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Impact of sexual trajectories of men who have sex with men on the reduction in HIV transmission by pre-exposure prophylaxis

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ABSTRACT

Changes in sexual risk behavior over the life course in men who have sex with men (MSM) can influence population-level intervention efficacy. Our objective was to investigate the impact of incorporating sexual trajectories describing long-term changes in risk levels on the reduction in HIV prevalence by pre-exposure prophylaxis (PrEP) among MSM. Based on the Amsterdam Cohort Study data, we developed two models of HIV transmission in a population stratified by sexual behavior. In the first model, individuals were stratified into low, medium and high risk levels and did not change their risk levels. The second model had the same stratification but incorporated additionally three types of sexual behavior trajectories. The models assumed universal antiretroviral treatment of HIV^+ MSM, and PrEP use by high risk HIV^- MSM. We computed the relative reduction in HIV prevalence in both models for annual PrEP uptakes of 10% to 80% at different time points after PrEP introduction. We then investigated the impact of sexual trajectories on the effectiveness of PrEP intervention. The impact of sexual trajectories on the overall prevalence and prevalence in individuals at low, medium and high risk levels varied with PrEP uptake and time after PrEP introduction. Compared to the model without sexual trajectories, the model with trajectories predicted a higher impact of PrEP on the overall prevalence, and on the prevalence among the medium and high risk individuals. In low risk individuals, there was more reduction in prevalence during the first 15 years of PrEP intervention if sexual trajectories were not incorporated in the model. After that point, at low risk level there was more reduction in the model with trajectories. In conclusion, our study predicts that sexual trajectories increase the estimated impact of PrEP on reducing HIV prevalence when compared to a population where risk levels do not change.

1. Introduction

In the Netherlands, men who have sex with men (MSM) continue to be the group most affected by the HIV epidemic. Despite the increase of antiretroviral treatment (ART) uptake and shortening of time between infection and diagnosis, in 2016 68% of new HIV diagnoses were in MSM (van Sighem et al., 2017).

A recent systematic review of European studies on HIV prevention interventions among MSM has shown the most effective interventions to be condom use, peer outreach, peer-led groups, universal ART coverage and treatment as prevention (Strömdahl et al., 2015). A further reduction in HIV transmission in this population is expected to occur after the rollout of pre-exposure prophylaxis (PrEP) (Reyniers et al., 2017; Hoornenborg et al., 2017). PrEP was shown to be highly effective in preventing HIV acquisition among MSM in several trials (e.g. McCormack et al., 2016; Molina et al., 2015) and clinical practice studies (e.g. Liu et al., 2016; Volk et al., 2015). In the Netherlands, a prospective, longitudinal, open-label demonstration study named the Amsterdam pre-exposure prophylaxis (AMPrEP) project was initiated to assess the uptake and acceptability of daily versus event-driven PrEP among MSM, as part of a comprehensive HIV reduction package offered at a large sexually transmitted infections clinic (Hoornenborg et al., 2018a).

Several modelling studies demonstrated a positive effect of PrEP on

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the reduction in HIV transmission among MSM. Punyacharoensin and colleagues (Punyacharoensin et al., 2016) predicted that without PrEP HIV incidence in MSM in the UK would be unlikely to decrease substantially by the end of this decade. PrEP was shown to be cost-effective for HIV prevention among MSM in the Netherlands (Nichols et al., 2016) and other countries (Schneider et al., 2014; Juusola et al., 2012).

Although the body of literature showing a positive effect of PrEP for HIV prevention is growing, the real-world effect of nation-wide PrEP intervention is not evident. One of the difficulties in making such a prediction is the fact that changes in sexual risk behavior are likely to occur over time, which might hamper the effectiveness of population-level interventions. Population-level temporal changes in the behavior of MSM in the Netherlands since the start of the HIV epidemic have been well documented (van Griensven et al., 1989; Stolte et al., 2004; Bezemer et al., 2008, 2010; Jansen et al., 2011; Heijman et al., 2012). In the AMPrEP study, an increase in condomless anal sex acts with casual partners was observed over the first 6 months after initiation of PrEP by the Dutch MSM (Hoornenborg et al., 2018b). Individual heterogeneity in sexual behavior of MSM over time has been described by Romero-Severson et al. (2012, 2015). Recent modelling studies showed that behavioral heterogeneity due to the number of sexual partners (Rozhnova et al., 2016) and short-term changes in risk behavior (sometimes referred to as episodic risk) (Henry and Koopman, 2015) have a strong influence on the prospects of HIV elimination by test-and-treat strategies, confirming that individual-level sexual behavior is a major determinant of population-level intervention efficacy. Our recent modeling study has shown that PrEP could have a large impact on the HIV epidemic among MSM in the Netherlands if sexual risk behavior does not change (Rozhnova et al., 2018). The impact of behavioral changes on the effectiveness of PrEP intervention has received less attention in the literature, mainly because one needs good quality longitudinal data to characterize behavior change among MSM.

Recently our research group (Basten et al., 2018) studied changing patterns of sexual behavior across the life course in MSM. Using data from the Amsterdam Cohort Studies on HIV and AIDS (ACS) we identified three typical trajectories of changing sexual behavior from sexual debut onwards (Basten et al., 2018). The sexual trajectories aim to capture long-term changes in sexual behavior within the MSM population and not the secular trends in the general MSM population, so that people with a certain level of risk at sexual debut can increase or decrease their risk level over their life course. The changes we focus on in this study are slow, implying that the average duration of stay at any risk level is of the order of several years to decades. It is not clear whether these sexual behavior trajectories may undermine or enhance the impact of PrEP interventions. Therefore, the objective of this study was to investigate the impact of long-term changes in sexual risk behavior (sexual trajectories) of MSM on the reduction in HIV prevalence by PrEP in the Netherlands.

2. Material and methods

2.1. Epidemiological data

The long-term sexual behavior trajectories estimated by Basten et al. (2018) formed the basis of this study. The estimated trajectories were based on data from the ACS among MSM, which started in 1984 (van Griensven et al., 1989; Jansen et al., 2011). The ACS is a population-based open cohort study to investigate the epidemiology, psychosocial determinants, course of infection and pathogenesis of HIV. At each biannual visit, MSM are asked to fill in a questionnaire about their sexual behavior in the past six months and they are tested for HIV and sexually transmitted infections.

In this study, data was used from 803 HIV-negative MSM who participated in the ACS between 2007 and 2017, which comprised a total of 8198 visits. The average number of visits per participant was 10.2 (sd 5.9). A behavioral risk score predictive of HIV acquisition was developed, which consisted of several behavioral variables including number of receptive and insertive anal intercourse partners, condom use and group sex. The detailed information about the risk score can be found in the Supplementary Material. Subsequently, this risk score was used to study trajectories of sexual risk behavior from sexual debut with a man onwards using latent class growth mixture modeling. Three linear trajectories were identified that describe longitudinal changes in sexual behavior within the MSM population: a low risk trajectory of low sexual risk behavior with a small increase over time (90.3% of the sample); a decreasing risk trajectory (6.5%) with very high levels of sexual risk behavior during the first years after sexual debut and a decrease to low risk over time; and an increasing risk trajectory (3.3%) with low levels of sexual risk behavior in the first years after sexual debut and a rapid increase over time (see Supplementary Fig. 1 adapted from Basten et al. (2018)).

Based on these data, we developed two models of HIV transmission in a population stratified by sexual risk behavior. In the first model, the MSM population was stratified into three risk levels and individuals did not change their risk levels throughout their lives. The risk score was used to define three levels of sexual risk behavior: low risk level (risk score below 0.75), medium risk level (risk score between 0.75 and 2.5) and high risk level (risk score above 2.5) (Supplementary Fig. 1). The population fractions for the three risk levels ($l = 1, 2, 3$) were provided by calculating the proportion of visits at each risk level over all visits (Supplementary Table 1).

The second model had the same risk level stratification, but allowed for long-term changes in risk levels according to the three trajectories described above. In this model, MSM were stratified according to risk level ($l = 1, 2, 3$) and the three sexual trajectories ($b = 1, 2, 3$). Visits at which MSM in the low risk trajectory reported high risk were treated as if they were visits from MSM in the decreasing risk trajectory. This resulted in eight different strata (Supplementary Table 1). The initial population fractions of this model were calculated as the proportions of visits within each stratum over all visits. The average duration of stay at each risk level for MSM in the decreasing risk and increasing risk trajectories was based on the estimated growth parameters of the latent class growth mixture model. We assumed that behavior was stable in the years that fall outside the estimated trajectories (Supplementary Table 3). Although on the population level, MSM following the low risk trajectory always stayed at the low risk level, individual-level data of MSM in this trajectory showed that they also had periods of higher risk behavior. Therefore, we allowed MSM in the low risk trajectory to transit between the low and medium risk levels. To determine these transition rates we calculated the proportions of MSM in the low risk trajectory that move from low risk to medium (or high) risk level between two consecutive biannual visits. Subsequently, biannual rates were transformed to annual transition rates. Reverse transition rates were based on the average time that MSM who follow the low risk trajectory spend at the medium risk (or high risk) level (Supplementary Table 4).

For both models, risk level specific partner change rates were based on the average number of reported casual partners with whom they had unprotected receptive or insertive anal intercourse in the past six months over all visits at each risk level (Supplementary Table 2). We multiplied the averages by 1.5 to obtain number of partners per year, because some partnerships are likely to last more than 6 months (Heijne et al., 2017). Since sexual behavior data of MSM more than 45 years after first sexual contact was scarce, the average duration of stay after sexual debut was set to 45 years in both models.

Table 1 summarizes the parameters estimated from the ACS data as described in this section.

2.2. Model without sexual trajectories

The model without sexual trajectories is a version of the model in (Rozhnova et al., 2016) extended to include PrEP (Fig. 1). It assumes

Table 1
Behavioral parameters estimated from the ACS data.

Notation	Baseline value, unit	Description
$1/\mu$	45 year^{-1}	Average duration of sexual activity
c_l, $l = 1, 2, 3$	$c_1 = 0.255$ year^{-1} $c_2 = 2.97$ year^{-1} $c_3 = 29.19$ year^{-1}	Partner change rates at risk level l
q_l, $l = 1, 2, 3$	$q_1 = 0.715$ $q_2 = 0.261$ $q_3 = 0.024$	Initial population fractions at risk level l
$q_{l,b}$, $l = 1, 2, 3$, $b = 1$	$q_{1,1} = 0.006$ $q_{2,1} = 0.013$ $q_{3,1} = 0.005$	Initial population fractions at risk level l, increasing risk trajectory
$q_{l,b}$, $l = 1, 2, 3$, $b = 2$	$q_{1,2} = 0.015$ $q_{2,2} = 0.029$ $q_{3,2} = 0.019$	Initial population fractions at risk level l, decreasing risk trajectory
$q_{l,b}$, $l = 1, 2$, $b = 3$	$q_{1,3} = 0.694$ $q_{2,3} = 0.219$	Initial population fractions at risk level l, low risk trajectory
$1/\alpha_{ll',b}$, $b = 1$	$1/\alpha_{12,1} = 10.1$ years $1/\alpha_{23,1} = 7.6$ years	Average duration of stay at risk level l, increasing risk trajectory
$1/\alpha_{ll',b}$, $b = 2$	$1/\alpha_{21,2} = 15.8$ years $1/\alpha_{32,2} = 15.1$ years	Average duration of stay at risk level l, decreasing risk trajectory
$1/\alpha_{ll',b}$, $b = 3$	$1/\alpha_{12,3} = 5.618$ years	Average duration of stay at risk level l, low risk trajectory
$1/\nu_{ll',b}$, $b = 3$	$1/\nu_{21,3} = 1.56$ years	

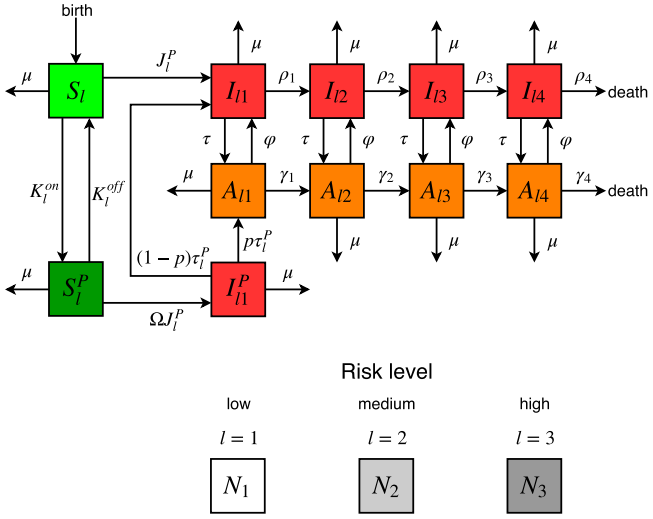

Fig. 1. Diagram of the model without sexual trajectories. The upper diagram describes HIV transmission dynamics for individuals at risk level l ($l = 1$, 2, 3). The lower diagram represents an MSM population as stratified by the number of sexual partners into three risk levels (low, medium and high) where individuals do not change their risk level during their life course.

that an MSM population of size $N(t)$ is stratified into three risk levels of size $N_l(t)$ with partner change rates c_l, $l = 1, 2, 3$. The risk levels represent individuals with low ($l = 1$), medium ($l = 2$) and high ($l = 3$) number of sexual partners. In the model without sexual trajectories we assume that individuals do not change their risk level during their lifetime. For risk level l, the population is further stratified according to HIV and PrEP status into susceptible, $S_l(t)$, susceptible on PrEP, $S_l^P(t)$, infected, $I_{lk}(t)$, infected despite taking PrEP, $I_{lk}^P(t)$, and treated, $A_{lk}(t)$, individuals. HIV infected individuals can be in one of $k = 1, 2, 3, 4$ infection stages: 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 total population size can be expressed as $N(t) = \sum_{l=1}^{3} N_l(t)$, where population size for level l is given by $N_l(t) = S_l(t) + S_l^P(t) + \sum_{k=1}^{4} [I_{lk}(t) + I_{lk}^P(t) + A_{lk}(t)]$.

The dynamics of the model is as follows (see Fig. 1). Individuals at risk level l enter the sexually active population at rate $\mu N_0 q_l$ as susceptible, where μ is the recruitment rate, N_0 and q_l are the total population size and population fraction at risk level l. Susceptible MSM take daily PrEP with rate K_l^{on} and drop off PrEP with rate K_l^{off}. MSM become infected with force of infection $J_l^P(t)$. MSM on PrEP may still get infected but with reduced force of infection $\Omega J_l^P(t)$, where $(1 - \Omega)$ quantifies PrEP effectiveness. PrEP is fully effective if $\Omega = 0$. $\Omega = 1$ corresponds to the situation of complete ineffectiveness because PrEP users get infected with the same force of infection as non-PrEP users. Infected individuals either progress through infection stages and die from AIDS with rates ρ_k ($k = 1, 2, 3, 4$) or start ART at rate τ in any stage. Individuals on ART progress through four stages and die with rates γ_k ($k = 1, 2, 3, 4$) or can stop taking ART due to virological failure or other reasons with rate φ. The majority of individuals on PrEP is regularly monitored, that is why we assumed that individuals infected while on PrEP can only be in the primary stage of infection, I_{l1}^P. A fraction $p \in [0, 1]$ of them start taking ART with rate $\tau_l^P > \tau$. The remaining fraction $(1 - p)$ moves into the compartment of HIV infected individuals in the first stage who did not take PrEP. All individuals leave the sexually active population at rate μ.

The model is described by a set of differential equations for the number of individuals in different compartments as follows

$$
\begin{aligned}
\frac{dS_l(t)}{dt} &= \mu N_0 q_l - \mu S_l(t) - J_l^P(t) S_l(t) - K_l^{on} S_l(t) + K_l^{off} S_l^P(t),\\
\frac{dS_l^P(t)}{dt} &= -\mu S_l^P(t) - \Omega J_l^P(t) S_l^P(t) + K_l^{on} S_l(t) - K_l^{off} S_l^P(t),\\
\frac{dI_{l1}(t)}{dt} &= J_l^P(t) S_l(t) - (\mu + \rho_1 + \tau) I_{l1}(t) + \varphi A_{l1}(t) + (1-p)\tau_l^P I_{l1}^P(t),\\
\frac{dI_{l1}^P(t)}{dt} &= \Omega J_l^P(t) S_l^P(t) - \mu I_{l1}^P(t) - \tau_l^P I_{l1}^P(t),\\
\frac{dI_{lk}(t)}{dt} &= \rho_{k-1} I_{l,k-1}(t) - (\mu + \rho_k + \tau) I_{lk}(t) + \varphi A_{lk}(t),\\
\frac{dA_{l1}(t)}{dt} &= \tau I_{l1}(t) - (\mu + \gamma_1 + \varphi) A_{l1}(t) + p\tau_l^P I_{l1}^P(t),\\
\frac{dA_{lk}(t)}{dt} &= \tau I_{lk}(t) + \gamma_{k-1} A_{l,k-1}(t) - (\mu + \gamma_k + \varphi) A_{lk}(t),
\end{aligned}
\tag{1}
$$

where $k = 2, 3, 4$ and $l = 1, 2, 3$.

The force of infection (per year) at level l is given by

$$
J_l^P(t) = \lambda c_l \sum_{l'=1}^{3} M_{ll'}(t) \left[\epsilon^P \frac{I_{l'1}^P(t)}{N_{l'}(t)} + \sum_{k=1}^{4} \left(h_k \frac{I_{l'k}(t)}{N_{l'}(t)} + \epsilon \frac{A_{l'k}(t)}{N_{l'}(t)} \right) \right]. \tag{2}
$$

The force of infection takes into account that infectivities of untreated individuals, h_k, depend on infection stage $k = 1, 2, 3, 4$.

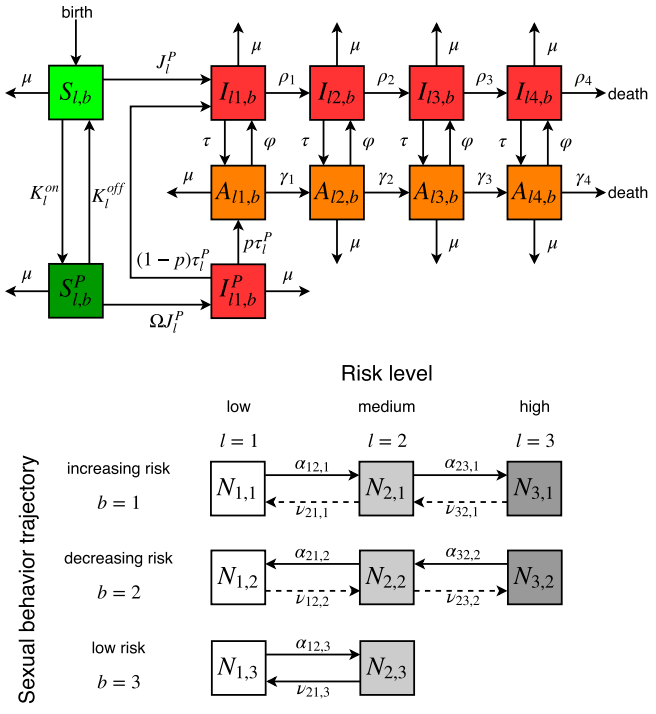

Fig. 2. Diagram of the model with sexual trajectories. The upper diagram shows HIV transmission dynamics for individuals at risk level l ($l = 1, 2, 3$) and sexual trajectory b ($b = 1, 2, 3$). For a given l and b this dynamics is the same as in the model without sexual trajectories (Fig. 1). The lower diagram represents an MSM population as stratified by the number of sexual partners into three risk levels (low, medium and high) where individuals exhibit three types of sexual behavior trajectories (increasing risk trajectory, decreasing risk trajectory and low risk trajectory). Transitions identifying these sexual trajectories are shown as solid arrows between different risk levels. Reverse transitions between risk levels shown as dashed arrows were used only in the sensitivity analyses.

Infectivity of individuals on ART, ϵ, is stage independent. We further assumed that individuals who get infected despite taking PrEP may have lower viral loads levels and thus lower infectivity in the primary stage, ϵ^P, than individuals who do not take prophylaxis, h_1, $\epsilon^P \leq h_1$. The force of infection depends also on the transmission probability per partnership, λ, partner change rates, c_l ($l = 1, 2, 3$), and mixing between susceptible MSM at level l and infected MSM at level $l' = 1, 2, 3$. Mixing is described by a matrix with the elements $M_{ll'}(t)$

$$M_{ll'}(t) = \omega \frac{c_{l'} N_{l'}(t)}{\sum_{l''=1}^{3} c_{l''} N_{l''}(t)} + (1-\omega)\delta_{ll'}, \tag{3}$$

where $\delta_{ll'} = 1$ if $l = l'$ and $\delta_{ll'} = 0$ otherwise. Mixing parameter $\omega \in [0, 1]$ allows to change mixing from assortative ($\omega = 0$) to proportionate ($\omega = 1$). Values of ω between 0 and 1 correspond to intermediate levels of mixing.

2.3. Model with sexual trajectories

In the model with sexual behavior trajectories MSM can change their risk level during their lifetime. Motivated by the analysis of the ACS data we incorporate three types of trajectories (Fig. 2). The increasing risk trajectory is comprised of individuals who increase their risk level from low to medium to high throughout their life course. The decreasing risk trajectory is comprised of individuals who decrease their risk level from high to medium to low throughout their life course. The low risk trajectory is comprised of the remaining individuals who switch their risk level between low and medium throughout their life course. The described transitions represent the baseline scenario of the model with trajectories. They are shown as solid arrows in Fig. 2. In the sensitivity analyses, we considered additional transitions between risk levels which allow individuals to move in the reverse direction along the trajectories. These additional transitions are shown as dashed arrows in Fig. 2 and are referred to as reverse transitions in the following text. Except for allowing changes in risk level, the model with sexual trajectories has the same HIV dynamics as the model without trajectories. In particular, PrEP uptake depends on risk level and is independent of the sexual trajectory.

The transition rates from risk level l to risk level l' ($l, l' = 1, 2, 3$) along trajectory b ($b = 1, 2, 3$) are denoted as $\alpha_{ll',b}$. The reverse transition rates from risk level l to risk level l' along trajectory b are denoted as $\nu_{ll',b}$. As before, the subscript l stands for risk level: $l = 1$ (low risk level), $l = 2$ (medium risk level), and $l = 3$ (high risk level). The subscript b stands for sexual trajectory: $b = 1$ (increasing risk trajectory), $b = 2$ (decreasing risk trajectory), $b = 3$ (low risk trajectory). We denote as $N_{l,b}$ the number of individuals at risk level l who belong to sexual trajectory b. For future comparison with the model without sexual trajectories we note that the total population size is $N(t) = \sum_{l=1}^{3} N_l(t)$, where population sizes at level l are given by $N_l(t) = \sum_{b=1}^{3} N_{l,b}(t)$. This means that in the model with trajectories we obtain the number of individuals at risk level l by summing over all trajectories b.

The model equations for the number of susceptible, $S_{l,b}(t)$, susceptible on PrEP, $S^P_{l,b}(t)$, infected, $I_{lk,b}(t)$, infected despite taking PrEP, $I^P_{l1,b}(t)$, and treated, $A_{lk,b}(t)$, individuals can be written in a compact form as follows

$$\begin{aligned}
\frac{\mathrm{d}S_{l,b}(t)}{\mathrm{d}t} =& \ \mu N_0 q_{l,b} - \mu S_{l,b}(t) - J^P_l(t) S_{l,b}(t) - K^{\mathrm{on}}_l S_{l,b}(t) \\
&+ K^{off}_l S^P_{l,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] S_{l,b}(t) + \alpha_{(l+l')l,b} S_{l+l',b}(t) \\
&+ \nu_{(l-l')l,b} S_{l-l',b}(t), \\
\frac{\mathrm{d}S^P_{l,b}(t)}{\mathrm{d}t} =& -\mu S^P_{l,b}(t) - \Omega J^P_l(t) S^P_{l,b}(t) + K^{on}_l S_{l,b}(t) \\
&- K^{off}_l S^P_{l,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] S^P_{l,b}(t) + \alpha_{(l+l')l,b} S^P_{l+l',b}(t) \\
&+ \nu_{(l-l')l,b} S^P_{l-l',b}(t), \\
\frac{\mathrm{d}I_{l1,b}(t)}{\mathrm{d}t} =& \ J^P_l(t) S_{l,b}(t) - (\mu + \rho_1 + \tau) I_{l1,b}(t) + \varphi A_{l1,b}(t) \\
&+ (1-p)\tau^P_l I^P_{l1,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] I_{l1,b}(t) \\
&+ \alpha_{(l+l')l,b} I_{(l+l'),1,b}(t) + \nu_{(l-l')l,b} I_{(l-l'),1,b}(t), \\
\frac{\mathrm{d}I^P_{l1,b}(t)}{\mathrm{d}t} =& \ \Omega J^P_l(t) S^P_{l,b}(t) - \mu I^P_{l1,b}(t) - \tau^P_l I^P_{l1,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l),b}\right] I^P_{l1,b}(t) \\
&+ \alpha_{(l+l')l,b} I^P_{(l+l'),1,b}(t) + \nu_{(l-l')l,b} I^P_{(l-l'),1,b}(t), \\
\frac{\mathrm{d}I_{lk,b}(t)}{\mathrm{d}t} =& \ \rho_{k-1} I_{l,k-1,b}(t) - (\mu + \rho_k + \tau) I_{lk,b}(t) + \varphi A_{lk,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] I_{lk,b}(t) \\
&+ \alpha_{(l+l')l,b} I_{(l+l'),k,b}(t) + \nu_{(l-l')l,b} I_{(l-l'),k,b}(t), \\
\frac{\mathrm{d}A_{l1,b}(t)}{\mathrm{d}t} =& \ \tau I_{l1,b}(t) - (\mu + \gamma_1 + \varphi) A_{l1,b}(t) + p\tau^P_l I^P_{l1,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] A_{l1,b}(t) \\
&+ \alpha_{(l+l')l,b} A_{(l+l'),1,b}(t) + \nu_{(l-l')l,b} A_{(l-l'),1,b}(t), \\
\frac{\mathrm{d}A_{lk,b}(t)}{\mathrm{d}t} =& \ \tau I_{lk,b}(t) + \gamma_{k-1} A_{l,k-1,b}(t) - (\mu + \gamma_k \\
&+ \varphi) A_{lk,b}(t) \\
&- \left[\alpha_{l(l-l'),b} + \nu_{l(l+l'),b}\right] A_{lk,b}(t) \\
&+ \alpha_{(l+l')l,b} A_{(l+l'),k,b}(t) + \nu_{(l-l')l,b} A_{(l-l'),k,b}(t),
\end{aligned} \tag{4}$$

where $l = 1, 2, 3$, $b = 1, 2, 3$, $k = 2, 3, 4$, $l' = (-1)^b$, $\alpha_{ll',b} = 0$ and $\nu_{ll',b} = 0$ if $l < 1$ or $l' < 1$ or $l > 3$ or $l' > 3$.

Table 2
HIV infection parameters and their baseline values.

Notation	Baseline value, unit	Description
ρ_k	$\rho_1 = 1/0.142$ year^{-1} $\rho_2 = 1/8.439$ year^{-1} $\rho_3 = 1/1.184$ year^{-1}	Rate of transition from stage k to stage $k+1$ for untreated individuals (k = 1, 2, 3)
ρ_4	$\rho_4 = 1/1.316$ year^{-1}	HIV related mortality for untreated individuals
γ_k	$\gamma_1 = 1/8.21$ year^{-1} $\gamma_2 = 1/54.0$ year^{-1} $\gamma_3 = 1/2.463$ year^{-1}	Rate of transition from stage k to stage $k+1$ for treated individuals (k = 1, 2, 3)
γ_4	$\gamma_4 = 1/2.737$ year^{-1}	HIV related mortality for treated individuals
h_k	$h_1 = 0.62$ $h_2 = 0.12$ $h_3 = 0.642$ $h_4 = 0.0$	Infectivity of untreated individuals in stage k of infection (k = 1, 2, 3, 4)
N_0	330,000	Initial population size
ϵ	0.01	Infectivity of treated individuals
ω	0.5	Mixing parameter ($\omega = 0$ and $\omega = 1$ — assortative and proportionate mixing)
φ	$-\ln[1 - 5\%/100\%]$ year^{-1}	Annual ART dropout rate
τ	$-\ln[1 - 30\%/100\%]$ year^{-1}	Annual ART uptake rate
λ	0.1	Transmission probability per partnership
$1 - \Omega$	0.95	PrEP effectiveness
p	1	Fraction of PrEP users starting ART after HIV infection
ϵ^P	$h_1/2$	Infectivity of MSM on PrEP
τ_l^P	$-\ln[1 - 95\%/100\%]$ year^{-1}	Annual ART uptake rate for persons infected despite taking PrEP
$1/K_l^{\text{off}}$	5 years	Average duration of PrEP uptake
K_l^{on}, $l = 3$	$-\ln[1 - R/100\%]$ year^{-1} $R \in$ [0–80%]	Annual PrEP uptake rate

The force of infection, $J_l^P(t)$, is given by Eq. (2), where population size at risk level l is given by $N_l(t) = \sum_{b=1}^{3} N_{l,b}(t) = \sum_{b=1}^{3} [S_{l,b}(t) + S_{l,b}^P(t) + I_{l1,b}^P(t), l = 1, 2, 3.$
$+ \sum_{k=1}^{4} (I_{lk,b}(t) + A_{lk,b}(t))]$

2.4. Model parameterisation for HIV infection

The remaining parameters and their baseline values are summarized in Table 2. The values for initial population size, transition rates between stages, disease related mortality and infectivity for treated individuals were taken from our previous work (Rozhnova et al., 2016). For untreated individuals, we adjusted infectivity and transition rates between primary and chronic stages according to their estimates in (Bellan et al., 2015). Since estimates of the degree of assortative mixing in the population of MSM in the Netherlands are not available, we considered an intermediate level of mixing.

We presented our results in terms of annual uptake and dropout percentages both for PrEP and ART. The annual rates of uptake and dropout used in the model equations were computed from the expression for the probability that uptake or dropout event occurs within one year as $percentage = [1 - \exp(-\text{rate} \times 1\text{year})]100\%$. The annual ART dropout percentage was fixed at 5% for all infection stages, risk levels and trajectories (Rozhnova et al., 2016). ART uptake was uniform for all infection stages, risk levels and trajectories during all analyses. In the models without PrEP we varied annual ART uptake percentage between 0% and 100%. In the models with PrEP, ART uptake percentage was always 30%. This uptake corresponded to ART coverage of about 80% observed in the Netherlands (van Sighem et al., 2017). Transmission probability per partnership was chosen so that before ART was initiated the basic reproduction number in both models was similar and close to its estimates obtained for Western MSM populations (Kretzschmar et al., 2013).

For consistent PrEP users, its effectiveness is now considered to be very high (Duwal et al., 2016). In the model PrEP effectiveness was fixed at 0.95. We considered the scenario where PrEP was taken only by high risk individuals, setting uptake by individuals with low and medium risk to zero. The annual PrEP uptake was varied between 0% and 80%, and average duration of PrEP use was 5 years (Nichols et al., 2016). Since the majority of individuals on PrEP is regularly monitored, we assumed that for all individuals who got infected despite using PrEP annual uptake was 95% (Rozhnova et al., 2018). It is important to note that although in both models PrEP was taken only by high risk individuals, in the model with sexual trajectories there could be PrEP users at medium and low risk levels as well, because this model allowed for high risk MSM to decrease sexual risk behavior along decreasing risk trajectory. Estimates of infectivity in the primary stage for PrEP users have not been obtained but are likely to be lower than for non-PrEP users. In our study the default value for this parameter was half the infectivity of non-PrEP users (Rozhnova et al., 2018).

2.5. Model outcome measures

We computed the effective reproduction number, R_e, using the next generation matrix theory (Diekmann et al., 2010; van den Driessche and Watmough, 2002). R_e is defined as the average number of secondary infections caused by a typical infectious individual in a population, where intervention measures are implemented. HIV elimination occurs if $R_e < 1$.

We numerically solved the model equations for PrEP uptake by high risk individuals of 10%, 20%, 50% and 80% annually, starting from the baseline scenario without PrEP. For both models, we quantified the impact of PrEP on HIV prevalence as the relative reduction in HIV prevalence. This measure was computed as (1-prevalence after PrEP/prevalence before PrEP)×100% at several time points during the course of the epidemic. The time points were 5, 15 and 40 years after PrEP introduction, and also in the steady state. The steady state was included to quantify PrEP impact on a long time scale.

Since we were interested in understanding the differences between the models caused by sexual trajectories, we presented the results in terms of the absolute difference between the relative reduction in HIV prevalence in the model with sexual trajectories and the relative reduction in HIV prevalence in the model without sexual trajectories. In what follows, we refer to this quantity as the contribution of sexual trajectories to impact of PrEP on HIV prevalence. A positive contribution of sexual trajectories indicates that the model with sexual trajectories predicts a higher impact of PrEP on HIV prevalence. A negative contribution of sexual trajectories means that PrEP impact on HIV prevalence is higher for the model without trajectories. Zero contribution of sexual trajectories indicates that PrEP impact on HIV prevalence

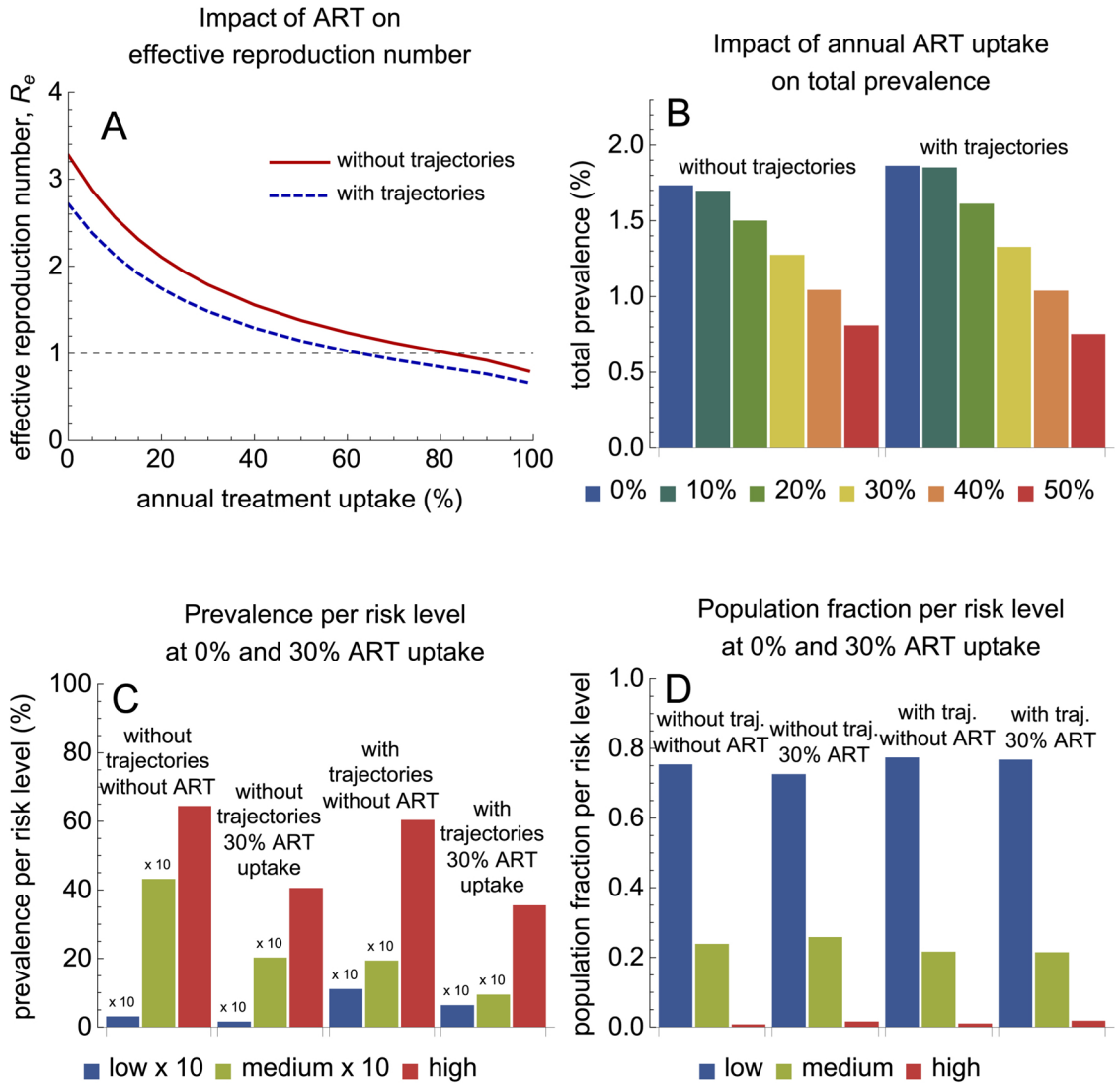

Fig. 3. Dynamics of the models with and without sexual trajectories without PrEP. A and B show effective reproduction number and steady-state HIV prevalence for different levels of annual ART uptake. C and D show steady-state prevalence and population fractions at low, medium and high risk levels without ART and at annual ART uptake of 30%. In both models, prevalence in low and medium risk individuals was much lower than prevalence in high risk individuals. To be clearly visible in one chart, in C we multiplied former prevalence by 10.

is identical for both models, which in our analyses only happened when HIV was eliminated by PrEP.

3. Results

The model with and without sexual trajectories were very similar in terms of HIV transmission dynamics before the introduction of PrEP intervention (see Fig. 3). In both models, the effective reproduction number and the steady state HIV prevalence for different levels of ART uptake were similar (Fig. 3A and B). More importantly, steady state prevalence and population fractions at all risk levels were similar between the models as well (Fig. 3C and D). Departing from this baseline scenario, we investigated the impact of sexual trajectories of MSM on the reduction in HIV prevalence by PrEP.

Fig. 4 shows the contribution of sexual trajectories computed in the way described in Section 2. In this figure we distinguished PrEP impact on both overall (panel A) and risk level prevalence (panels B, C, and D). For the overall prevalence, the contribution of sexual trajectories to PrEP impact was always positive (Fig. 4A), which means that the incorporation of sexual trajectories into the model led to a higher reduction in the overall HIV prevalence by PrEP. For a time horizon of 5 to 40 years after PrEP introduction, the contribution of sexual trajectories was between 0.4% and 5.2%. The largest contribution of sexual trajectories (8.1%) was predicted for annual PrEP uptake of 10% in the steady state. In the steady state, both models predicted zero contribution of sexual trajectories for PrEP uptake above 50%, because at this level of PrEP uptake HIV was eliminated in the steady state in both models. For PrEP uptake of between 20% and 80% the maximum contribution was observed 40 years after PrEP initiation. These results are explained by the fact that the model with trajectories 'provides' PrEP to MSM at middle and low risk levels, as they transit from high risk level while taking PrEP. For a given level of PrEP uptake, the number of individuals on PrEP at low and medium risk increases with time. In the 40 years time horizon for PrEP uptakes of 10–80%, there are dozens to hundreds of people at low and medium risk who take PrEP due to behavior switch. In the model with trajectories the total fraction of individuals on PrEP is 0.1–0.3% higher than in the model without trajectories. Since there are many more individuals at low and medium risk level than at high risk level, small changes at these risk levels on HIV transmission risk can have a large impact on the overall HIV prevalence. Therefore, the model with trajectories estimates a larger impact on the overall prevalence than the model with fixed risk

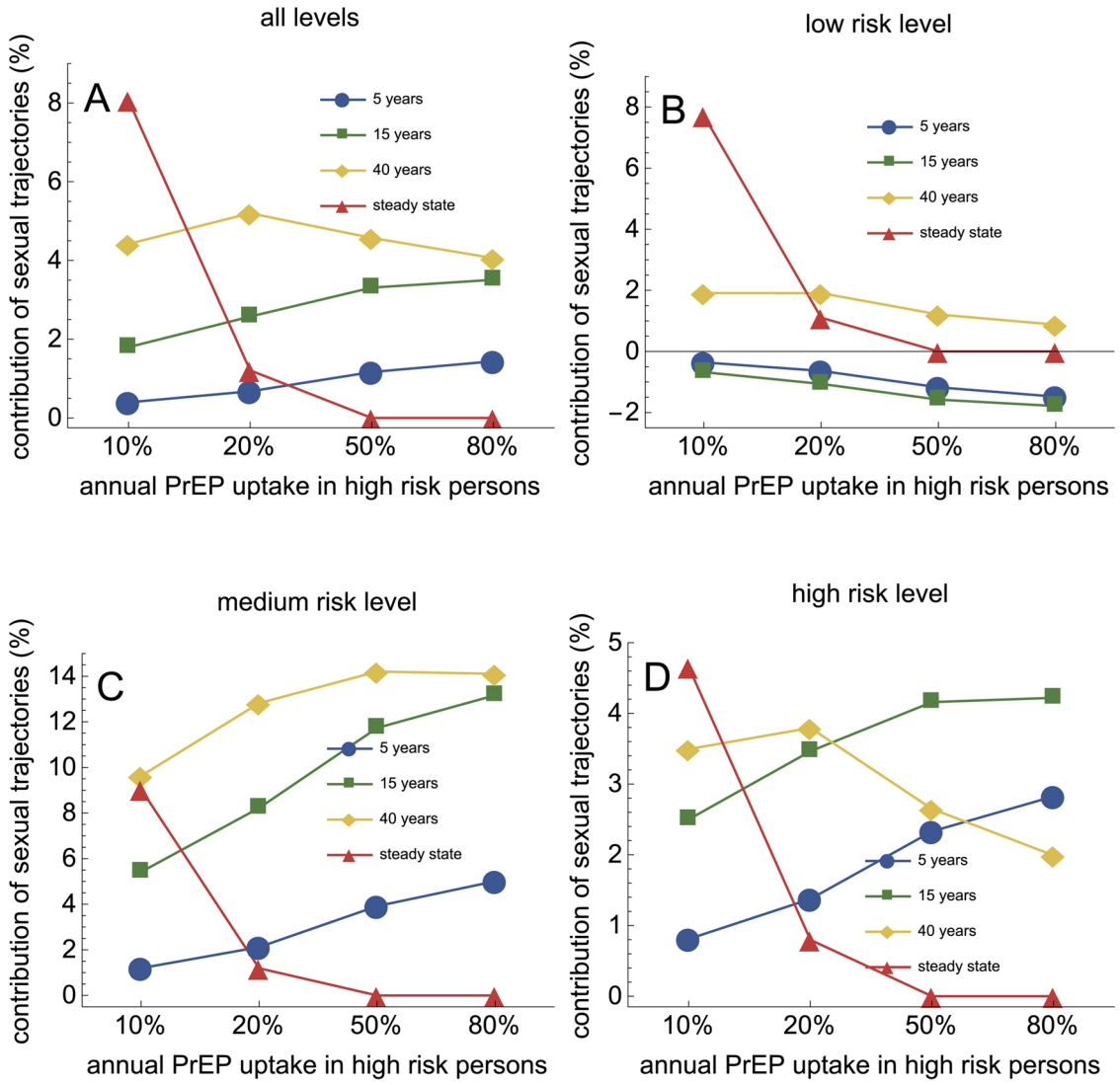

Fig. 4. Contribution of sexual trajectories to PrEP impact on HIV prevalence. Contribution of sexual trajectories was defined as the absolute difference between the relative reduction in HIV prevalence in the model with sexual trajectories and the relative reduction in HIV prevalence in the model without sexual trajectories due to PrEP. For both models, the relative reduction in prevalence measured in percentages was computed as (1 − prevalence after PrEP/prevalence before PrEP) × 100%. Positive/negative contribution of sexual trajectories indicates that PrEP impact on HIV prevalence is higher/lower in the model with sexual trajectories.

levels in which only people at high risk level take PrEP. These individuals are only a small fraction of the entire population, hence big changes at this risk level have little impact on the overall prevalence.

The contribution of sexual trajectories varied highly by risk level (Fig. 4B–D. The contribution to PrEP impact among low risk individuals (Fig. 4B) was negative in the first 15 years after PrEP introduction. At longer times however, the contribution became positive and stayed like that until the HIV epidemic reached the steady state. The model with trajectories predicts a larger impact on HIV prevalence at low risk level compared to the model without trajectories because in the former model there are also PrEP users at low risk level while in the latter model there are none. Since people stay on average long at each risk level (about 15 years), this effect becomes visible only after 40 years. The largest contribution of sexual trajectories to PrEP impact was seen in the medium risk individuals (Fig. 4C). This contribution increased with time and PrEP uptake up to the maximum of about 14.2% at 50% PrEP uptake after 40 years. For uptake above 50% the contribution dropped to zero in the steady state again because of HIV elimination. The larger contribution of sexual trajectories to PrEP impact in the medium risk individuals occurred because in the model with sexual trajectories high risk PrEP users could decrease their risk behavior and reduce HIV transmission within the medium risk individuals. For individuals at high risk, the contribution of sexual trajectories was positive but smaller than for individuals at medium risk (Fig. 4D). At high risk level, in both models people take PrEP, but in the model without trajectories people stay at high risk while in the model with trajectories people on PrEP move to the medium and low risk level. Therefore, a certain percentage of PrEP is ‘wasted’ to lower risk individuals, and hence, the difference between the two models is smaller at high risk level. This is also demonstrated with the decreasing line (yellow line) for 40 years time horizon (i.e. more and more PrEP is provided to low risk individuals instead of only high risk individuals in the model without trajectories).

Although the contribution of sexual trajectories to PrEP impact varied between risk levels, it never exceeded 15% for all parameter values explored. In the main analyses, we assumed that every individual followed one of three linear sexual trajectories. However, in real life people can have ‘relapses’ in higher or lower sexual risk behavior. Therefore, we performed sensitivity analyses (Fig. 5) to relax the statement of linearity. We included four theoretical scenarios with additional changes in sexual behavior of high risk individuals which would increase the contribution of sexual trajectories on PrEP impact.

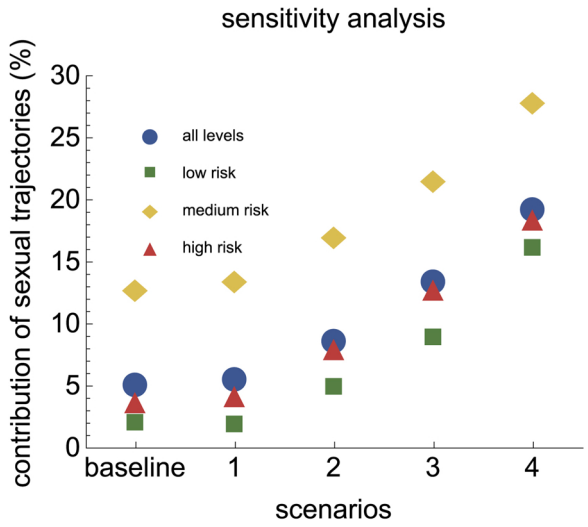

Fig. 5. Sensitivity analyses for the contribution of sexual trajectories to PrEP impact in the extended model. The *x*-axis shows four theoretical scenarios: (1) reverse transition from medium to high risk along decreasing risk trajectory; (2) ten times slower changes in risk levels along increasing risk trajectory; (3) reverse transition from high to medium risk level along increasing risk trajectory; (4) same as scenario 3 with twice as fast reverse transition rate. The parameter values describing these scenarios are given in the main text. The calculation of the contribution of sexual trajectories to PrEP impact was done for 20% PrEP uptake after 40 years. For the baseline scenario we took data from Figure 4.

The four arbitrarily chosen theoretical scenarios we considered were: (1) reverse transition from medium to high risk along decreasing risk branch ($1/\nu_{23,2} = 1/\alpha_{32,2} = 15.1$ years); (2) ten times slower changes in risk levels along increasing risk trajectory ($1/\alpha_{12,1} = 10.1 \times 10$ years; $1/\alpha_{23,1} = 7.6 \times 10$ years); (3) reverse transition from high to medium risk level along increasing risk trajectory ($1/\nu_{32,1} = 1/\alpha_{23,1} = 7.6$ years); (4) same as scenario 3 but with twice as fast reverse transition rate ($1/\nu_{32,1} = 1/(2 \times \alpha_{23,1}) = 7.6/2$ years). In Fig. 5, we showed the contributions of sexual trajectories in the four theoretical scenarios and in the default scenario, for which we took data from Fig. 4. The contribution of trajectories was calculated for 20% PrEP uptake after 40 years. In scenario 2, slower changes in risk behavior of individuals who increased risk during their lifetime increased the contribution from 5.2% to 8.7%, when compared to the baseline scenario. For scenarios 3 and 4 with reverse transitions from high to medium risk, the contribution increased from 5.2% to 13.5% and 19.3%, respectively. In these cases, PrEP intervention was more effective because fraction of individuals at medium risk became larger. In addition, people at medium in the increasing risk trajectory could also take PrEP. In scenario 1, where individuals experienced relapse in high risk behavior in the decreasing risk trajectory, the contribution was marginally larger (5.6%) than in the baseline scenario.

4. Discussion and conclusions

In this work, we studied the impact of long-term changes in sexual risk behavior of MSM on the impact of PrEP on HIV prevalence by comparing a mathematical model with fixed risk levels to a model where MSM could change their behavior over their sexual lifetime. These sexual trajectories represented slow changes in risk levels occurring during an individual's life course. We found that the model with sexual trajectories always predicted a larger impact of PrEP on the overall HIV prevalence. The contribution of trajectories, however, was rather modest and did not exceed 8.1%. Interestingly, the contribution to PrEP impact at different risk levels varied depending on the time after PrEP introduction and the level of PrEP uptake. The largest contribution was predicted for PrEP impact on HIV prevalence at medium risk level and after 40 years of PrEP intervention.

To our knowledge, this is the first study considering the impact of long-term behavioral changes on HIV transmission dynamics and the impact of PrEP. We used a unique data set with many years of longitudinal data to parameterize our model. Our model had several simplifications. First, it focused on intrinsic long-term changes in sexual risk behavior and did not incorporate short-term changes in behavior as a result of PrEP use (also known as risk compensation (Stolte et al., 2004; Bezemer et al., 2008; Jansen et al., 2011)). Second, in line with the current guidelines (Ryom et al., 2016) we considered PrEP uptake by high risk individuals while in reality individuals at medium and low risk levels could be using PrEP too. However, we think that the direction of effect that we found (i.e. model with trajectories estimates a larger impact of PrEP on HIV prevalence) will not be affected by this. Third, PrEP uptake was assumed to be non-intermittent with an average duration of 5 years. Other strategies for PrEP use such as PrEP on demand in which individuals take preventive medication shortly before and after high risk sexual behavior were shown to be effective for preventing HIV infections as well (Molina et al., 2015). Again, we do not think that adding this type of PrEP use in both models will change the direction of the main results. Lastly, our model did not account for many aspects of the partnership formation dynamics relevant for MSM. In particular, we did not consider the effects of sero-sorting, partnership concurrency and different degrees of assortative mixing. While these factors might be important to evaluating PrEP impact in real-world situations, neglecting them significantly simplified both models and made their analyses tractable.

A larger impact of PrEP on HIV prevalence in the model with sexual trajectories than in the model without sexual trajectories can mainly be explained by the fact that people in the model with sexual trajectories can move from high to medium risk level while on PrEP. As a consequence, it is possible that people at medium risk level are also taking PrEP. As the fraction of MSM at medium risk is relatively large compared to the fraction of MSM at high risk, small changes in the medium risk group transmission risk can have a larger impact on the overall HIV prevalence compared to a model where PrEP use is only concentrated in a small high risk group. However, this does not necessarily suggest that PrEP should be given to individuals with medium risk, since this comes down to cost-effectiveness analyses. Our developed model could be extended further to study the impact of a time tailored PrEP intervention. Targeting PrEP not only to high risk MSM but to specific periods of high risk behavior during an individual's life course or designing interventions that target MSM just before they enter a period of high risk behavior could have a large impact on HIV transmission combined with cost-effectiveness analyses.

We focused only on long-term changes in risk behavior and did not account for fast changes in risk levels, such as episodic risk (Zhang et al., 2012; Henry and Koopman, 2015). It was shown that the estimated impact of universal test and treat control strategies is heavily influenced by episodic risk, making elimination of HIV impossible under certain circumstances. It is expected that this might also hold for other interventions such as PrEP. Future work should focus on the impact of other types of behavioural change on the estimated impact of PrEP on HIV prevalence such as shorter changes in risk behavior or episodic risk.

Our study has implications for the interpretation of the estimated impact of PrEP in other published modelling studies. Some of these modelling studies, including two from the Netherlands (Nichols et al., 2016; Rozhnova et al., 2018), did not incorporate behavior change in the estimated impact of PrEP. Nichols et al. (2016) concluded that PrEP rollout among high risk MSM would be cost-effective in the Netherlands. Rozhnova et al. (2018) concluded that large uptake of PrEP by high risk MSM can lead to HIV elimination among the Dutch MSM. We showed that a model that does not incorporate long-term behavioural change underestimates the impact of PrEP on HIV prevalence, meaning that the estimates from models that do not incorporate long-term changes are conservative.

Conflicts of interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.epidem.2019.03.003.

References

Basten, M., Heijne, J., Geskus, R., Den Daas, C., Kretzschmar, M., Matser, A., 2018. Sexual risk behaviour trajectories among MSM at risk for HIV in Amsterdam, the Netherlands. AIDS 32 (9), 1185–1192.

Bellan, S.E., Dushoff, J., Galvani, A.P., Meyers, L.A., 2015. Reassessment of HIV-1 acute phase infectivity: accounting for heterogeneity and study design with simulated cohorts. PLoS Med. 12, e1001801.

Bezemer, D., de Wolf, F., Boerlijst, M.C., van Sighem, A., Hollingsworth, T.D., Prins, M., Geskus, R.B., Gras, L., Coutinho, R.A., Fraser, C., 2008. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. AIDS 22, 1071–1077.

Bezemer, D., de Wolf, F., Boerlijst, M.C., van Sighem, A., Hollingsworth, T.D., Fraser, C., 2010. 27 years of the HIV epidemic amongst men having sex with men in the Netherlands: an in depth mathematical model-based analysis. Epidemics 2, 66–79.

Diekmann, O., Heesterbeek, J.A., Roberts, M.G., 2010. The construction of next-generation matrices for compartmental epidemic models. J. R. Soc. Interface 7, 873–885.

Duwal, S., Sunkara, V., von Kleist, M., 2016. Multiscale systems-pharmacology pipeline to assess the prophylactic efficacy of NRTIs against HIV-1. CPT Pharmacometr. Syst. Pharmacol. 5, 377–387.

Heijman, T., Geskus, R.B., Davidovich, U., Coutinho, R.A., Prins, M., Stolte, I.G., 2012. Less decrease in risk behaviour from pre-HIV to post-HIV seroconversion among MSM in the combination antiretroviral therapy era compared with the pre-combination antiretroviral therapy era. AIDS 26, 489–495.

Heijne, J., van Liere, G., Hoebe, C., Bogaards, J., van Benthem, B., Dukers-Muijrers, N., 2017. What explains anorectal chlamydia infection in women? Implications of a mathematical model for test and treatment strategies. Sex. Transm. Infect. 93 (4), 270–275.

Henry, C.J., Koopman, J.S., 2015. Strong influence of behavioral dynamics on the ability of testing and treating HIV to stop transmission. Sci. Rep. 5, 9467.

Hoornenborg, E., Krakower, D.S., Prins, M., Mayer, K.H., 2017. Pre-exposure prophylaxis for MSM and transgender persons in early adopting countries. AIDS 31, 2179–2191.

Hoornenborg, E., Achterbergh, R., van der Loeff, M., Davidovich, U., van der Helm, J., Hogewoning, A., van Duijnhoven, Y., Sonder, G., de Vries, H., Prins, M., Amsterdam PrEP Project team in the HIV Transmission Elimination Amsterdam Initiative, 2018a. Men who have sex with men more often chose daily than event-driven use of pre-exposure prophylaxis: baseline analysis of a demonstration study in Amsterdam. J. Int. AIDS Soc. 21 (3), e25105.

Hoornenborg, E., Coyer, L., van Laarhoven, A., Achterbergh, R., de Vries, H., Prins, M., van der Loeff, M., Amsterdam PrEP Project team in the HIV Transmission Elimination AMsterdam Initiative, 2018b. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. AIDS 32 (11), 1527–1532.

Jansen, I.A., Geskus, R.B., Davidovich, U., Jurriaans, S., Coutinho, R.A., Prins, M., Stolte, I.G., 2011. Ongoing HIV-1 transmission among men who have sex with men in Amsterdam: a 25-year prospective cohort study. AIDS 25, 493–501.

Juusola, J.L., Brandeau, M.L., Owens, D.K., Bendavid, E., 2012. The cost-effectiveness of pre-exposure prophylaxis for HIV prevention in the United States in men who have sex with men. Ann. Intern. Med. 156, 541–550.

Kretzschmar, M.E., Schim van der Loeff, M.F., Birrell, P.J., De Angelis, D., Coutinho, R.A., 2013. Prospects of elimination of HIV with test-and-treat strategy. Proc. Natl. Acad. Sci. U.S.A. 110, 15538–15543.

Liu, A.Y., Cohen, S.E., Vittinghoff, E., Anderson, P.L., Doblecki-Lewis, S., Bacon, O., 2016. Pre-exposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. JAMA Internal Med. 176, 75–84.

McCormack, S., Dunn, D.T., Desai, M., Dolling, D.I., Gafos, M., Gilson, R., et al., 2016. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 387, 53–60.

Molina, J.-M., Capitant, C., Spire, B., Pialoux, G., Cotte, L., Charreau, I., et al., 2015. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N. Engl. J. Med. 373, 2237–2246.

Nichols, B.E., Boucher, C.A.B., van der Valk, M., Rijnders, B.J.A., van de Vijver, D.A.M.C., 2016. Cost-effectiveness analysis of pre-exposure prophylaxis for HIV-1 prevention in the Netherlands: a mathematical modelling study. Lancet Infect. Dis. 16, 1423–1429.

Punyacharoensin, N., Edmunds, W.J., De Angelis, D., Delpech, V., Hart, G., Elford, J., Brown, A., Gill, O.N., White, R.G., 2016. Effect of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the UK: a mathematical modelling study. Lancet HIV 3, e94–104.

Reyniers, T., Hoornenborg, E., Vuylsteke, B., Wouters, K., Laga, M., 2017. Pre-exposure prophylaxis (PrEP) for men who have sex with men in Europe: review of evidence for a much needed prevention tool. Sex. Transm. Infect. 93 (5), 363–367.

Romero-Severson, E.O., Alam, S.J., Volz, E.M., Koopman, J.S., 2012. Heterogeneity in number and type of sexual contacts in a gay urban cohort. Stat. Commun. Infect. Dis. 4, 4.

Romero-Severson, E.O., Volz, E., Koopman, J.S., Leitner, T., Ionides, E.L., 2015. Dynamic variation in sexual contact rates in a cohort of HIV-negative gay men. Am. J. Epidemiol. 182, 255–262.

Rozhnova, G., van der Loeff, M.F.S., Heijne, J.C.M., Kretzschmar, M.E., 2016. Impact of heterogeneity in sexual behavior on effectiveness in reducing HIV transmission with test-and-treat strategy. PLoS Comput. Biol. 12, e1005012.

Rozhnova, G., Bezemer, D., van Sighem, A., Heijne, J., Presanis, A., De Angelis, D., Kretzschmar, M., 2018. Elimination prospects of the Dutch HIV epidemic among men who have sex with men in the era of pre-exposure prophylaxis. AIDS 32 (17), 2615–2623.

Ryom, L., Boesecke, C., Gisler, V., Manzardo, C., Rockstroh, J.K., Puoti, M., Furrer, H., et al., 2016. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. HIV Med. 17, 83–88.

Schneider, K., Gray, R.T., Wilson, D.P., 2014. A cost-effectiveness analysis of HIV pre-exposure prophylaxis for men who have sex with men in Australia. Clin. Infect. Dis. 58, 1027–1034.

Stolte, I.G., Dukers, N.H., Geskus, R.B., Coutinho, R.A., de Wit, J.B., 2004. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS 18, 303–309.

Strömdahl, S., Hickson, F., Pharris, A., Sabido, M., Baral, S., Thorson, A., 2015. A systematic review of evidence to inform HIV prevention interventions among men who have sex with men in Europe. Euro Surv. 20 (15), 21096.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 29–48.

van Griensven, G.J., de Vroome, E.M., Goudsmit, J., Coutinho, R.A., 1989. Changes in sexual behaviour and the fall in incidence of HIV infection among homosexual men. BMJ 298, 218–221.

van Sighem, A., Boender, S., Wit, F., Smit, C., Matser, A., Reiss, P., 2017. HIV Monitoring Report 2017. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. https://www.hiv-monitoring.nl/index.php/download_file/view/1066/133/.

Volk, J.E., Marcus, J.L., Phengrasamy, T., Blechinger, D., Nguyen, D.P., Follansbee, S., Hare, C.B., 2015. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin. Infect. Dis. 61, 1601–1603.

Zhang, X., Zhong, L., Romero-Severson, E., Alam, S.J., Henry, C.J., Volz, E.M., Koopman, J.S., 2012. Episodic HIV risk behavior can greatly amplify HIV prevalence and the fraction of transmissions from acute HIV infection. Stat. Commun. Infect. Dis. 4, 1041.