# Supplement

# Epidemiological impact and budget effect of pre-exposure prophylaxis for HIV-1 prevention in Germany from 2018 to 2058



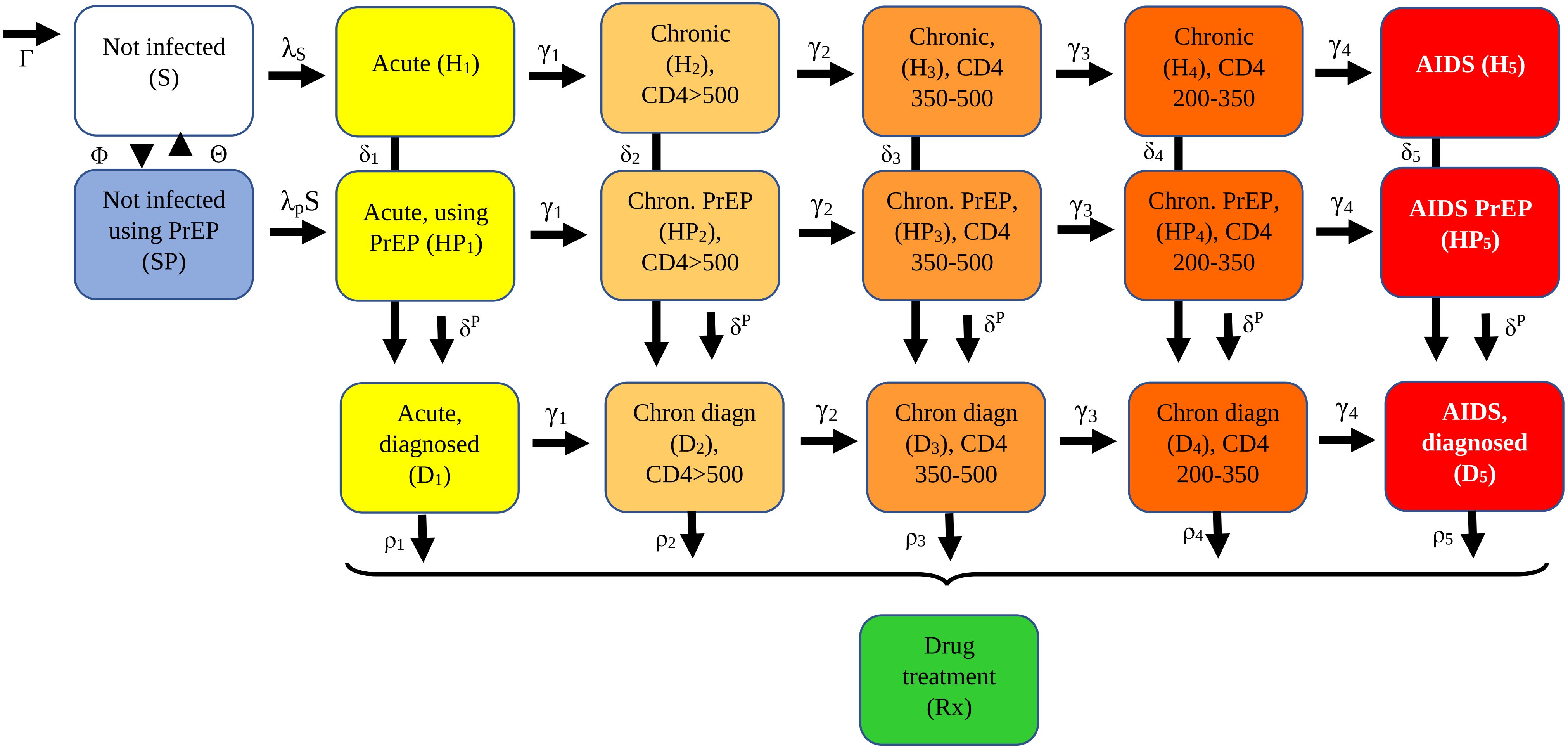
## Introduction

This document provides additional information on the mathematical model, calibration and multivariate sensitivity analysis of study on the cost-effectiveness and budget effect of preexposure prophylaxis (PrEP) in Germany.

## Mathematical transmission model

This study includes a compartmental deterministic mathematical transmission model that was developed for the HIV epidemic among men-who-have-sex-with-men (MSM) in the Netherlands[1, 2] and that was adapted to the HIV epidemic among MSM in Germany. The schematic representation of the model is presented in figure S1.

**Figure S1 –** *Schematic representation of the compartmental deterministic model (the mathematical equations can be found on pages 3-4 of the supplement). The state variables used in the equations are shown between brackets.*
*The parameters used in the equations are added next to the arrows that indicate the rate of change between the different compartments of the model. We assume that individuals can only start using PrEP when they are not infected with HIV. Individuals can become infected with HIV despite the use of PrEP.The arrows for infected (but not using PrEP) go through the boxes of individuals using PrEP that have an unrecognized HIV infection to the boxes of individuals that have been diagnosed but who do not use treatment (yet).*



## *Equations of the transmission model*

The model consists of 15 ordinary differential equations, including two equations that describe individuals that are not infected with HIV that use PrEP or do not use PrEP, ten equations that describe disease progression, two equations that describe the force of infection (or the rate by which individuals become infected)[3] and one equation that describes mixing between individuals of different risk groups[3, 4]. The equations are summarized below.

### *Ordinary differential equations for people not infected with HIV*

Individuals not infected with HIV are sub-divided into individuals that are not on PrEP, denoted as S (susceptible individuals modelled using equation 1) and individuals using PrEP denoted as SP (suspeptible individuals using PrEP, modelled using equation 2). The sexual activity classes are defined in the equations in four groups $a$ ranging from the group with the highest sexual activity ($a$ = 1) to the group with the lowest sexual activity ($a$ = 4). Susceptible individuals have a mortality rate $\mu$. Individuals that become sexually active enter the group of susceptible individuals not using PrEP at a rate $\Gamma$ times the proportion $\pi_a$ of each sexual activity group $a$. Values for the parameter $\Gamma$ have been calibrated to the German MSM population[5] (Table S1). Susceptible individuals can start PrEP at a rate $\Theta_a$ and discontinue PrEP at a rate $\Phi_a$ (the values $\Theta_a$ and $\Phi_a$ for the lowest sexual activity groups $a=3$ and $a=4$ were set to zero as we assumed that PrEP will only be used for MSM at high risk for HIV infection). The force of infection, denoted as $\lambda_a$ for individuals not using PrEP (modelled using equation 13) and $\lambda^P_a$ for individuals using PrEP (equation 14), represents the rate by which individuals become infected with HIV.

$$S_a' = \Gamma.\pi_a - S_a(\lambda_a + \Theta_a + \mu) + SP_a.\Phi_a \quad (1)$$

$$SP_a' = S_a.\Theta_a - SP_a(\lambda^P_a + \Phi_a + \mu) \quad (2)$$

### *Equations for undiagnosed HIV infected individuals*

Individuals that become infected with HIV but that have not been diagnosed yet (denoted with $H$ in equations 3 through 5), progress through five stages of infection that are denoted by the parameter $\sigma$. These stages of infection are the acute stage ($\sigma$ = 1, modelled using equation 3), the chronic stages ($\sigma$ = 2 if the CD4 cell count is > 500 cells/µl, $\sigma$ = 3 for a CD4 between 350 and 500 cells/µl and $\sigma$ = 4 for a CD4 between 200 and 350 cells/µl, all modelled using equation 4) and the AIDS stage ($\sigma$ = 5, modelled using equation 5). Individuals progress through infection at a rate $\gamma_\sigma$ that depends on the stage of infection $\sigma$[6]. Individuals are diagnosed at a rate $\delta_\sigma$ that has been calibrated to the proportion of MSM that are diagnosed at a particular CD4 threshold as reported by the Robert Koch Institute. The mortality rate depends on the stage of infection (denoted as $\mu_\sigma$).

$$H_{\sigma,a}' = \lambda_a.S_a - H_{\sigma,a}(\delta_\sigma + \gamma_\sigma + \mu_\sigma) \text{..... for } \sigma = 1 \quad (3)$$

$$H_{\sigma,a}' = H_{\sigma-1,a}.\gamma_{\sigma-1} - H_{\sigma,a}(\delta_\sigma + \gamma_\sigma + \mu_\sigma) \text{..... for } \sigma = 2, 3, 4 \quad (4)$$

$$H_{\sigma,a}' = H_{\sigma-1,a}.\gamma_{\sigma-1} - H_{\sigma,a}(\delta_\sigma + \mu_\sigma) \text{.......... for } \sigma = 5 \quad (5)$$

### *Equations for HIV infected undiagnosed individuals using PrEP*

The equations used to model individuals that become infected with HIV despite the use of PrEP (denoted as $HP$ in equations 6 through 8), are comparable to the equations used to model HIV-infected individuals that do not use PrEP (equations 3, 4 and 5). Individuals using PrEP are assumed to be tested for HIV every six months at a rate (denoted as $\delta^P$).

$$HP_{\sigma,a}' = \lambda^P_a.SP_a - HP_{\sigma,a}(\delta^P + \gamma_\sigma + \mu_\sigma) \text{..... for } \sigma = 1 \quad (6)$$

$$HP_{\sigma,a}' = HP_{\sigma-1,a}.\gamma_{\sigma-1} - HP_{\sigma,a}(\delta^P + \gamma_\sigma + \mu_\sigma) \text{..... for } \sigma = 2, 3, 4 \quad (7)$$

$$HP_{\sigma,a}' = HP_{\sigma-1,a}.\gamma_{\sigma-1} - HP_{\sigma,a}(\delta^P + \mu_\sigma) \text{.......... for } \sigma = 5 \quad (8)$$

### *Equations for HIV untreated infected individuals that have been diagnosed*

Individuals that are diagnosed with HIV but that are not treated with antiretroviral drugs (yet) are denoted as $D$ (equations 9 through 11). Diagnosed individuals start treatment at a rate $\rho_\sigma$. The rate $\rho_\sigma$ depends on the stage of infection $\sigma$ to reflect past changes in the CD4 cell count at which treatment was initiated. Per recent treatment guidelines, antiretroviral drugs are started irrespective of the stage of infection as of 2017 when we assumed that PrEP became available in Germany.

$$D_{\sigma,a}' = H_{\sigma,a}.\delta_\sigma. + HP_{\sigma,a}.\delta^P - D_{\sigma,a}(\gamma_\sigma + \rho_\sigma + \mu_\sigma) \text{ ..... for } \sigma = 1 \quad (9)$$

$$D_{\sigma,a}' = H_{\sigma,a}.\ \delta_\sigma.+ HP_{\sigma,a}.\delta^P + \gamma_{\sigma-1}.D_{\sigma-1,a} - D_{\sigma,a}(\gamma_\sigma + \rho_\sigma + \mu_\sigma) \text{ ..... for } \sigma = 2, 3, 4 \quad (10)$$

$D_{\sigma,a}' =$ $H_{\sigma,a}.\ \delta_{\sigma}. + HP_{\sigma,a}.\delta^{P} + \gamma_{\sigma-1}.D_{\sigma-1,a} - D_{\sigma,a}(\rho_{\sigma} + \mu_{\sigma})$ ….. for $\sigma = 5$ (11)

### *Equations for individuals using antiretroviral drug treatment*

Individuals that use antiretroviral drugs are represented by the state variable *Rx* (equation 12). People treated with antiretroviral drug treatment are assumed to have the same mortality as the general population[7].

$$Rx_a' = \sum_{\sigma=1}^{5} \rho_\sigma D_{\sigma,a} - Rx_a \mu \quad (12)$$

### *Equations for the force of infection*

The force of infection is modelled using equation 13 for individuals not using PrEP ($\lambda_a$), and using equation 14 for individuals using PrEP ($\lambda^P{}_a$). The force of infection depends on the rate of sexual partner change ($c_a$) for individuals with sexual activity *a*, and the probability by which these individuals form a sexual relationship with an individual with sexual activity *i* as determined by the mixing matrix $M_{a,i}$ (equation 15). The rate of infection also depends on the infectivity of the different stages of infection represented. The model uses three different parameters of infectivity that all depend on the stage of infection $\sigma$, including $\beta_\sigma$ for untreated HIV infected individuals that do not use PrEP, $\beta_\sigma{}^P$ for individuals using PrEP and $\beta_{Rx}$ for individuals using antiretroviral drug treatment.

$$\lambda_a = c_a \sum_{i=1}^{4} \frac{Ma,i}{Ni} \left(\sum_{\sigma=1}^{5} \beta_\sigma H_{\sigma,i} + \sum_{\sigma=1}^{5} \beta_\sigma{}^P HP_{\sigma,i} + \sum_{\sigma=1}^{5} \beta_\sigma D_{\sigma,i} + \beta_{Rx} Rx_i\right) \quad (13)$$

$$\lambda^P{}_a = c_a \sum_{i=1}^{4} \frac{Ma,i}{Ni} \left(\sum_{\sigma=1}^{5} \beta_\sigma{}^P H_{\sigma,i} + \sum_{\sigma=1}^{5} \beta_\sigma{}^P HP_{\sigma,i} + \sum_{\sigma=1}^{5} \beta_\sigma{}^P D_{\sigma,i} + \beta_{Rx}{}^P Rx_i\right) \quad (14)$$

### *Mixing matrix*

$M_{a,j}$ is a mixing matrix in which the elements *a,j* are the probability that an individual in sexual activity class *a* forms a sexual partnership with an individuals with sexual activity *j*. The mixing matrix includes a factor $\varepsilon$ which denotes the degree of assortative mixing, and $\delta_{a,j}$ denotes Kronecker delta which is equal to zero if individuals are in the same sexual activity class or equal to one if the individuals are in different sexual activity classes[4].

$$M_{a,i} = \varepsilon.\delta_{a,i} + (1 - \varepsilon)\ c_a \frac{N_i}{\sum_{a=1}^{4} c_a n_a} \quad (15)$$

## **Model calibration**

The model has been calibrated to the historic HIV epidemic based on: the estimated German MSM population size[5], number of MSM diagnosed with HIV, percentage diagnosed with a CD4 greater than 500 cells per µl and percentage diagnosed with a CD4 cell count less than 200 cells per µl, estimated number of MSM living with HIV in Germany and the estimated number of new infections[8] (Table S1).

**Table S1** *Variables used to calibrate and accept simulation using Monte Carlo filtering techniques. A total of 862 simulation were accepted (out of one million simulations run).*

| Parameter used for calibration | Data in real world | Values accepted in calibration<br>Median (minimum - maximum) | Source |
|---|---|---|---|
| MSM population (15+)<br>2013<br>2014<br>2015 | <br>850,000<br>856,000<br>866,000 | <br>862,000 (820,000 – 900,000)<br>863,000 (820,000 – 910,000)<br>864,000 (820,000 – 920,000) | [5] |
| Number of new diagnosis among MSM<br>2013<br>2014<br>2015 | <br>1728<br>1894<br>1851 | <br>1892 (1502- 2196)<br>1972 (1653- 2397)<br>2072 (1833 – 2513) | [8-10] |
| Proportion diagnosed at a CD4 of<br>>500 cells/µl<br>350 – 500 cells/ µl<br>200 – 350 cells/ µl<br><200 cells/ µl | <br>31%<br><br><br>30% | Proportions add up to 100%<br>33% (20 – 40%)<br>22% (10 – 30%)<br>22% (10 - 30%)<br>23% (15 – 30%) | [8-10] |
| Number of MSM living with HIV | 56,000 | 50,000 (45,000 – 65,000) | [8-10] |

## Costs

The costs are considered from the perspective of the health care payer (statutory health insurance).

### *Costs of PrEP*

In our analysis we assumed that PrEP will be reimbursed by the German health care payer. As such we included the costs of PrEP into our analysis. The cost for PrEP comprise regular physician visits and laboratory testing during PrEP according to the German practice guidelines [11]. Unit costs for each service are derived from the Uniform Value Scale (UVS; Einheitlicher Bewertungsmaßstab)[12] for the SHI (statutory health insurance) perspective (Table S2). The annual costs for providing PrEP, including monitoring and costs of the drugs, are € 823.91.

**Table S2** – *Annual costs per service from the SHI (Statutory Health Insurance) for use of Pre-exposure prophylaxis (PrEP)*

| Type of service | Frequency of service | Costs | |
|---|---|---|---|
| | | **Year 1** | **Year 2 and further** |
| Physician visit | Initial visit, 1 month after initiation, after that every 3 months | 67.80 € | 67.80 € |
| HIV-test | Initial visit, 1 month after initiation, after that every 3 months | 16.40 € | 16.40 € |
| Hepatitis C | Initial visit, after that once per year | 9.80 € | 9.80 € |
| Syphilis | Initial visit, 1 month after initiation, after that every 3 months | 18.40 € | 18.40 € |
| HBc-Antibodies | Initial visit | 5.90 € | - € |
| HBs-Antigens | Initial visit | 5.50 € | - € |
| HBs-Antibodies | Initial visit | 5.50 € | - € |
| Hepatitis B vaccination | initial visit, after 4 and 24 weeks; every ten years | 67.27 € | - € |
| Creatinine | Initial visit, 1 month after initiation, after that every 3 months | 1.60 € | 1.60 € |
| Liver enzymes, (ALT, ALAT) | Initial visit, 1 month after initiation, after that every 3 months | 1.00 € | 1.00 € |
| Urine culture | Initial visit, 1 month after initiation, after that every 3 months | 2.00 € | 2.00 € |
| **Total services** | | **201.17 €** | **117.00 €** |
| Cost PrEP | Daily intake | 664.82 € | |
| **Total cost PrEP** | | **823.91** €* | |

* Based on an average cost of € 159.08

### *Cost of HIV Treatment*

We previously reported that expenditure on HIV is mainly driven by the costs of antiretroviral drugs [13] The costs of antiretroviral drugs are reimbursed by the health care payer.

The cost of antiretroviral drug treatment was based on the price of the recommended antiretroviral drug regimens for treatment of HIV in Germany[11]. The German treatment guidelines recommend to always include a backbone of two nucleoside reverse transcriptase inhibitors (NRTI) in combination with a third drug which is either a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI)[14]. For these ART components the mean cost per DDD (defined daily dose) was calculated based on the price of the largest package size given in the Lauer-Taxe® pharmacy price formulation[15]. In the cost calculation single-tablet preparations are distinguished from multi-tablet regimes.

To reflect current clinical practice the proportion of HIV-infected MSM receiving a given antiretroviral drug regimen is used to calculate a weighted mean ART cost. The Seroconvert-Study run by the Robert Koch-Institute (RKI) includes HIV-infected patients with a confirmed seroconversion within the three years prior to study participation [16]. Information on the antiretroviral drug regimen among MSM in this study who initiated ART in 2015 or 2016 was provided by the RKI (table S3). The annual cost per ART-regime and the weighted mean cost of ART are given in table S3. Based on these data the costs of treating a HIV-infected individual in Germany is at average € 15,010.78 per year. The main paper includes a sensitivity analysis which showed that the impact of reducing the price of antiretroviral drugs by up 90% (Table 2 and Table 3).

**Table S3** *Annual costs of antiretroviral drug regimens from the SHI (Statutory Health Insurance) perspective. The costs are calculated using a backbone of two nucleoside reverse transcriptase inhibitors plus a third drug*

| **Third drug** | **Frequency** | **Costs** |
|---|---|---|
| Protease inhibitor | 4.9% | 17,189.54 € |
| NNRTI | 0.8% | 13,180.19 € |
| NNRTI single-tablet | 6.9% | 12,207.50 € |
| Integrase inhibitor | 32.4% | 17,711.11 € |
| Integrase inhibitor single-tablet | 55.0% | 13,607.44 € |
| **Weighted mean** | | **15,010.78 €** |

We also considered costs, other than antiretroviral drugs, of treating HIV that are paid by the health care payer. These other costs physician visits, hospitalization, rehabilitation, home care, domestic help, travel cost and productivity loss that is covered by health care payer (partial or full inability to work, and sick leave after six weeks. The first six weeks of sick leave were not considered as these are paid by the employer). We based these costs on the values reported in the K3A study[13], which performed a detailed micro-costing on treatment of HIV-positive patients in 2008 in German clinical practice[13]. The values reported for 362 MSM participating in the K3A study[13] have been adjusted to reflect 2016 values using the harmonized German general consumer price index[17]. The total annual costs of treating HIV-infected MSM in Germany is € 17,015.93**,** which includes € 2,005 for non-antiretroviral drug related costs and € 15,010.78 for antiretroviral drugs (Table S4).

**Table S4** *Annual costs for treating HIV, excluding the costs of antiretroviral drug treatment. Costs are presented from the SHI (Statutory Health Insurance) perspective*.

| **Cost component** | **Costs** |
|---|---|
| Outpatient visits HIV specialist | 269.18 € |
| Outpatient visits other specialists | 69.91 € |
| Hospitalization | 1,150.86 € |
| Rehabilitation | 64.32 € |
| ***Subtotal direct cost*** | ***1,554.27 €*** |
| Home care | 73.74 € |
| Domestic help | 135.20 € |
| Travel costs | 3.15 € |
| Sick leave | 238.79 € |
| ***Subtotal indirect cost*** | ***450.88 €*** |
| **Total cost without antiretroviral drug treatment** | **2,005.15 €** |
| Antiretroviral drug treatment | 15,010.78 € |
| **Total cost HIV treatment** | **17,015.93 €** |

## Utility weights

The utility weights of the quality adjusted life years (QALYs) are based on estimates from Tengs and colleagues[18]. For individuals using PrEP, we assumed a utility weight of 1[1] (Table S5).

**Table S5 –** *Assumed utility weighting for Quality Adjusted Life Years (QALYs), as derived from a study by Tengs and colleagues[18]*

| Status | Utility weight |
|---|---|
| Not infected with HIV/using PrEP | 1 |
| CD4 > 350 cells/ | 0.94 |
| CD4 cell count 200-350 cells/ | 0.82 |
| AIDS stage | 0.7 |
| HIV infected using antiretroviral drug treatment | 0.94 |

## Multivariate sensitivity analysis using recursive partitioning

Recursive partitioning using the rpart library in R version 3.5.0 was used for multivariate analysis[19]. The primary endpoint in this analysis is the median budget effect for PrEP at 85% effectiveness and 30% coverage. All 32 model parameters that were varied by simulation were entered in this analysis. The N of the recursive partitioning tree represents the number of simulations that fulfill all of the given criteria for a branch in the tree. The percentage represents the proportion of simulations which are lower than the median budget effect of PrEP at current generic price with 80% effectiveness (a median saving of €5.1 billion over 40 years). The percentages highlighted in red represent branches of the tree in which 50% or more of the simulations resulted in a higher-than-median budget effect. The percentages highlighted in green represent branches of the tree in which 50% or less of the simulations resulted in a lower-than-median budget effect. Observations for which less than 90 simulations (equal to less than 10% of all simulations) were found were not included.
In our model, the proportion of MSM in in the second-highest sexual activity group (>24.8%) was the strongest predictor for lower-than-median cost savings (Figure S2).

**Figure S2** – *Results of multivariate sensitivity analysis using recursive partitioning*

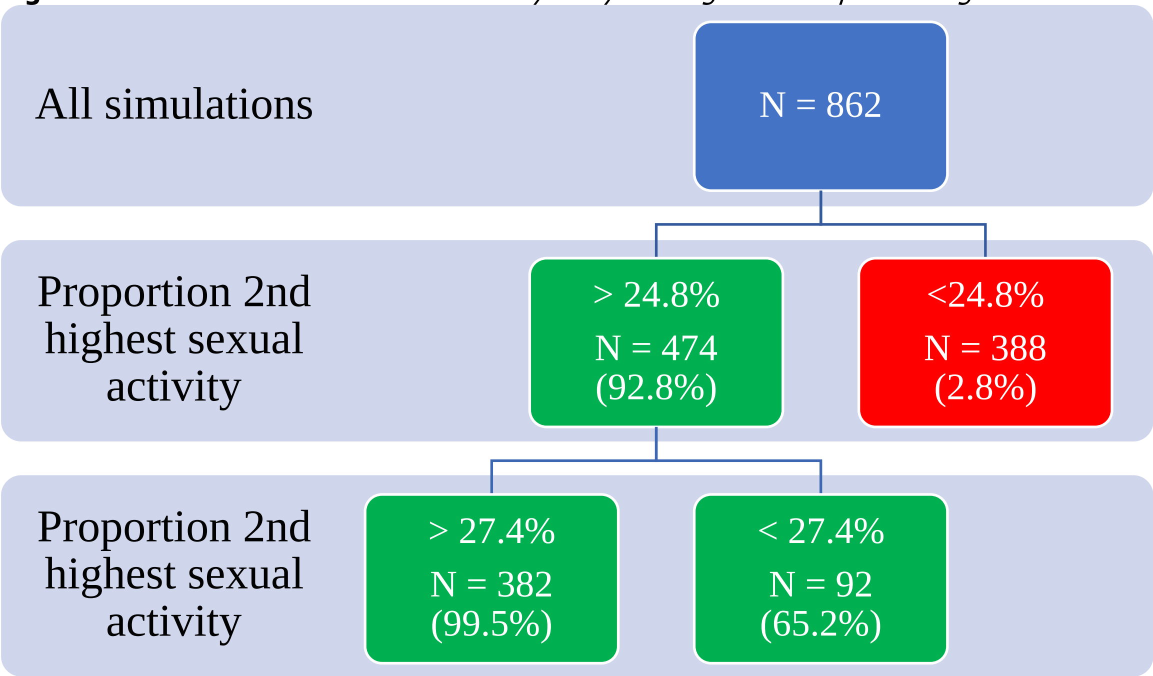


**Table S6** Undiscounted cumulative costs in million Euro's during first ten years (2018-2029) after introduction of PrEP stratified by effectiveness of PrEP and by reduction in costs of antiretroviral drug treatment. The discounting costs (yearly rate of 3%) are presented in Table 2 of the main paper.

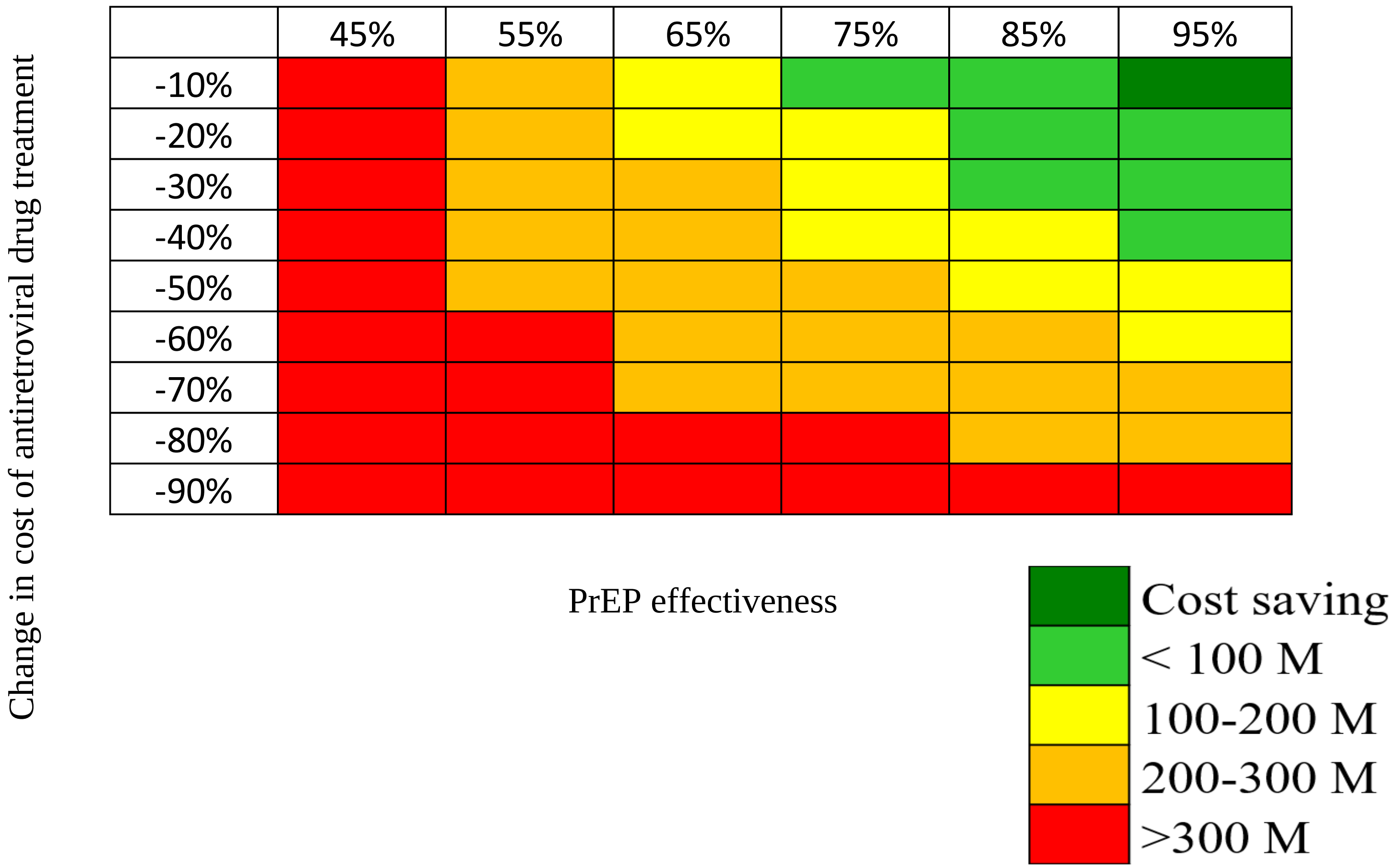
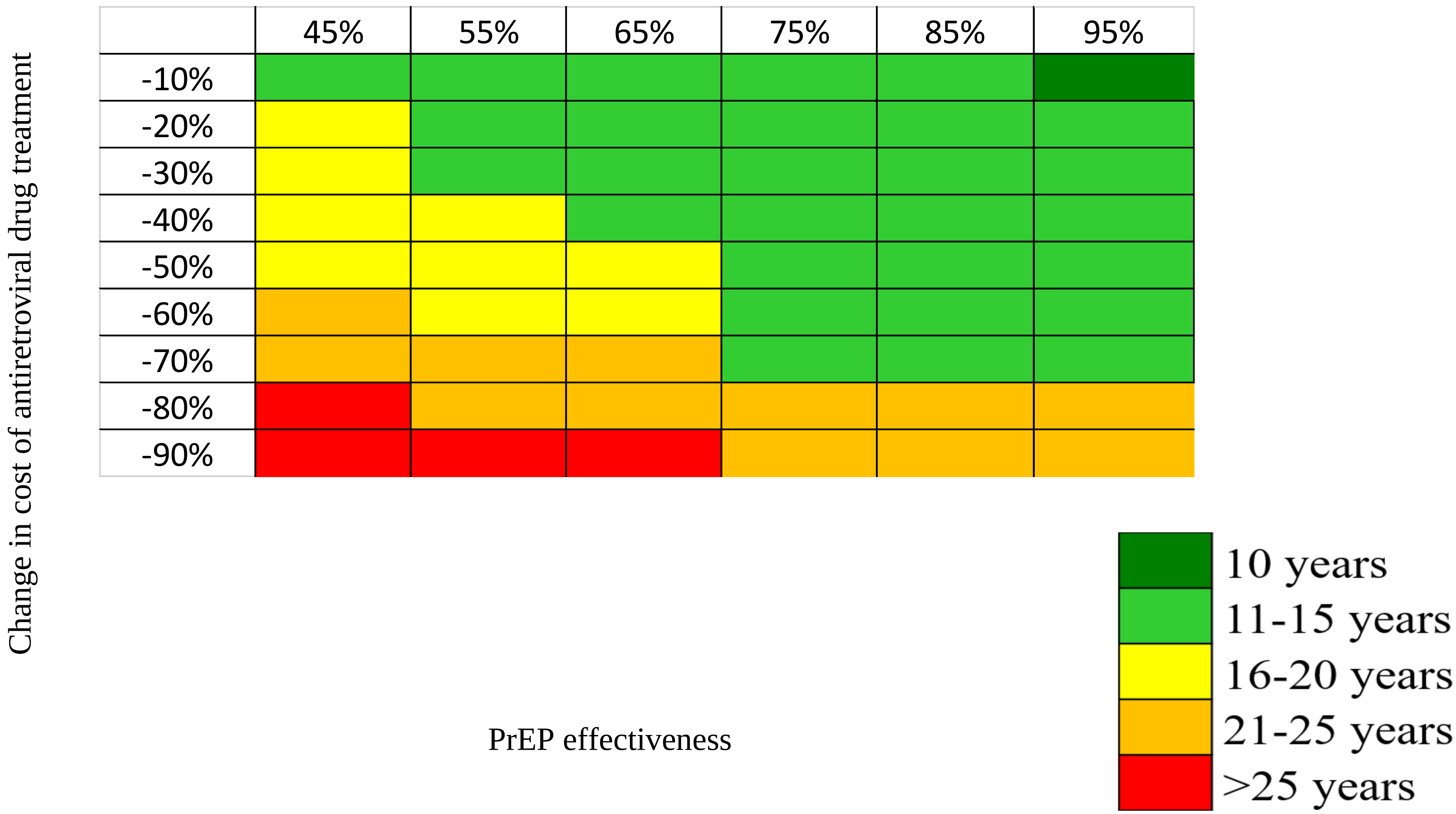


**Table S7** *Minimum of years to reach break-even point in which the cumulative undiscounted costs of HIV infections averted exceed the costs of a PrEP programme. The analysis are stratified by the effectiveness of PrEP in reducing the risk of HIV infection and the future costs of antiretroviral drug treatment compared to the current costs. PrEP is assumed to be initiated in 2018. The break-even point for the discounted costs (at an annual rate of 3%) are presented in Table 3 of the main paper.*



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