \( f_{jk}^j(t) \) the probability densities of the times taken to move through the first \( k \) stages of disease, where the superscript \( j = i, a \) refers to the untreated and treated populations, respectively. Then \( F_{jk}^j(t) = 1 - \int_0^t f_{jk}^j(s)ds \) is the probability that the time to move through the first \( k \) stages of untreated and treated infections, respectively, is \( > t \).

For \( k = n \) the \( F_{jk}^j(t) \) describe the probability of surviving until time \( t \) from infection. We can now compute the probability of an infected individual to be in stage \( k \) of infection at time \( t \) after infection as

\[ F_{jk}^j(t) - F_{jk-1}^j(t) = \int_0^t f_{jk-1}^j(s)ds - \int_0^t f_{jk}^j(s)ds \]

for \( j = i, a \). We set \( F_{jk}^j(0) = 0 \) for \( t > 0 \).

For Granich’s model it was assumed that the sojourn times in respectively all untreated and all treated stages are equal (i.e. \( \rho \) and \( \sigma \) are the same for all \( k \)). The distribution of time taken to move through \( k \) stages of infection for untreated and treated individuals is then given by a Gamma distribution with parameters \( k \) and \( 1/\rho \)

\[ f_k^i(t) = t^{k-1} \frac{e^{-t\rho}}{\rho^k \Gamma(k)} \]

for \( k = 1, \ldots, n \) and similarly \( f_k^a(t) \) for the treated population with parameters \( k \) and \( 1/\sigma \).

For the more general case of \( n \) infection stages with varying exponentially distributed sojourn times the probability density of the time \( t \) taken to move through
\( k \) stages of infection is given by

\[
 f_k^j(t) = \prod_{l=1}^{k} (\rho_l + \mu) \sum_{l=1}^{k} \frac{e^{-(\rho_l + \mu)t}}{\prod_{j=1, j \neq l}^{k} (\rho_j - \rho_l)}
\]  

(5)

and again similarly \( f_k^u(t) \) for the treated population, where the \( \rho_l \) are replaced by the \( \sigma_l \).

In our numerical computations we chose \( n = 4 \). The transition rates between infection stages \( \rho_k \) and \( \sigma_k \) are chosen such that they reproduce survival distributions as reported by the CASCADE study [6, 7]. Estimates of \( \rho_1 \) and \( \rho_2 \) were derived through a CD4 based multistate model of HIV progression using longitudinal data from the CASCADE collaboration [8]. Table 1 gives these expected times spent in each disease stage expressed in years, both pre and post the ART era. The expected time to death is 11.1 years in the pre ART era and 61.0 years in the post ART era. We interpreted CD4 count \( > 900 \) as primary infection. From these times we computed progression rates between states.

**Table 1: Expected time in each state for any seroconverter, in both the pre- and post-1996 eras. All times are measured in years.**

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>&gt;900</th>
<th>700-900</th>
<th>500-700</th>
<th>350-500</th>
<th>350-200</th>
<th>&lt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected time in state, pre-96</td>
<td>0.271</td>
<td>0.617</td>
<td>1.67</td>
<td>2.17</td>
<td>2.16</td>
<td>1.69</td>
</tr>
<tr>
<td>Expected time in state, post-96</td>
<td>8.21</td>
<td>10.7</td>
<td>17.3</td>
<td>14.6</td>
<td>8.38</td>
<td>1.97</td>
</tr>
</tbody>
</table>

The parameter values used in the simulations are given in Table 2. To convert the parameters \( \tau \) and \( \phi \) into treatment coverage and drop out percentages we used the relationship \( P(t) = 1 - \exp(-rate \times t) \) for the probability that an event takes place in the time interval \([0, t] \). This implies that rates have to go to infinity to achieve a probability \( P(t) = 1 \) for any finite \( t \).

### 4 Distribution of infectivity

Infectivity is defined as the rate of transmission per time unit from an infectious person in a contact with a susceptible person. Infectivity may depend on viral load and therefore changes during the course of an infection. For HIV/AIDS it is known that infectivity is high during the primary phase of the infection and low during chronic infection [9]. In the late stage of infection when symptoms become apparent, infectivity is also higher [11], however, in the late stage of AIDS
Table 2: Parameter definitions and default values. All rates are expressed in 1/year.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Default value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Background mortality rate</td>
<td>0.018/yr</td>
<td>[2]</td>
</tr>
<tr>
<td>$\rho_k$</td>
<td>Transition rate per year from stage $k$ to stage $k + 1$ for untreated individuals</td>
<td>$\rho_1 = 1/0.271$, $\rho_2 = 1/8.31$, $\rho_3 = 1/1.184$, $\rho_4 = 1/1.316$</td>
<td>[6], [8],[10]</td>
</tr>
<tr>
<td>$\sigma_k$</td>
<td>Transition rate per year from stage $k$ to stage $k + 1$ for treated individuals</td>
<td>$\sigma_1 = 1/8.21$, $\sigma_2 = 1/54.0$, $\sigma_3 = 1/2.463$, $\sigma_4 = 1/2.737$</td>
<td>[7],[8]</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Rate per year of moving from the untreated to the treated population</td>
<td>Range 0 – 100%</td>
<td>-</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Rate per year of moving from the treated to the untreated population</td>
<td>Range 0 – 100%</td>
<td>-</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Infectivity of individuals under treatment</td>
<td>0.01</td>
<td>[2]</td>
</tr>
<tr>
<td>$h_k$</td>
<td>Infectivity of untreated individuals in stage $k$ of infection per year</td>
<td>$h_1 = 2.76$, $h_2 = 0.106$, $h_3 = 0.642$, $h_4 = 0.0$</td>
<td>[10]</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Rate of transmission between susceptible and infected individuals</td>
<td>Estimated from $R_0$ or exponential growth rate $r$</td>
<td>-</td>
</tr>
</tbody>
</table>
it may in practice decrease to low levels, because illness precludes sexual activity. Infectivity was estimated for various stages of HIV infection from discordant couples studies by Hollingsworth and colleagues[10]. We used their estimates as baseline values for the $h_i$ in the model with four stages. To investigate the impact of different assumptions on how infectivity is distributed over the infectious period, we then varied the distribution as follows. We introduced the parameters $w_1$ and $w_2$ with $0 \leq w_1 \leq 1$ and $w_2 \geq 1$. We then analysed infectivity distributions with $\tilde{h}_1 = w_1 h_1$ and $\tilde{h}_2 = w_2 h_2$ with the condition that $\tilde{H} = H$, i.e. that the total infectivity during the entire infectious period remains constant. The infectivity during the later stages of infection remained unchanged, i.e. $\tilde{h}_i = h_i$ for $i > 2$, because there is less controversy about their values and impact on transmission dynamics.

Table 3: Exact values of $h_1$ and $h_2$ used in figure 5 of the main text.

<table>
<thead>
<tr>
<th>percent baseline value</th>
<th>$h_1$</th>
<th>$h_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>2.76</td>
<td>0.106</td>
</tr>
<tr>
<td>90</td>
<td>2.484</td>
<td>0.116</td>
</tr>
<tr>
<td>80</td>
<td>2.208</td>
<td>0.127</td>
</tr>
<tr>
<td>70</td>
<td>1.932</td>
<td>0.137</td>
</tr>
<tr>
<td>60</td>
<td>1.656</td>
<td>0.147</td>
</tr>
<tr>
<td>50</td>
<td>1.380</td>
<td>0.157</td>
</tr>
<tr>
<td>40</td>
<td>1.104</td>
<td>0.168</td>
</tr>
<tr>
<td>30</td>
<td>0.828</td>
<td>0.178</td>
</tr>
<tr>
<td>20</td>
<td>0.552</td>
<td>0.188</td>
</tr>
<tr>
<td>10</td>
<td>0.276</td>
<td>0.199</td>
</tr>
</tbody>
</table>
5 **Exponential growth rate, $R_0$ and doubling time**

The basic reproduction number $R_0$ and the exponential growth rate are related via the equation

$$
\frac{1}{R_0} = \int_0^\infty e^{-rs} g(s) ds
$$

where $g(s)$ denotes the generation time distribution, i.e. the probability density for the interval between the times of infection of an index and his secondary cases [12, 13]. In our model the generation time distribution is related to the infectivity during the different stages of infection as follows.

$$
g(s) = \frac{1}{H} \sum_{k=1}^n h_k (F_k^i(s) - F_{k-1}^i(s)).
$$

We get the following relationship between the basic reproduction number, the exponential growth rate and the infectivity

$$
\frac{1}{R_0} = \left( \sum_{k=1}^n h_k \prod_{l=1}^{k} \frac{\rho_l-1}{\rho_l} \right) \int_0^\infty e^{-rs} \sum_{k=1}^n h_k (F_k^i(s) - F_{k-1}^i(s)) ds
$$

(6)

If the exponential growth rate $r$ is known from data, $R_0$ can be inferred assuming
that the natural history parameters $\rho_k$ and the relative infectiousness parameters $h_k/H$ can be estimated from data and are the same for all populations. The estimate for $R_0$ can then be used to quantify $\lambda$ by combining equations (1) and (6). We get

$$\lambda = \frac{1}{\int_0^{\infty} e^{-rs} \sum_{k=1}^{n} h_k(F'_k(s) - F'_k(s)) ds}$$

This expression is then used in the computation of $R_e$ (see equ. (4)). We then define the elimination threshold by setting $R_e = 1$. This is an implicit equation depending on the parameters $\tau$ and $\phi$. Solving the equation in the $\tau - \phi$-plane gives the boundary curves above which elimination is possible (see figure 6 of main text).

The doubling time of an epidemic is related to the exponential growth rate by $d = \log(2)/r$. Estimates for $R_0$, $r$, and $d$ for various populations extracted from the literature and calculated using our model are given in Table 4.

## 6 Heterogeneous contact rates

We extended the model to incorporate heterogeneity in contact rates by subdividing the population into $m$ groups of size $q_l$ with contact rates $c_l$, $l = 1, \ldots, m$. Here $q_l \leq 1$ for all $l$ and $\sum_{l=1}^{m} q_l = 1$. We assumed that disease progression is independent of contact rates and equal for all subgroups. Furthermore, we assumed proportionate mixing between groups. The model equations are then given by

$$\frac{ds_l}{dt} = \beta - \lambda s_l c_l j - \mu s_l$$

$$\frac{di_{l1}}{dt} = \lambda s_l c_l j - \mu i_{l1} - \rho_1 i_{l1} - \tau i_{l1} + \phi a_{l1}$$

$$\frac{di_{lk}}{dt} = \rho_{k-1} i_{l,k-1} - \mu i_{lk} - \rho_k i_{lk} - \tau i_{lk} + \phi a_{lk}$$

$$\frac{da_{l1}}{dt} = \tau i_{l1} - \mu a_{l1} - \sigma_1 a_{l1} - \phi a_{l1}$$

$$\frac{da_{lk}}{dt} = \tau i_{lk} + \sigma_1 a_{l,k-1} - \sigma_k a_{lk} - \mu a_{lk} - \phi a_{lk}$$

with $k = 2, \ldots, n$ and $l = 1, \ldots, m$. With the notation

$$C = \sum_{l=1}^{m} c_l q_l$$
we can write the force of infection as

$$j = \frac{1}{C} \sum_{l=1}^{m} c_l q_l (\sum_{k=1}^{n} h_k i_{lk} + \epsilon a_{lk}).$$

As before we can define matrices $\bar{T}$ and $\bar{\Sigma}$ to compute the elimination threshold. Now the matrix $\bar{T}$ will consist of $m^2$ blocks $T_{kl}$ describing the transmission to the $k$-th subgroup from the $l$-th subgroup of the population. The $T_{kl}$ are given by

$$T_{kl} = \frac{\lambda}{C} \left( \begin{array}{cccccc}
  h_1 c_k c_l q_l & \epsilon c_k c_l q_l & h_2 c_k c_l q_l & \epsilon c_k c_l q_l & \ldots & h_n c_k c_l q_l & \epsilon c_k c_l q_l \\
  0 & 0 & 0 & 0 & \ldots & 0 & 0 \\
  \ldots & \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
  0 & 0 & 0 & 0 & \ldots & 0 & 0 \\
\end{array} \right)$$

Then we get

$$\bar{T} = (T_{kl})_{k,l=1,\ldots,m}$$

The matrix $\bar{\Sigma}$ will now consist of $m$ blocks of identical sub-matrices $\Sigma$ as defined in equ(3):

$$\bar{\Sigma} = \left( \begin{array}{cccccc}
  \Sigma & 0 & 0 & 0 & \ldots & 0 \\
  0 & \Sigma & 0 & 0 & \ldots & 0 \\
  0 & 0 & \Sigma & 0 & \ldots & 0 \\
  0 & 0 & 0 & \Sigma & \ldots & 0 \\
  \ldots & \ldots & \ldots & \ldots & \ldots & \ldots \\
  0 & 0 & 0 & \ldots & 0 & \Sigma \\
  0 & 0 & 0 & \ldots & 0 & \Sigma \\
\end{array} \right)$$

The reason is that disease progression is the same in all subgroups. So the heterogeneity in contact rates affects transmission as quantified in $T$, but not progression through different stages as described by $\Sigma$. As before, the matrix $K = \bar{T} \bar{\Sigma}^{-1}$ has rank 1 and the elimination threshold is given by the dominant eigenvalue of $K$. The analysis carries over, because of our choice of proportional mixing. It can be generalized to all situations, where mixing is separable [3]. So for example, one could perform the same analysis on an age-structured model, where mixing between age classes is separable mixing (i.e. a product of contact rates of different age classes).
7 Sensitivity analyses

7.1 Faster progression to AIDS

We considered the situation that progression through chronic infection is faster than in our base case. We assumed that the time to AIDS is around 4.5 years instead of 8.58 years as used in our base case analysis. The survival to death is then 7.3 years. As infected individuals then have less time to transmit before death, the basic reproduction number is lower for the same value of the exponential growth rate. In other words, to obtain the same exponential growth rates, transmissions are shifted more towards early HIV infection. The fraction of transmissions occurring in the first year after infection is now 43% (as opposed to 36% in the base case). This implies that the same speed of spread can be reached with a lower $R_0$. Because of a shorter infectious period, the prospect of elimination becomes somewhat more favorable (Figure 3).

![Figure 3: Relative threshold quantity $R_f$ for a mean survival to death of 7.3 years as a consequence of faster progression to AIDS. $R_f$ is plotted as a function of annual treatment uptake (blue) and dropout rate (red). The respective other parameter is kept constant: the blue curve assumes a dropout rate of 5%, the red curve assumes annual treatment uptake of 80%. The horizontal lines show where the elimination threshold is reached for different values of the exponential growth rate. The uppermost line denotes the threshold for $r=0.273$, the lines below for multiples of that value.](image-url)

However, the consequence is also that elimination thresholds comparable to the
base case are now in place for lower values of $R_0$, i.e. we need an annual treatment uptake of 60% at a dropout rate of 5% already for an $R_0 = 1.7$ (figure 4).

![Graph showing the elimination threshold for the model with a mean survival to death of 7.3 years. Similar requirements for elimination as in the base case hold, but now for lower values of $R_0$.]

**Figure 4**: The elimination threshold for the model with a mean survival to death of 7.3 years. Similar requirements for elimination as in the base case hold, but now for lower values of $R_0$.

### 7.2 Lower transmission probability under treatment

If the transmission probability under treatment is lower than the baseline value, prospects of elimination become more favorable.
Figure 5: Elimination threshold as function of annual treatment uptake and dropout rate for various values of the basic reproduction number R0. The two curves describe the threshold for R0 = 2.0 and for R0 = 3.0. For parameter combinations above the lines, elimination is possible, for combinations below the curve it is not possible. We assumed here that probability of transmission under treatment is $\epsilon = 0.005$.

### 7.3 Additional intervention efforts

If the test and treat strategy is implemented in combination with other interventions, elimination can become easier to achieve depending on the effectiveness of the additional interventions. If one considers interventions that impact on transmission, one may describe their effect as a reduction of the transmission parameter $\lambda$. Lowering the reproduction rate by additional interventions shifts the thresholds downwards; we computed the additional effort required in terms of lowering the transmission rate $\lambda$ to reach elimination for a given treatment rate and dropout rate (Figure 7). The additional intervention effort was quantified as the factor by which $\lambda$ had to be reduced to bring $R_e$ below 1 given a specific annual uptake rate of treatment and a given dropout rate.
Figure 6: The additional intervention effort needed to reach the elimination threshold is shown as a function of the basic reproduction number for different values of annual treatment uptake ranging from 0 (red) to 100% (green) at a dropout rate of 5% per year. The additional effort is measured in proportion reduction of the transmission parameter $\lambda$.

### 7.4 Heterogeneous population and higher exponential growth rate

If epidemic growth rates at the onset of the epidemic are high, a substantial reduction of risk behaviour in the high risk sexual activity group is needed to bring the elimination threshold into a region where elimination might be achievable. In the example of figure 7, a reduction of partner change rates by at least 40% is needed before a realistic choice of annual treatment uptake and dropout rate may still lead to elimination.
Figure 7: Elimination threshold in a heterogeneous population, where partner change rates declined between onset of the epidemic and start of prevention test and treat intervention. The epidemic growth rate at onset of the epidemic is 0.834 per year. Elimination thresholds are shown as function of annual treatment uptake and dropout rate for various reduction percentages of the partner change rates of the high risk population. For parameter combinations above the lines, elimination is possible, for combinations below the curve it is not possible.

The analysis was carried out in Mathematica 8.0. The Mathematica notebook is available from the authors on request.
Table 4: Estimates of basic reproduction number $R_0$, exponential growth rate $r$, and doubling time $d$, for various populations. Data extracted from the literature and calculated from our model. In black bold face are numbers as reported in the original articles; in red numbers as reported in the original articles, which, according to our model, are inconsistent with black numbers from the same papers; in blue values computed by our model, based on either the reported $d$, $r$ or $R_0$.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Population</th>
<th>Exponential growth rate $r$ (1/yr)</th>
<th>Basic reproduction number $R_0$</th>
<th>Epidemic doubling time $d$ (yrs)</th>
<th>Data type; Estimation method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>General population (mainly heterosexual)</td>
<td>-</td>
<td>7.0</td>
<td>1.25</td>
<td>Incidence; Logistic curve fitted to prevalence Calculation based on $d$ Calculation based on $R_0$</td>
<td>[2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.866 5.13</td>
<td>2.62</td>
<td>-</td>
<td>- 0.135</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>General population (mainly MSM)</td>
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<td>3.65</td>
<td>-</td>
<td>Incidence; Backcalculation from AIDS cases Calculation based on $r$</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>3.43</td>
<td>0.603</td>
<td></td>
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</tr>
<tr>
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<td>4.08</td>
<td>-</td>
<td>Incidence; Backcalculation from AIDS cases Calculation based on $r$</td>
<td>[13]</td>
</tr>
<tr>
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<td>-</td>
<td>4.43</td>
<td>0.322</td>
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<td>General population (mainly MSM)</td>
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<td>3.67</td>
<td>-</td>
<td>Incidence; Backcalculation from AIDS cases Calculation based on $r$</td>
<td>[13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>3.499</td>
<td>0.573</td>
<td></td>
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<tr>
<td>Country</td>
<td>Risk Group</td>
<td>Incidence</td>
<td>Transmission Model</td>
<td>Sub Saharan Africa countries</td>
<td>Genetic; Fit of growth model to skyline plot</td>
<td>Genetic; Fit of growth model to skyline plot</td>
</tr>
<tr>
<td>--------------------</td>
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<tr>
<td>England &amp; Wales</td>
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<td>0.9049</td>
<td>10.05</td>
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<td>Incidence; Backcalculation from AIDS cases</td>
<td>Calculation based on $r$ Calculation based on $R_0$</td>
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<tr>
<td>Netherlands</td>
<td>MSM</td>
<td>-</td>
<td>2.39</td>
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<td>Incidence; Fit of transmission model to HIV and AIDS case data</td>
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<tr>
<td>Switzerland</td>
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<td>MSM</td>
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<td>-</td>
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<td>Calculation based on $r$</td>
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<tr>
<td>Sub Saharan Africa countries</td>
<td>General population (mainly heterosexual) subtype C</td>
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<td>-</td>
<td>2.536</td>
<td>Genetic; Fit of growth model to skyline plot</td>
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</tr>
</tbody>
</table>
### High income countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Population Group (mainly MSM and IDU)</th>
<th>subtype</th>
<th>$\mathbf{r}$</th>
<th>$\mathbf{t}$</th>
<th>$\mathbf{t}_f$</th>
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</thead>
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<td>-</td>
<td>2.49</td>
<td>1.477</td>
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<td>0.69</td>
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<td></td>
<td></td>
<td></td>
<td>2.84</td>
<td>1.00</td>
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<td></td>
<td>General population subtype B</td>
<td></td>
<td>0.136</td>
<td>1.41</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.61</td>
<td>5.097</td>
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</tr>
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<td></td>
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<td></td>
<td></td>
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<td>-</td>
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<td>1.26</td>
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References


