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ORIGINAL PAPER

Health and budget impact of combined HIV prevention – first results of the BELHIVPREV model

Sebastian Vermeersch[a], Steven Callens[b], Stéphane De Wit[c], Jean-Christophe Goffard[d], Marie Laga[e], Dominique Van Beckhoven[f] and Lieven Annemans[g]

[a]hict, Brugge, Belgium; [b]Department of Internal Medicine and Infectious Diseases, Ghent University Hospital, Gent, Belgium; [c]Department of Infectious Diseases, CHU Saint-Pierre, Brussels, Belgium; [d]Service of Internal Medicine, HIV Reference Centre, ULB – Hôpital Erasme, Brussels, Belgium; [e]HIV and Sexual Health Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium; [f]Epidemiology of Infectious Diseases Unit, Scientific Institute of Public Health (WIV-ISP), Brussels, Belgium; [g]Faculty of Medicine and Health Science, Department of Public Health, Ghent University, Gent, Belgium

ABSTRACT

Objectives: We developed a pragmatic modelling approach to estimate the impact of treatment as prevention (TasP); outreach testing strategies; and pre-exposure prophylaxis (PrEP) on the epidemiology of HIV and its associated pharmaceutical expenses.

Methods: Our model estimates the incremental health (in terms of new HIV diagnoses) and budget impact of two prevention scenarios (outreach+TasP and outreach+TasP+PrEP) against a 'no additional prevention' scenario. Model parameters were estimated from reported Belgian epidemiology and literature data. The analysis was performed from a healthcare payer perspective with a 15-year-time horizon. It considers subpopulation differences, HIV infections diagnosed in Belgium having occurred prior to migration, and the effects of an ageing HIV population.

Results: Without additional prevention measures, the annual number of new HIV diagnoses rises to over 1350 new diagnoses in 2030 as compared to baseline, resulting in a budget expenditure of €260.5 million. Implementation of outreach+TasP and outreach+TasP+PrEP results in a decrease in the number of new HIV diagnoses to 865 and 663 per year, respectively. Respective budget impacts decrease by €20.6 million and €33.7 million.

Conclusion: Foregoing additional investments in prevention is not an option. An approach combining TasP, outreach and PrEP is most effective in reducing the number of new HIV diagnoses and the HIV treatment budget. Our model is the first pragmatic HIV model in Belgium estimating the consequences of a combined preventive approach on the HIV epidemiology and its economic burden assuming other prevention efforts such as condom use and harm reduction strategies remain the same.

KEYWORDS

Prevention and control; HIV; pre-exposure prophylaxis; health impact assessment; budgets

Introduction

The prevalence of HIV in the Western world is still rising [1]. Improved efficacy of treatment with antiretroviral therapy (ART) and improved follow-up have turned HIV into a condition that can be successfully managed on a long-term basis [2]. HIV incidence has however been difficult to control, and despite the still higher than average use of preventive measures such as condom use [3], high-risk behaviour among people at risk for HIV is still a concern [4–6]. New HIV diagnosis rates in Belgium remain high with respect to the West European WHO region [7]. The lack of control of the epidemic leads to an increasing economic burden related to the management of a continuously increasing number of HIV patients. A significant part of this economic burden is associated with the long-term pharmaceutical management of these patients [8,9].

Several large trials have shown the effect of ART use to reduce HIV transmission and acquisition [10–13]. In this context, the panel of available preventive strategies, including treatment as prevention, has enlarged. In order to counter the increasing epidemiologic and economic impact, a stronger focus on the use of these preventive measures is required. Different preventive strategies are possible and might be combined:

- overall population-based primary prevention strategies such as condom and lubricant distribution and awareness raising campaigns;
- reducing the number of patients unaware of their infection by identifying previously undiagnosed

CONTACT Sebastian Vermeersch sebastian.vermeersch@hict.be

HIV patients (for instance, outreach programmes designed to access people at high risk of acquiring HIV, including testing of people unaware of their HIV status);
- reducing the number of diagnosed patients not on ART through prompt initiation of treatment in all patients diagnosed with HIV, including those with high CD4 levels (immediate ART/treatment as prevention – TasP);
- ensure an optimal retention in care and adherence of the HIV patients receiving ART;
- preventing HIV infection through prophylactic treatment after a possible recent exposure (post-exposure prophylaxis – PEP);
- preventing HIV infection through prophylactic treatment in uninfected individuals at high risk of infection (pre-exposure prophylaxis – PrEP).

The projected impact of these measures on the epidemiology and economic burden of HIV has not been adequately studied in a Belgian context. Health policy makers have limited resources and seek evidence to better allocate these resources into those strategies and measures that increase health and are cost-effective. Modelling techniques are required to better understand the implication of different strategic choices on the epidemiology of HIV, patient outcomes, health economic benefits and impacts on health care systems.

Aim

The aim of this paper is to present a new pragmatic modelling approach, the BELHIVPREV (Belgian HIV Prevention) model, to estimate the impact of (1) immediate ART/TasP; (2) reducing the number of patients unaware of their infection (outreach); and (3) PrEP; on the epidemiology of HIV and the associated pharmaceutical expenses. In a secondary analysis, the added value of increased investments in other primary prevention interventions will also be assessed. This secondary analysis is not part of the current paper.

Methods

Modelling approach

We developed a predictive model estimating the annual number of new HIV diagnoses and the total number of HIV patients in medical follow-up.

The model outcomes included the annual estimated number of new HIV diagnoses, the annual estimated number of patients in medical follow-up, and the estimated total treatment cost for routine HIV and preventive treatment for various preventive scenarios. In addition, the annual and total cost of treating newly and previously infected HIV patients is included in the analyses to gain an understanding of the potential economic benefits of preventive treatment strategies. Model parameters were estimated based on reported Belgian HIV epidemiology figures from 2007 to 2015 supplemented by data extracted from literature.

The model estimated the incremental budget and health (in terms of total number of patients on HIV treatment and the annual number of new HIV infections) impact of different scenarios in which the implementation of one or more types of prevention strategies were assumed against a base case scenario in which no additional effort on prevention was assumed to occur. Thereby, the (pharmaceutical) costs and (epidemiological) effects of preventive measures such as outreach testing, immediate ART/TasP and PrEP as well as the (pharmaceutical) cost for the routine treatment of HIV-positive patients were taken into account.

Analysis perspective

The budget analysis was performed from the perspective of the pharmaceutical healthcare payer budget. Consequently, it did not consider non-pharmaceutical costs, such as cost of outreach testing activities, diagnosis and HIV patient follow-up.

Time horizon

The model results included the health and budget impact of the preventive strategies for a 15-year-time horizon, up to 2030. This time horizon was selected to investigate mid- to long-term effects while minimizing potential distortion of outcomes associated with long-term extrapolations.

Model framework

The model consisted of three core components:

(1) An estimation of the annual number of new HIV diagnoses, based on the estimate of the total number of 'infectious' patients and the degree of their infectiousness.
(2) Estimation of the annual number of patients in medical follow-up, based on the calculated estimate of new HIV diagnoses entering follow-up, minus death and dropout added to those already in follow-up from previous years.
(3) Integration of the effect of increasing the number of diagnosed patients on ART (immediate ART/TasP), decreasing the number of undiagnosed patients (outreach testing) and reducing the number of new HIV infections through prophylactic treatment (PrEP).

In the following paragraphs, we outline the dynamics and data inputs associated with these three components. More details on the model's mechanics and calculations can be found in Appendix 1.

(1) Estimating the annual number of new HIV diagnoses

To estimate the annual number of new HIV diagnoses, first an estimate of the total 'infectious' population was calculated. For the purposes of our model, an HIV patient was deemed to be 'infectious' if:

(a) the patient was undiagnosed;
(b) the patient was diagnosed but had not initiated treatment;
(c) the patient was being treated but had not achieved a controlled (undetectable; <200 copies/ml) viral load.

The number of undiagnosed HIV patients has not clearly been established. Based on available research and modelling data, it is assumed that between 10% and 20% of the current HIV population is undiagnosed [14]. For our model, we used an estimate of 12% undiagnosed HIV patients at the end of 2014. To simulate the effect of currently ongoing efforts in identifying undiagnosed patients, we furthermore assumed this percentage to gradually decrease to 10% in 2020, even in the absence of additional investments in prevention, after which it was assumed to remain constant.

The number of diagnosed patients not having initiated treatment was determined from reported percentages of patients on ART. At the end of 2013, 89% of patients followed up in an AIDS Reference Centre were on ART treatment [15]. In the absence of additional efforts, we assumed this percentage to gradually increase up to 92% in 2020, after which it was assumed to remain constant.

Finally, the model assumed that a proportion of patients on ART treatment remain infectious. This proportion was approximated based on reported numbers of patients not achieving a viral load (VL) of <200 copies/ml after receiving at least 6 months of antiretroviral therapy. According to Sasse et al., 96% of patients treated in an AIDS reference centre at the end of 2015 achieved a VL < 200 [14], meaning that 4% of treated patients were still infectious. This percentage was assumed to remain constant over time.

Using this approach, the total number of 'infectious patients' was calculated and compared to the reported number of newly diagnosed HIV infections [14] for each year between 2007 and 2015. The average result of this ratio was 23.7%. We labelled this ratio as a propagation factor: for each 1000 infectious patients, there are 237 new diagnoses. This propagation factor was then assumed to remain constant in the base case for future extrapolation. Based on reported figures for the Belgian continuum of care [16], we assumed around 90% of these newly diagnosed patients entered HIV care.

(2) Estimating the annual number of patients in medical follow-up

The estimated annual number of patients in medical follow-up was calculated year-to-year based on:

- the number of patients in medical follow-up at the end of the previous year;
- the number of newly diagnosed patients expected to enter follow-up, calculated as detailed above;
- the expected mortality rate;
- a 'net loss' factor, reflecting the net difference in patients lost to follow-up during that year and patients re-entering follow-up in the same year having been lost to follow-up in previous years [16].

The estimated mortality rate was calculated from the annual reported mortality and the annual number of newly diagnosed patients or patients in medical follow-up between 2007 and 2015 (0.3%) [14]. The estimate of the annual number of patients in medical follow-up was obtained by adding new diagnoses to, and subtracting estimated mortality from the previous estimate of the yearly number of patients in medical follow-up. This was compared to reported numbers from 2007 and 2015 [14] to calculate the 'net loss' factor (2.1%), which was then assumed to remain constant for future extrapolation. This net loss is the result of patients lost to follow up and other patients having been lost to follow up for a while but entering again into the system.

(3) Integrating the effects of outreach, immediate ART/TasP and PrEP

The effects of outreach and immediate ART/TasP were calculated in the model as a result of a decrease in the number of undiagnosed and untreated HIV patients, respectively.

To integrate the effect of PrEP, a stepwise approach was implemented: first, a theoretical annual 'population at risk' was defined from the calculated annual new HIV diagnoses and published HIV acquisition rates [17–19] (how many times the virus is likely to be acquired per 100 persons per year). Based on the ratio between both parameters, the size of the 'pool' of the population at risk can be derived. The impact of PrEP was modelled through a calculated decrease in the size of the annual 'population at risk', taking into account published PrEP effectiveness rates [17–19]. Finally, the estimated number of infections avoided was calculated by recalculating the annual number of new HIV diagnoses from the reduced 'population at risk', using the aforementioned HIV infection rates.

Taking into account (sub)population differences

The HIV epidemic in Belgium is mainly concentrated in two subpopulations: men who have sex with men and sub-Saharan African migrants having acquired the disease through heterosexual contact [14]. Given the concentrated epidemic in Belgium, prevention is also

tailored to these two priority groups. As a result, the model inputs needed for the above-described dynamics were different between different HIV subpopulations:

- men who have sex with men (MSM);
- heterosexuals;
- people who inject drugs (PWID).

The model allowed us to specify subpopulation-specific values for the following two parameters: the percentage of undiagnosed patients, with lower percentages for MSM (Odds Ratio of 0.39 for MSM [20]); and the HIV acquisition and transmission rates used to calculate the size of the 'population at risk' for estimation of the impact of PrEP: 6.6 per 100 person years for MSM; 3.1 per 100 person years for heterosexuals and 0.68 for PWID [17–19].

Moreover, the model accounted for the difference in HIV infectiousness depending on the stage of the HIV care continuum in which an infectious patient can be (undiagnosed, diagnosed but untreated, treated and VL ≥ 200 copies/ml) [21]. To achieve this, the 'propagation factor' used to calculate the estimated number of annual new HIV diagnoses was scaled to take into account the proportion of patients in each stage of the care continuum for each year in the model.

Finally, the model took into account that a number of newly diagnosed HIV patients were migrants who had acquired HIV in their home country prior to their arrival in Belgium. These patients were not expected to be influenced by Belgian efforts in HIV prevention. Our model assumed that 71% of HIV infections newly diagnosed in migrants were acquired outside of Belgium [22]. The resulting estimated number of new HIV diagnoses was assumed not to change regardless of the additional prevention effort simulated.

Including the effects of an aging HIV Population

The population living with HIV is on average getting older and the average age of people living with HIV is expected to continue to increase [23]. The model applied an expected gradual age increase from 41.6 years in 2010 to 54.3 years in 2030, based on the results of an extrapolation model applied to the Belgian HIV population. This age increase resulted in a higher background mortality over time. Background mortality rates were extracted from 2015 Belgian mortality tables [24].

Cost data

The model included the following costs:

- The pharmaceutical cost for ART treatment estimated at €1,027.5 per month [25]
- The cost-for PrEP-treatment estimated at €527.36 per month (based on 2017 RIZIV/INAMI prices). For the cost of PrEP treatment, the model took into account an expected 60% price decrease to €216.34 during 2017 due to the introduction of generics in July and cluster opening in October.

As stated previously, the perspective of the study was from the pharmaceutical budget holder and costs of outreach, testing, diagnosis and follow up costs were not included.

Analysis scenarios

The budget and health impact of combined prevention was assessed by two prevention scenarios compared to the same base case analysis.

The base-case analysis assumed:

- No additional preventive effort beyond the limited reduction of the percentage of undiagnosed patients (down from 12% in 2014 to 10% in 2020) and an increase in patients on ART (up to 92% in 2020 from 89% in 2013);

Hence, the base case represents a realistic scenario consisting of a spontaneous small improvement in the number of diagnosed and treated patients.

The first prevention (Outreach+TasP) scenario assumed:

- Additional efforts in reducing the percentage of undiagnosed patients through outreach testing programs leading to an additional 5% reduction over 5 years, reducing the absolute percentage of undiagnosed patients to 5%;
- Additional efforts in increasing the percentage of diagnosed patients on ART through immediate ART/TasP (additional 4% increase in ART treatment over 5 years, increasing the percentage of diagnosed patients on ART to 96%);

The second prevention scenario (Outreach+TasP+PrEP) assumed in addition to the preventive efforts outline in the first prevention scenario, a treatment of up to 2633 people with PrEP, of which 90% MSM.

Model validation and sensitivity analyses

We validated the model with historically available data, starting from 2007 data and extrapolating up until 2015 and comparing the model's predictions to the published data for that period.

Additionally, we tested the sensitivity of the model through a one-way sensitivity analysis (OWSA) on the expected budget impact and estimated number of new HIV diagnoses in 2030. The one-way sensitivity analysis included the following parameters: additional effort in reducing the number of undiagnosed patients (outreach testing); additional effort in increasing the percentage of patients on ART (immediate ART/TasP); the number of patients treated with PrEP; the annual cost of HIV

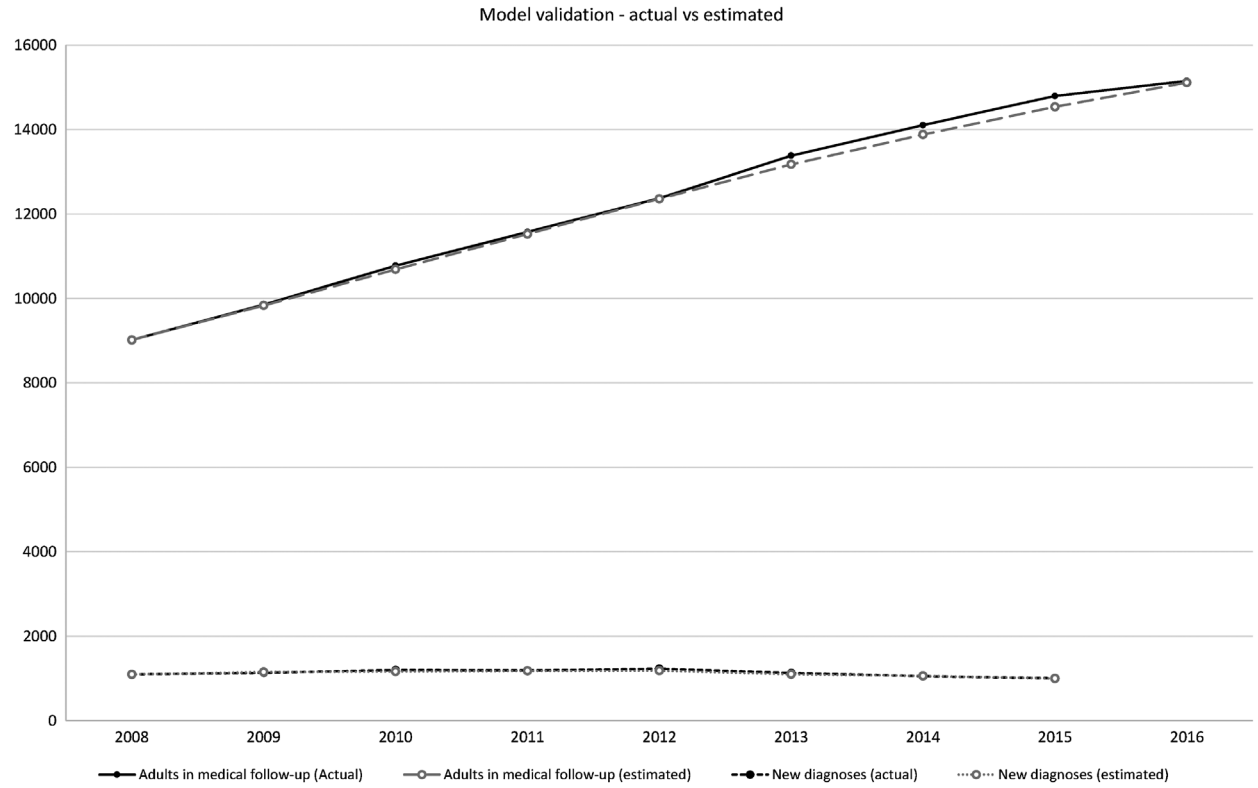

Figure 1. Results of the model validation comparing actual to estimated values for the number of patients in medical follow-up and new HIV diagnoses.

treatment; and the monthly cost of PrEP. Parameters were varied between 70% and 130% of their baseline values.

Results

Validation with historical data

Figure 1 illustrates the results of the model's validation. Estimated values for number of patients in medical follow-ups and newly diagnosed patients entering follow-up differed no more than 1.7% and 3.9% from actually recorded values, respectively.

Scenario 1 vs. baseline

In the absence of additional prevention and when maintaining current prevention efforts, the estimated number of annual new HIV diagnoses, after an initial period of decline, was expected to increase to over 1350 new diagnoses per year by 2030.

Implementation of Outreach+TasP resulted in a pronounced initial decline in new diagnoses, coupled with a gradual increase from 2020 on. This resulted in an expected reduction in the annual number of new HIV diagnoses from the 1350 projected in the baseline scenario down to 865 in 2030. From a budgetary perspective, the Outreach+TasP scenario is expected to be cost-saving from 2025 onwards (€3 million to €20.6 million annual savings from 2025 to 2030 – Figure 2).

Scenario 2 vs. baseline

In comparison to the baseline scenario, implementation of Outreach+TasP+PrEP resulted in a pronounced initial decline in new diagnoses with followed by a gradual increase from 2021 on. In comparison to Scenario 1, the initial decrease is slightly more pronounced and the gradual uptake less after the initial decrease is less important. This resulted in an expected reduction to 663 annual new HIV diagnoses in 2030. From a budgetary perspective, the outreach+TasP scenario is expected to be cost-saving from 2024 onwards (€1.9 million to €33.7 million annual savings from 2024 to 2030 – Figure 3).

Total budget – scenario 1 and 2 vs. baseline

In the absence of additional prevention and when maintaining current prevention efforts, the total (pharmaceutical) budget for HIV treatment is expected to increase to over €260 million in 2030. Even taking into account the additional treatment cost for immediate ART/TasP and PrEP, this total budget expenditure is expected to be significantly reduced, with expected total expenditures in 2030 of €239 million and €227 million for scenario 1 and scenario 2, respectively (Figure 4).

One-way sensitivity analyses

The results of the one-way sensitivity analysis are illustrated in the tornado diagram in (Figure 5). The tornado

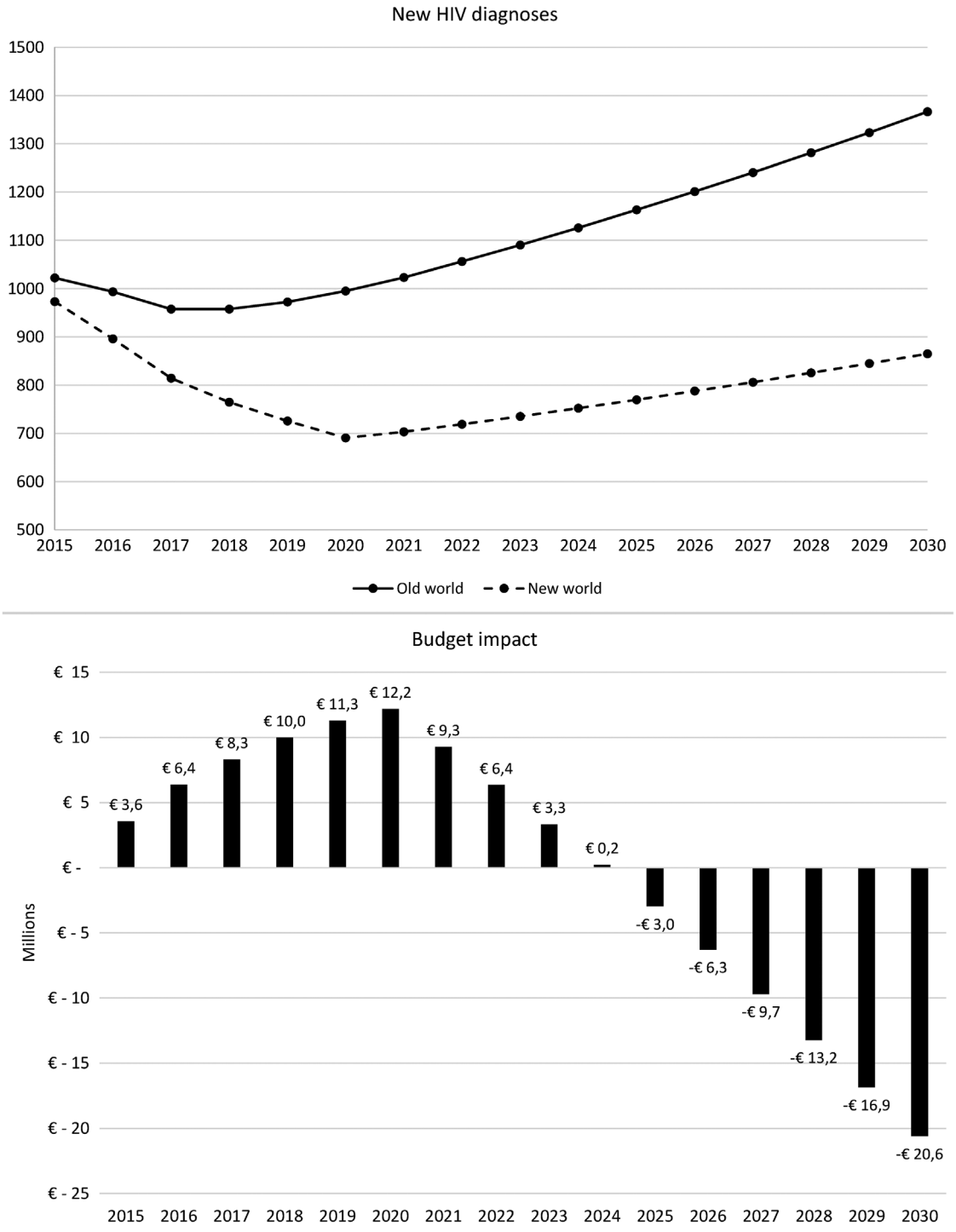

Figure 2. (Top) Yearly estimates for number of new HIV diagnoses for the outreach+TasP (new world) vs. no additional prevention (old world) analysis scenario. (Bottom) Yearly estimates of budget impact (outreach+Tasp additional expenditure/savings versus no additional prevention).

diagrams list, from top to bottom, in decreasing order the parameters the model is most sensitive to. Dark bars indicate the deviation from the base case result (33.7 million € for the estimated budget impact and 663 new diagnoses for the estimated number of new diagnoses) for the increase of the parameter specified to 130% of its base case value. Light bars indicate the deviation from the base case result for a decrease of the specified parameter to 70% of its base case value. The diagrams demonstrate that our model is most sensitive to the cost of HIV treatment with respect to its estimates for the estimated budget impact in 2030; and to the number of undiagnosed patients identified and initiated on ART (% outreach in the model) with respect to the number of new HIV diagnoses expected in 2030.

Discussion

The purpose of this model was to assess the possible impact of a series of preventive measures compared to a base-case scenario whereby no additional efforts are undertaken.

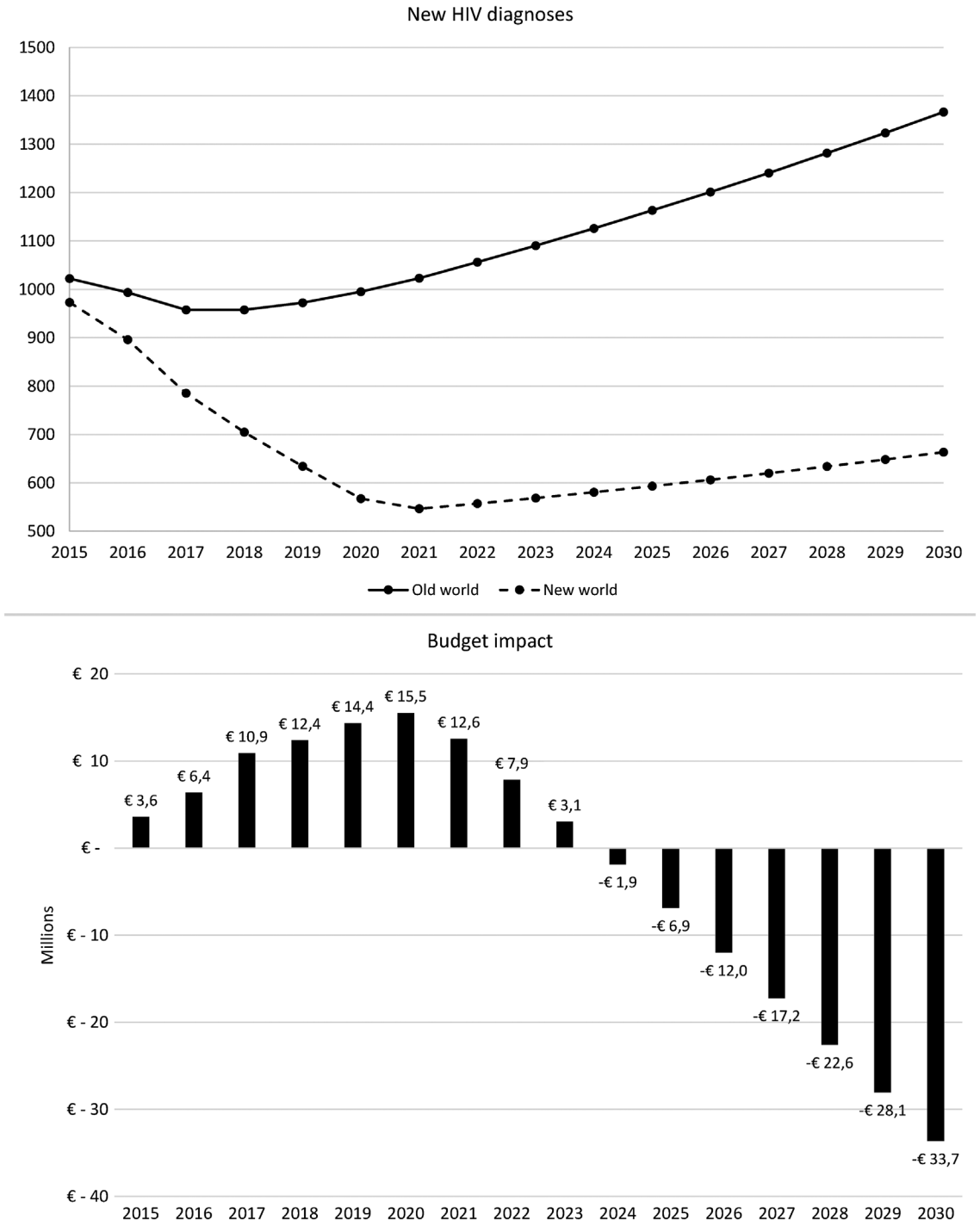

Figure 3. (Top) Yearly estimates for number of new HIV diagnoses for the outreach+TasP+PrEP (new world) vs. no additional prevention (old world) analysis scenario. (Bottom) Yearly estimates of budget impact (outreach+Tasp+PrEP additional expenditure/savings versus no additional prevention).

It should be noted that our base case, which presumes a natural, gradual increase in the number of patients diagnosed and treated, does not yet fully include recent efforts in promoting immediate ART/TasP. Since end 2016, RIZIV/INAMI – the Belgian public healthcare insurer – is reimbursing ART for all. The immediate ART/TasP included in both scenario 1 and scenario 2 in our analysis thus now represents the Belgian 'base case' scenario. We have opted not to include this effect in our base case scenario to fully capture the effect of 'combined prevention' and the added value in terms of health (new HIV diagnoses) and budget impact.

Our analysis indicates that, without explicit new efforts, the number of new HIV diagnoses in Belgium is expected to increase by 33% in 2030 when compared to 2015. With additional efforts in terms of immediate ART/TasP, outreach and PrEP, this figure can be reduced by 51% (down to 65% of the 2015 number of new diagnoses). This would lead to an expected budgetary savings of €33.7 million in 2030 alone.

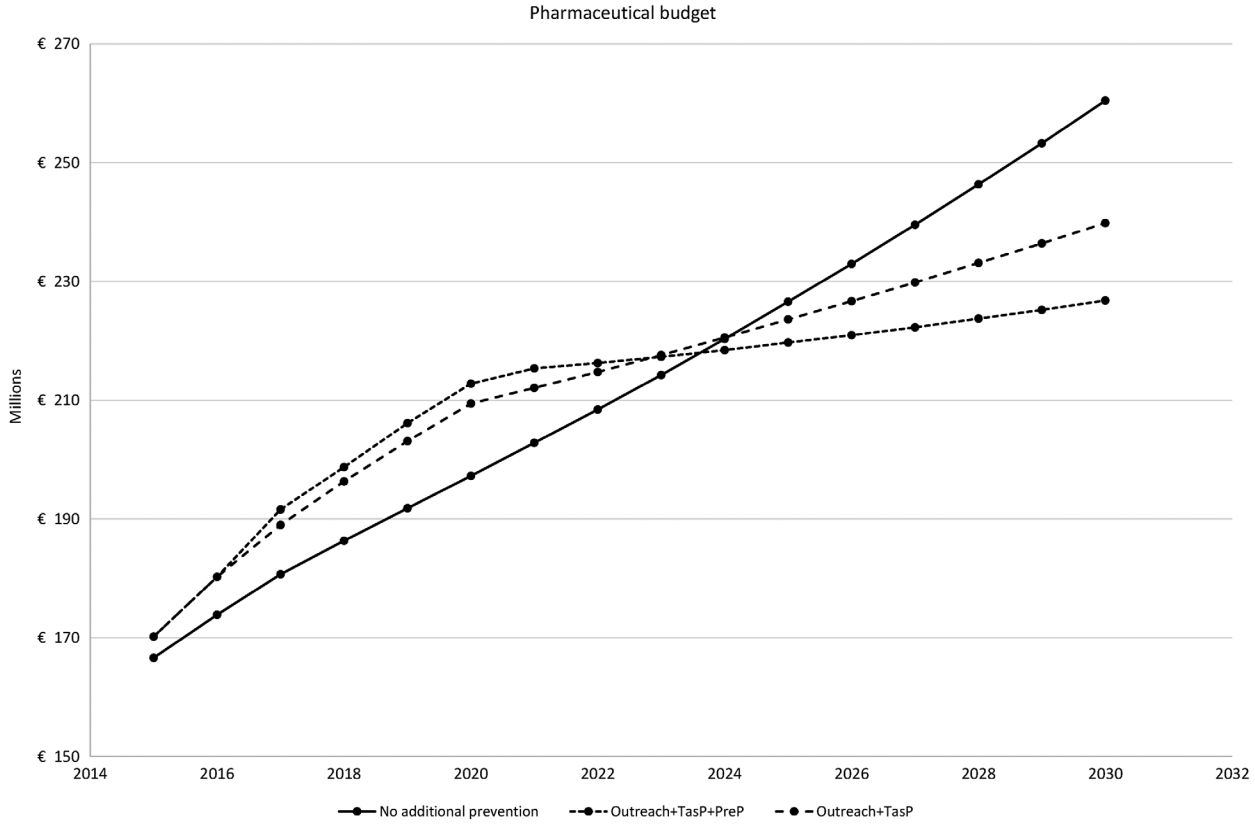

Figure 4. Estimated total (pharmaceutical) budget for the baseline (no additional prevention), outreach+TasP and outreach+Tasp+PrEP scenarios.

Based on this analysis, it is clear prevention provides good health-economic value, reducing the projected burden of disease at an overall cost savings. Investing in prevention programmes, therefore, appears cost-effective. A multifaceted approach would require an initial investment via additional drug expenditure that would be recovered over time leading to a break-even situation by the year 2025. The multifaceted approach combining immediate ART/TasP, outreach and PrEP appears the most cost-effective.

We investigated the sensitivity of our model to its most important determinants in terms of its main outcomes: cost of treatment (PrEP and HIV treatment) for budget impact and the number of patients reached through the different preventive efforts (outreach, immediate ART/TasP, PrEP) for budget impact and health impact (new HIV diagnoses). In terms of budget impact, the cost of HIV treatment is the parameter our model is most sensitive to. This is unsurprising, given that two of the three preventive approaches included in our model (outreach and immediate ART/TasP) involve diagnosing and/or treating previously undiagnosed and/or untreated patients, increasing the volume of patients on ART. Reducing the cost of ART, either through use of generics or specific agreements with pharmaceutical firms would further increase annual cost savings. However, even in the unlikely case of a 30% increase in HIV treatment cost by 2030, an annual cost saving of €22 million would still be realized with the multifaceted approach. In terms of health impact (number of new HIV diagnoses), our model is most sensitive to the number of undiagnosed patients additionally diagnosed and treated (outreach). This highlights the importance of improving performance at the start of the treatment cascade: the earlier people are made aware of and treated for their HIV infection, the better.

Health-economic models for the prevention of HIV have previously been proposed. In practice, however, these often relate to health-economic or budget impact analyses in a single product [26] or investigating a particular type of preventive approach [27]. In addition, models often either focus on budget or health/cost-effectiveness impact [26,28,29]. Our model offers an integrated view of different types of prevention programs and is specifically focused on the Belgian context. As such, it offers a comprehensive analysis framework for investigating budget and healthcare impact of prevention.

As with every model applied in predicting health and cost outcomes, the BELHIVPREV model has some limitations. First, some of the data available to populate the model were based on assumptions, such as the subpopulation-specific parameter estimates and the estimates of the number of undiagnosed patients. Second, the model shows macro-level results, and it remains difficult what the implications in terms of resources and organizational changes would be on a micro-level, i.e. the level of daily

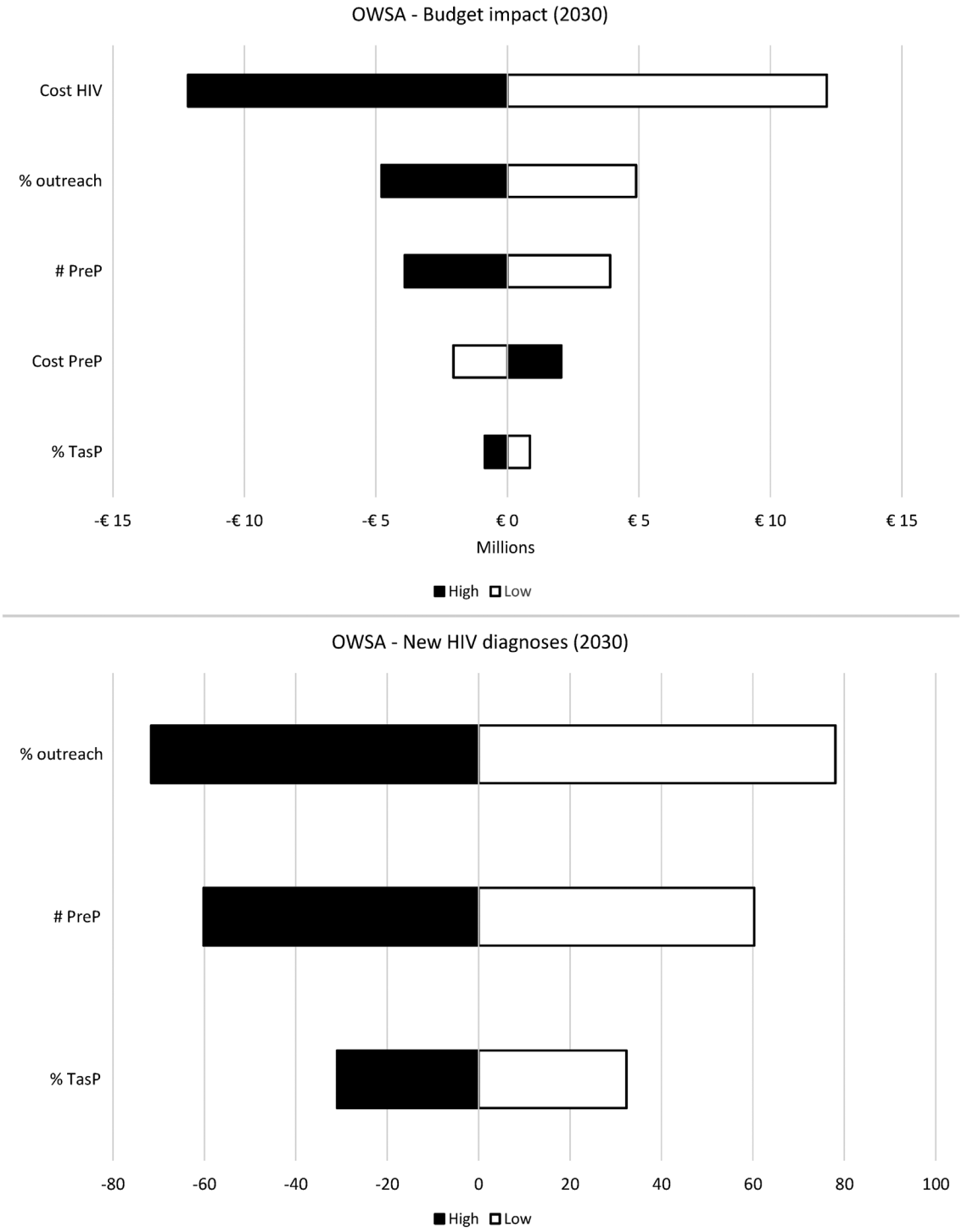

Figure 5. Tornado diagram illustrating the OWSA on key model parameters with respect to (top panel) the expected budgetary savings realized in 2030 (base case = 33.7 million €) and (bottom panel) the expected number of new HIV diagnoses in 2030 (base case = 663 new diagnoses). The OWSA was run on the scenario comparing baseline to outreach+TasP+PrEP.

practice. Third, the focus on pharmaceutical costs alone does not allow consideration of associated costs, e.g. identifying undiagnosed patients through outreach or other programs, or the cost impact of reduced hospitalizations or more effective management of comorbidities. Fourth, despite the fact that the model was validated against historical data, there remains uncertainty on the prediction of evolution of the HIV epidemic and budget impact. If the preventive multifaceted approach were to be formally introduced, it would be advisable to track the epidemic closely and to compare updated figures with the predictions of the model. This would allow recalibration of the model in accordance with a PDCA (plan-do-check-act) policy. Finally, the current results do not yet include the impact of 'general' prevention measures such as community actions and preventive campaigns.

Future work with the BELHIVPREV model will include the incorporation of this general prevention approach, updating the model data set as new data comes in, and refining the model assumptions whenever

new data permit investigators to challenge the current assumptions.

In conclusion, this is the first pragmatic model in the field of HIV in Belgium that allows for an estimation of the consequences of a combined preventive approach on the HIV epidemiology and its economic burden. The current predictions suggest that a combined preventive approach would lead to a significant decrease in the incidence of the disease and important net savings on the pharmaceutical budget, even when not yet explicitly including additional general primary prevention measures.

Disclosure statement

- *Sebastian Vermeersch*: hict has received consultancy fees from Gilead Sciences Belgium.
- *Steven Callens:* has received grant support from ViiV & Gilead and has received honoraria for speaking engagements and/or consultancy meetings from the following: Gilead, ViiV, Janssens, Merck, Pfizer, MSD & GSK. He has also received limited unrestricted funding, paid to his institution, from ViiV.
- *Stéphane De Wit*: none.
- *Jean-Christophe Goffard:* has received consultancy fees from Gilead and ViiV.
- *Marie Laga:* none.
- *Dominique Van Beckhoven:* none.
- *Lieven Annemans:* has received consultancy fees from Gilead Sciences Belgium.

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Notes on contributors

Sebastian Vermeersch [PhD] is a passionate health-economic professional. After graduating as a computer science engineer in 2003 and obtaining an additional degree in biomedical and clinical engineering, he obtained his PhD working in Ghent and Paris on practical applications of arterial stiffness modelling and the development of European reference values for arterial Stiffness. After a brief stay as research coordinator at the Heymans Institute of Pharmacology, he has been working at hict, an independent healthcare consultancy company, since 2012. As coresponsible of the Value Management team, his main interests lie in health-related value quantification and health-economics.

Steven Callens is an internist and infectious disease specialist at the Ghent University Hospital. He started his career as a district medical officer in Homa Bay on the shores of Lake Victoria in Kenya in the late nineties. He specialized at the University of Leuven and conducted his doctoral research on the treatment of children with HIV in Kinshasa, Democratic Republic of Congo. He is interested in tuberculosis, import pathology, travel medicine and vaccinations, as well as general internal medicine clinic and diagnostics. His main research topics include epidemiology of tuberculosis and HIV in Africa and Belgium.

Stéphane De Wit is Chief of the Department of Infectious Diseases at the Saint-Pierre University Hospital in Brussels. He is also Professor of Infectious Diseases at the Free University of Brussels. As a clinician and clinical researcher, Stéphane De Wit has been active in the field of HIV/AIDS since 1983. He is author or co-author of more than 200 articles and more than 360 communications at conferences. He is Coordinator of the Brussels Saint Pierre Cohort, Chair of the Belgian HIV Research Consortium BREACH, Chair of the COHERE Executive Committee, Founding member and Vice- chair of the European NEAT-ID Foundation. He is also member and secretary of the Governing Board of the European AIDS Clinical Society (EACS). He has been Chair of the "8ème Conférence Internationale Francophone HIV/Hépatites" (AFRAVIH) which was held in Brussels in April 2016 and co chair of the EACS Standard of care meeting held in Brussels in November 2016.

JC Goffard is head of the ULB Erasme AIDS reference centre and primary immunodeficiency unit. He is teaching internal medicine and semiology at medical school of ULB. His team is participating in many clinical trials, either academic or industry driven.

Marie Laga [MD 1982 Louvain University; MPH 1987 at LSHTM; PhD 1990 University of Antwerp] is Professor and Head of HIV and Sexual Health group at the Institute of Tropical Medicine (ITM) in Antwerp Belgium. Marie and her team contributed significantly to HIV prevention science in the areas of sexual transmission and its co-factors, prevention programs for vulnerable groups such as female sex workers, youth and MSM, evaluation of female controlled methods and linkages of sexual and reproductive health. In recent years, Marie has become a leading expert in HIV prevention, advocating for intensifying HIV Prevention worldwide.

Dominique Van Beckhoven is a medical epidemiologist. She graduated in medicine at the UCL in 1997 and has worked in humanitarian missions with Médecins Sans Frontières between 1998 and 2004 in several African countries. After having studied public health and nutrition at the LSHTM in 2005, she joined Epicentre as epidemiologist for nutrition surveys and outbreak investigations. Since 2007, she works at the Scientific Institute of Public Health (WIV-ISP), as responsible of the national HIV cohort in the Epidemiology of Infectious Diseases unit.

Lieven Annemans is senior full professor Health Economics at the Faculty of Medicine of Ghent University. For 8 years, he was chairman of the Flemish Health Council. In 2004 he was elected President of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). He also served as cabinet member (2000–2003) to Minister of Health Frank Vandenbroucke. Lieven Annemans was awarded a Francqui Chair in 2013 and 2016. He is the author of the books 'Health economics for non-economists' (2008) and 'De prijs van uw gezondheid – is onze gezondheidszorg in gevaar?' (2014). He has authored or co-authored over 250 international peer reviewed publications in the field of health economics.

ORCID

Sebastian Vermeersch http://orcid.org/0000-0002-8979-8244
Steven Callens http://orcid.org/0000-0002-7245-527X
Jean-Christophe Goffard http://orcid.org/0000-0002-2730-7673
Lieven Annemans http://orcid.org/0000-0001-8305-7210

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Appendix 1. Model calculations

Introduction

The BELHIVPREV model consists of three core components:

(1) An estimation of the annual number of new HIV diagnoses, based on the estimate of the total number of 'infectious' patients, and the degree of their infectiousness.
(2) Estimation of the annual number of patients in medical follow-up, based on the calculated estimate of new HIV diagnoses entering follow-up, minus death and dropout added to those already in follow-up from previous years.
(3) Integration of the effect of increasing the number of diagnosed patients on ART (immediate ART/TasP), decreasing the number of undiagnosed patients (outreach testing), and reducing the number of new HIV infections through prophylactic treatment (PrEP).

The following paragraphs detail the model mechanics and calculation approach for these three core components.

Propagative core model

Our model is based on a year-to-year estimate (Figure A1) of

- the number of patients in medical follow-up (# PIMF);
- the number of new HIV diagnoses (# ND).

Estimating the number of new HIV diagnoses

The yearly number of new HIV infections is calculated year-to-year from the estimated number of 'infectious' patients:

$$(\#\mathrm{ND})_{\mathrm{year+1}} = (\#\text{'infectious'patients})_{\mathrm{year}} \times (\text{'propagationfactor'}) \quad (1)$$

For the purposes of our model, an HIV patient was deemed to be 'infectious' (Figure A2) if:

- the patient was undiagnosed;
- the patient was diagnosed, but had not initiated treatment;
- the patient was being treated, but had not achieved a controlled (undetectable;<200 copies/ml) viral load.

or

$$(\#\text{'infectious'patients}) = (\#\text{unknown}) + (\#\text{untreated}) + (\#\mathrm{VL} \geq 200) \quad (2)$$

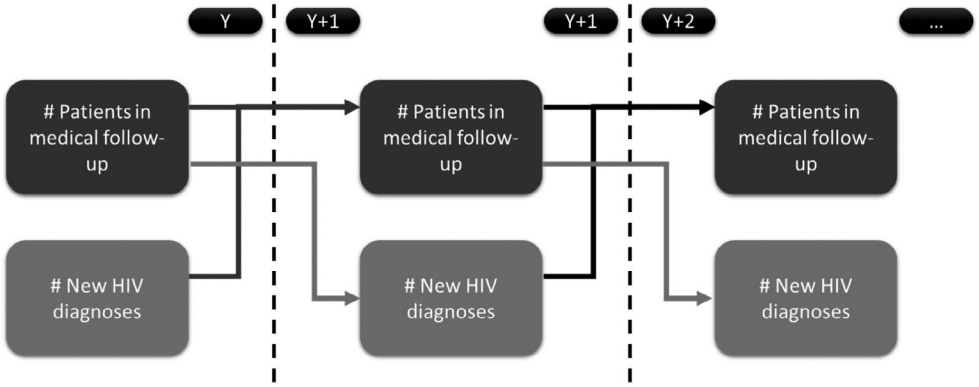

Figure A1. Propagative core model.

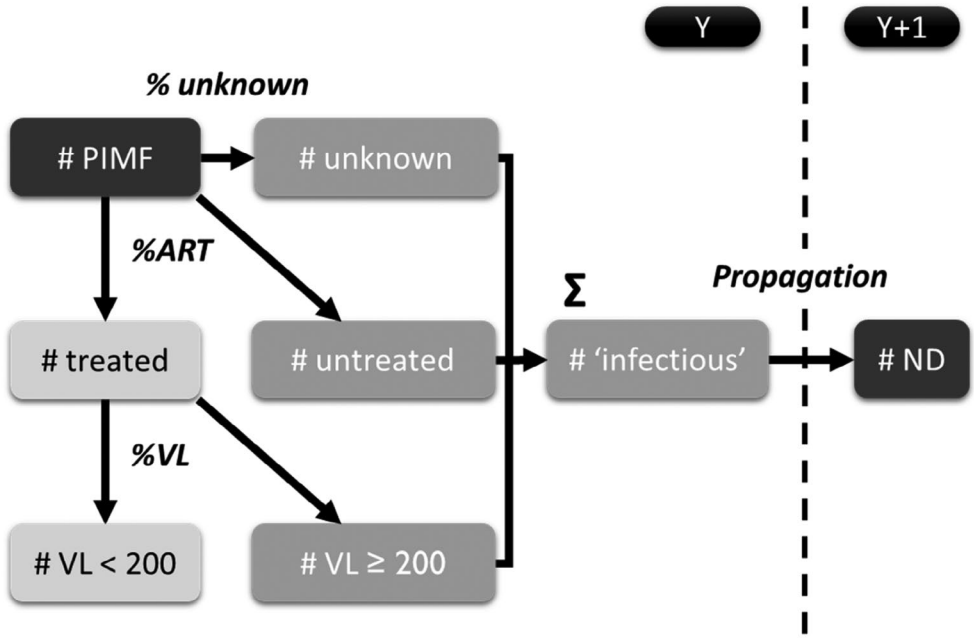

Figure A2. Estimating the number of new HIV diagnoses.

The number of undiagnosed patients (# unknown) was calculated taking into account the percentage of undiagnosed patients (% UD):

$$(\#\text{unknown}) = (\#\text{PIMF})\left(\frac{\%\ \text{UD}}{1-\%\ \text{UD}}\right) \quad (3)$$

The number of untreated patients (# untreated) was calculated taking into account the percentage of patients on ART (% ART):

$$(\#\text{untreated}) = (\#\text{PIMF})(1-\%\text{ART}) \quad (4)$$

The number of patients not having achieved a controlled (undetectable; <200 copies/ml) viral load) was calculated taking into account the percentage of patients achieving a controlled viral load (% VL):

$$(\#\text{VL} \geq 200) = (\#\text{PIMF})(\%\text{ART})(\%\text{VL}) \quad (5)$$

The source data and resulting model values for these model parameters are outlined in the main text.

Taking into account Equations (2)–(5), Equation (1) becomes:

$$(\#\text{ND})_{\text{year+1}} = \left[(\#\text{PIMF})_{year}\left(\frac{(\%\ \text{UD})_{\text{year}}}{1-(\%\ \text{UD})_{\text{year}}}\right) + (\#\text{PIMF})_{\text{year}}\left(1-(\%\ \text{ART})_{\text{year}}\right) + (\#\text{PIMF})_{\text{year}}(\%\ \text{ART})_{\text{year}}(\%\ \text{VL})\right] (\text{propagationfactor}) \quad (6)$$

The (% VL) and (propagation factor) parameters are assumed constant.

Finally, based on reported figures for the Belgian continuum of care, we assumed 90% (% FU) of newly diagnosed patients (# ND) enter HIV care (and are thus retained in the model).

Estimating the annual number of patients in medical follow-up

The estimated annual number of patients in medical follow-up was calculated year-to-year (Figure A3) based on:

- the number of patients in medical follow-up at the end of the previous year;
- the number of newly diagnosed patients expected to enter follow-up, calculated as detailed above;
- the expected mortality rate.

Or

$$(\#\text{PIMF})_{\text{year+1}} = \left[(\#\text{PIMF})_{\text{year}} + (\#\text{ND})_{\text{year}}(\%\ \text{FU}) - \left((\#\text{PIMF})_{\text{year}} + (\#\text{ND})_{\text{year}}\right)(\%\ \text{death})_{\text{year}}\right] (\text{retention}) \quad (7)$$

The source data and resulting model values for these model parameters are outlined in the main text. The (% FU) and (retention) parameter s are assumed constant. Mortality varied year to year to take into account the effects of an ageing HIV population (as outlined in the main text).

Integrating the effects of outreach, immediate ART/TasP and PrEP

Outreach and immediate ART/TasP

The impact of immediate ART/TasP and outreach are included in the model as modifiers to the (% ART) and (% UD) parameters in Equation (6)

PrEP

To integrate the effect of PrEP, a stepwise approach was implemented.

First, a theoretical annual 'population at risk' was defined from the calculated annual new HIV diagnoses and published HIV acquisition rates:

$$(\text{population at risk}) = (\#\text{ND})\left(\frac{100}{\text{HIV acquisition rate}}\right) \quad (8)$$

The impact of PrEP was modelled through a calculated decrease in the size of the annual 'population at risk', taking into account published PrEP effectiveness rates. The estimated number of infections avoided was calculated by recalculating the annual number of new HIV diagnoses from the

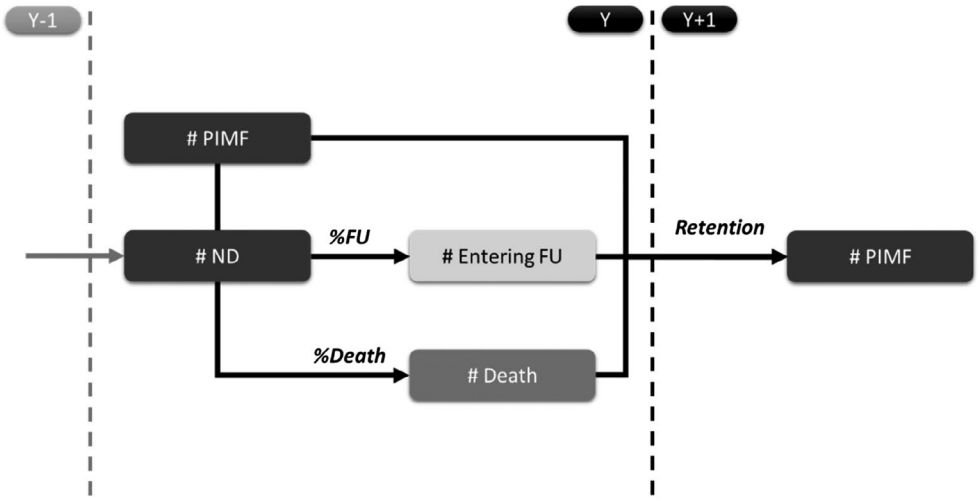

Figure A3. Estimating the annual number of patients in medical follow-up.

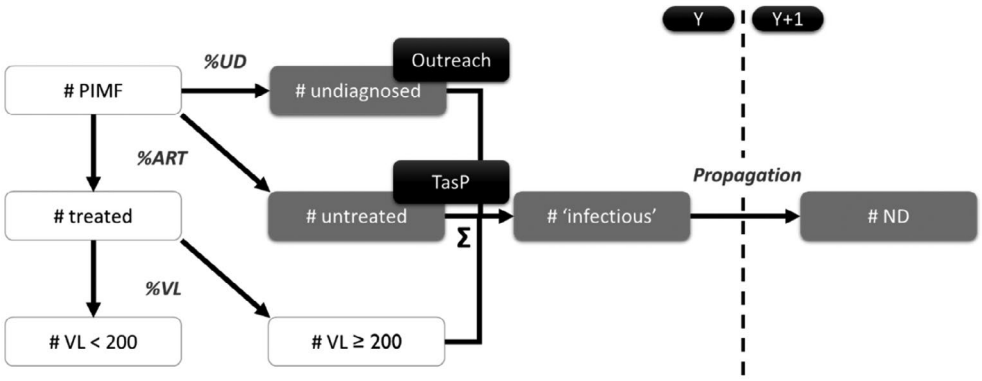

Figure A4. Integrating the effect of outreach and immediate ART/TasP

reduced 'population at risk', using the aforementioned HIV infection rates.

$$(\text{infections avoided}) = \left(\frac{\#\text{treated with PrEP}}{100}\right) \quad (9)$$
$$(\text{PrEP effectiveness})(\text{HIV infection})$$

Taking into account (sub)population differences

The model allows us to specify subpopulation-specific values for all model parameters. The following parameters were implemented population-specific:

- the percentage of undiagnosed patients;
- the HIV acquisition and transmission rates used to calculate the size of the 'population at risk' for estimation of the impact of PrEP.

The model accounts for the difference in HIV infectiousness depending on the stage of the HIV care continuum in which an infectious patient can be (undiagnosed, diagnosed but untreated, treated and VL ≥ 200 copies/ml). To achieve this, scaled 'propagation factors' were used to calculate the estimated number of annual new HIV diagnoses taking into account the proportion of patients in each stage of the care continuum for each year in the model.

The model takes into account that a number of newly diagnosed HIV patients were migrants who had acquired HIV in their home country prior to their arrival in Belgium. These patients were not expected to be influenced by Belgian efforts in HIV prevention, i.e. the estimated number of infections newly diagnosed does not change, regardless of the additional prevention effort simulated.