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ABSTRACT

Introduction: In British Columbia (BC), the HIV epidemic continues to disproportionally affect the gay, bisexual and other men who have sex with men (MSM). In this study, we aimed to evaluate how Treatment as Prevention (TasP) and pre-exposure prophylaxis (PrEP), if used in combination, could lead to HIV elimination in BC among MSM.

Methods: Considering the heterogeneity in HIV transmission risk, we developed a compartmental model stratified by age and risk-taking behaviour for the HIV epidemic among MSM in BC, informed by clinical, behavioural and epidemiological data. Key outcome measures included the World Health Organization (WHO) threshold for disease elimination as a public health concern and the effective reproduction number (R_e). Model interventions focused on the optimization of different TasP and PrEP components. Sensitivity analysis was done to evaluate the impact of sexual mixing patterns, PrEP effectiveness and increasing risk-taking behaviour.

Results: The incidence rate was estimated to be 1.2 (0.9–1.9) per 1000 susceptible MSM under the Status Quo scenario by the end of 2029. Optimizing all aspects of TasP and the simultaneous provision of PrEP to high-risk MSM resulted in an HIV incidence rate as low as 0.4 (0.3–0.6) per 1000 susceptible MSM, and an R_e as low as 0.7 (0.6–0.9), indicating that disease elimination was possible when TasP and PrEP were combined. Provision of PrEP to younger MSM or high-risk and younger MSM resulted in a similar HIV incidence rate, but an R_e with credible intervals that crossed one.

Conclusion: Further optimizing all aspects of TasP and prioritizing PrEP to high-risk MSM can achieve the goal of disease elimination in BC. These results should inform public health policy development and intervention programs that address the HIV epidemic in BC and in other similar settings where MSM are disproportionately affected.

1. Introduction

Gay, bisexual and other men who have sex with men (MSM) have been disproportionally affected by the HIV epidemic (The Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016). In the province of British Columbia (BC), Canada, at the end of 2016, the Public Health Agency of Canada estimated that 9836 individuals were known to be living with HIV, and 54% of those were estimated to be MSM (Public Health Agency of Canada, 2020; British Columbia Centre for Disease Control (BCCDC), 2019a). Since 2007, the number of new HIV infections diagnosed each year among MSM has been relatively constant between 127 and 181 cases (British Columbia Centre for Disease Control

Abbreviations: MSM, Gay, bisexual and other men who have sex with men; TasP, Treatment as Prevention; PrEP, Pre-exposure prophylaxis; ART, Antiretroviral treatment; STOP HIV/AIDS, Seek and Treat for Optimal Prevention of HIV/AIDS; R_e, The effective reproduction number; BC, British Columbia; WHO, World Health Organization; PWID, People who inject drugs; CAI, Condomless anal intercourse; IPR, HIV incidence to prevalence ratio; IMR, HIV incidence to all-cause mortality ratio.

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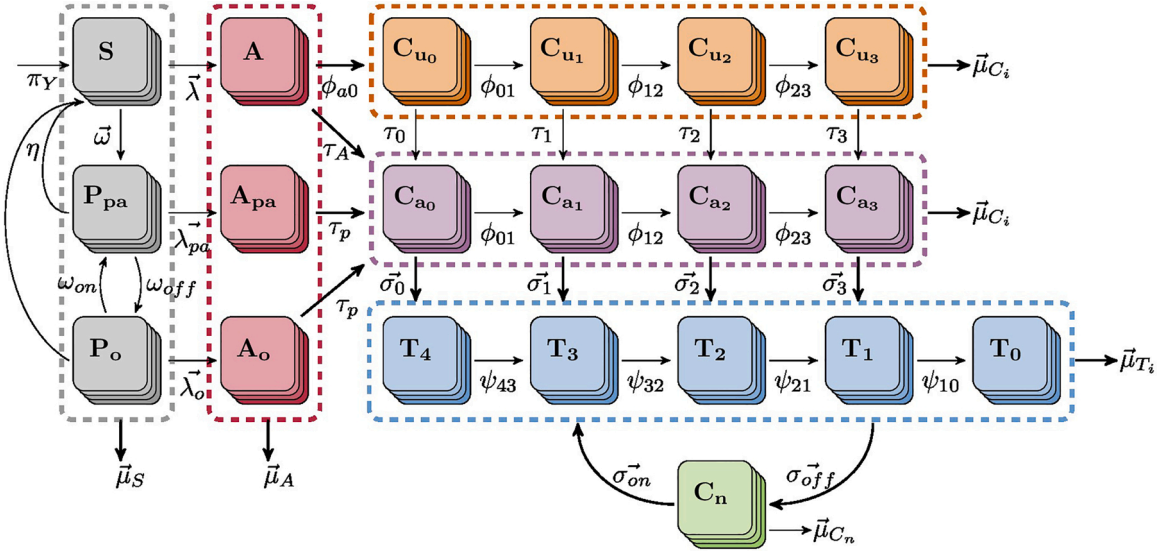

Fig. 1. HIV transmission and disease progression model schematic.

(BCCDC), 2019a; British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a), and at the end of 2016, it was estimated that 115 (range 70-160) MSM became newly infected with HIV (Public Health Agency of Canada, 2020; British Columbia Centre for Disease Control (BCCDC), 2019a).

There is strong evidence demonstrating that effective antiretroviral treatment (ART) amongst people living with HIV (PLWH) plays a substantial role in decreasing HIV transmission (Cohen et al., 2011; Eisinger et al., 2019). BC has actively expanded access to free, publicly funded ART starting in the mid 2000's, and in 2010, BC formally adopted "Treatment as Prevention" (TasP) as public health policy to maximize engagement of PLWH along the HIV continuum of care. By increasing virologic suppression, it has been shown that we can decrease HIV-related morbidity and mortality, and secondarily new HIV infections (Gardner et al., 2011). Current guidelines around the world have embraced this strategy, and in 2014, the Joint United Nations Programme on HIV/AIDS adopted the 90-90-90 target to "End AIDS as a Pandemic by 2030" (The Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014).

However, in BC, TasP has been relatively less responsive to the effects of ART in reducing transmission among MSM than other population subgroups, chiefly people who inject drugs (PWID) (British Columbia Centre for Disease Control (BCCDC), 2019a; British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a; Montaner et al., 2014). We have previously shown this is likely attributable to the favorable synergistic interaction between TasP and harm-reduction strategies among PWID (Nosyk et al., 2017). It is well-known that HIV does not affect any population homogeneously. Rather, different population subgroups share specific behaviours and they experience a variety of societal barriers, which may impact ART access, uptake, and effectiveness (The Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016; Centers for Disease Control and Prevention, 2014). Recently, an evaluation of the HIV continuum of care in BC demonstrated that young MSM (age <30 years) consistently experienced the highest attrition across each step of the HIV continuum of care than those experienced by other population subgroups (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a). Additionally, some studies suggested that the preventive impact of ART can be potentially offset by an increase in HIV risk behaviour (e.g., unprotected anal intercourse), often due to a reduced perceived risk of transmitting or acquiring HIV (Chen, 2013; Prestage et al., 2012). This phenomenon, known as "ART optimism" has been observed in cohorts in San Francisco, Australia, Switzerland, to cite a few (Chen, 2013; Prestage et al., 2012). In turn, this may lead to an increase in risky sexual encounters evidenced by the fact that rates of sexually transmitted infections in this population have been rapidly increasing during the last 10 years, with infectious syphilis being the one with the highest attributable proportion among MSM (>80%) at the end of 2018 in BC (British Columbia Centre for Disease Control (BCCDC), 2019b).

Traditionally, HIV-uninfected MSM at high-risk for HIV infection have attempted to mitigate HIV risk by using condoms or by sero-adaptative practices, including having sexual contact with only HIV-negative partners if one was HIV-negative or only HIV-positive partners with an undetectable viral load (Bogowicz et al., 2016; Khosropour et al., 2016; McFarland et al., 2011). Additionally, in Canada, post-exposure prophylaxis has been made available on an emergency case-by-case basis, after a high-risk non-occupational related exposure, albeit this practice has not been widely used (Tan et al., 2017). In 2010, pre-exposure prophylaxis (PrEP), in the form of daily oral ART combination of tenofovir and emtricitabine, was shown to be protective against HIV infection among high-risk sero-discordant heterosexual and MSM couples (Grant et al., 2010; Mayer et al., 2016; Molina et al., 2015; McCormack et al., 2016; Molina et al., 2017; CATIE, 2016 Grulich et al., 2018; The Kirby Institute, 2019). In the MSM population, the efficacy of PrEP in clinical trials ranged from 44% to 97%, mostly due to the level of adherence to this intervention (Grant et al., 2010; Molina et al., 2015, 2017). PrEP was formally recommended for the prevention of HIV infection among high-risk HIV-negative MSM and was approved for use by Health Canada in 2016 (Gilead Sciences, 2016; WHO, 2015). In the summer of 2017, an oral generic combination of tenofovir and emtricitabine was approved in the United States and Canada. As such, its cost has been greatly reduced making PrEP more affordable to individuals and governments, and sustainable in the long-term (U.S. Food and Drug Administration, 2017; Health Canada, 2017). In Canada, PrEP is now partially subsidized (i.e., with a deductible) by the governments of Ontario and Québec (Yoong, 2019; Greenwald et al., 2019). In BC, PrEP has been fully subsidized by the BC government since January 2018 (Toy et al., 2019; The Centre for Gobal Public Health - University of Manitoba, 2016).

Based on a recent study focused on the HIV epidemic among MSM in Denmark, a setting similar to BC where treatment coverage and virologic suppression is quite high, the authors concluded that highly optimized TasP and the introduction of PrEP could substantially reduce the HIV incidence and possibly lead to the elimination of the HIV epidemic (Okano et al., 2016; Palk et al., 2018). Therefore, in this study, we developed a mathematical transmission model to evaluate how to

Table 1
Intervention Scenarios for TasP and PrEP.

Interventions	Modified Parameters	Status Quo Scenario	Low Scenario	Medium Scenario	High Scenario
TasP					
Testing	Diagnosis rate (per 1000 undiagnosed individuals per month)[a]	(20.74–55.47)	(22.81–61.02)	(24.88–66.57)	(29.03–77.66)
Treatment initiation	ART initiation rate (per 1000 diagnosed individuals without ART initiation per month)[b]	(36.44–104.33)	(40.08–114.77)	(43.72–125.20)	(51.01–146.07)
Time suppressed on ART	Average time on ART (process from T_4 to T_0) before disengagement (month)[c]	52.46	57.71	62.96	73.45
ART re-engagement	ART re-initiation rate (per 1000 off-ART individuals per month)[d]	133.33	146.67	160.00	186.67
	Time staying on presumed-appropriate PrEP use (month)[c]	8.85	9.73	10.62	12.38
PrEP (offered to all subgroups, high-risk subgroups, younger subgroups, high-risk & younger subgroup)	Transition rate from other types of PrEP use to presumed-appropriate PrEP use (per 1000 individuals per month)[d]	92.45	101.69	110.93	129.42
	Time staying on PrEP use before discontinuation (month)[c]	118.40	130.24	142.08	165.76
	Annual number of PrEP enrollments by the end of 2029[d]	521	573	625	729

PrEP: pre-exposure prophylaxis; TasP: Treatment as Prevention; ART: antiretroviral treatment.

[a] The range of the diagnosis rates were the minimum and maximum medians from the acute and each chronic unaware stages for different CD4 count categories based on model calibration. Under each scenario, all the diagnosis rates were improved simultaneously by 10% (Low), 20% (Medium) and 40% (High).

[b] The ranges for the ART initiation rate were for older subgroups, as the minimum and maximum medians for different CD4 counts based on model calibration. Under each scenario, ART initiation rates were improved simultaneously by 10% (Low), 20% (Medium) and 40% (High).

[c] Under each scenario, average time on ART was increased by 10% (Low), 20% (Medium) and 40% (High), same for time staying on presumed-appropriate PrEP use and time staying on PrEP use before discontinuation.

[d] Under each scenario, ART re-initiation rates were increased by 10% (Low), 20% (Medium) and 40% (High), same for PrEP transition rate from other types of PrEP use to presumed-appropriate use, and annual number of PrEP enrollments by the end of 2029.

optimize the combined use of TasP and PrEP could lead to disease elimination in BC. As HIV transmission risk varies by different MSM subgroups, we stratified the population by age and risk-taking behaviour.

2. Methods

2.1. HIV transmission model

We developed an age-risk stratified deterministic compartmental model for HIV transmission among the MSM population in BC. The MSM population was stratified into two age subgroups: younger (15–29 years old) and older (30–79 years old) (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a; Smith et al., 2012). Each age subgroup was further stratified into two risk groups: high- and low-risk, determined by the average number of partners with condomless anal intercourse (CAI) acts per year. The risk stratification was based on the data available from a cohort of HIV-negative and positive MSM in Vancouver (The Engage Team, 2017). Individuals enter the younger subgroups once they become 15 years old, they age into the older subgroups and eventually move out of the system due to aging or death. We assumed that during the aging process, the risk level did not change, but the average number of partners with CAI acts per year decreased due to aging.

Each age-risk subgroup was further classified into 20 compartments to describe HIV transmission and disease progression (Fig. 1). Younger MSM entered the model as new susceptible individuals (S) at a rate π_Y, determined by BC population growth (Statistics Canada, 2017, 2018). Acute HIV infections (I) were acquired at a rate $\overrightarrow{\lambda}$, which was determined by the probability of HIV transmission based on HIV stage, number of partners with CAI acts, mixing pattern between subgroups and HIV disease stage in each subgroup. Then individuals with acute infection became chronically infected with slowly decreasing CD4 counts ($C_{u_0} :\geq 500$, $C_{u_1} : 350-499$, $C_{u_2} : 200-349$, $C_{u_3} :< 200$ cells/mm^3). Individuals in each undiagnosed compartment (I, C_{u_0}, C_{u_1}, C_{u_2}, and C_{u_3}) were diagnosed at a rate τ_i ($i = A,0,1,2,3$) and moved into the diagnosed compartment with the same CD4 category (C_{a_0}, C_{a_1}, C_{a_2}, and C_{a_3}). Once diagnosed, individuals initiated treatment at a rate $\sigma_{i,j}$ ($i = 0, 1, 2, 3$, corresponding to CD4 categories and $j = Y, O$, corresponding to younger and older subgroups), and their viral load progressed towards virologic suppression, which was defined as viral load <200 copies/mL ($T_4 :\geq 5$, $T_3 : 4-4.99$, $T_2 : 3-3.99$, $T_1 : 2.30-2.99$, $T_0 :< 2.30$ $\log_{10}$ copies/mL). Those on treatment may experience virologic failure or treatment interruption, and move to compartment C_N at a rate $\sigma_{off,i}$ ($i = Y, O$). At a rate $\sigma_{on,i}$ ($i = Y, O$), individuals in the compartment C_N re-initiated ART and re-experienced viral load decline until virologic suppression (T_0). We stratified ART initiation, drop-off and re-initiation rates by age, due to the high level of heterogeneity along the continuum of care between younger and older MSM (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a; Wilton et al., 2019; Wang et al., 2017; Lee et al., 2018; O'Connor et al., 2017; Sabin et al., 2009). The mortality rate for each compartment depends on the age, HIV disease stage, CD4 count and viral load. To reduce the complexity of the model and lack of data on migration, we assumed a closed HIV epidemic in BC and no migration in or out of the province. Starting from 2016, susceptible individuals initiated PrEP at a rate ω, presumed to appropriately follow the guidance for the use of PrEP in BC (P_{pa}, daily or on-demand), which is associated with a high PrEP effectiveness (McCormack et al., 2016; Molina et al., 2017; British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020c; Grant et al., 2014). Those with presumed-appropriate PrEP use could turn into other types of PrEP use (P_o, neither daily nor on-demand) at a rate ω_{off}, with lower PrEP effectiveness than those in P_{pa}. At a rate ω_{on}, individuals in the compartment P_o can move back to compartment P_{pa}. Individuals actively on PrEP (P_{pa} and P_o) could discontinue PrEP at a rate η. The

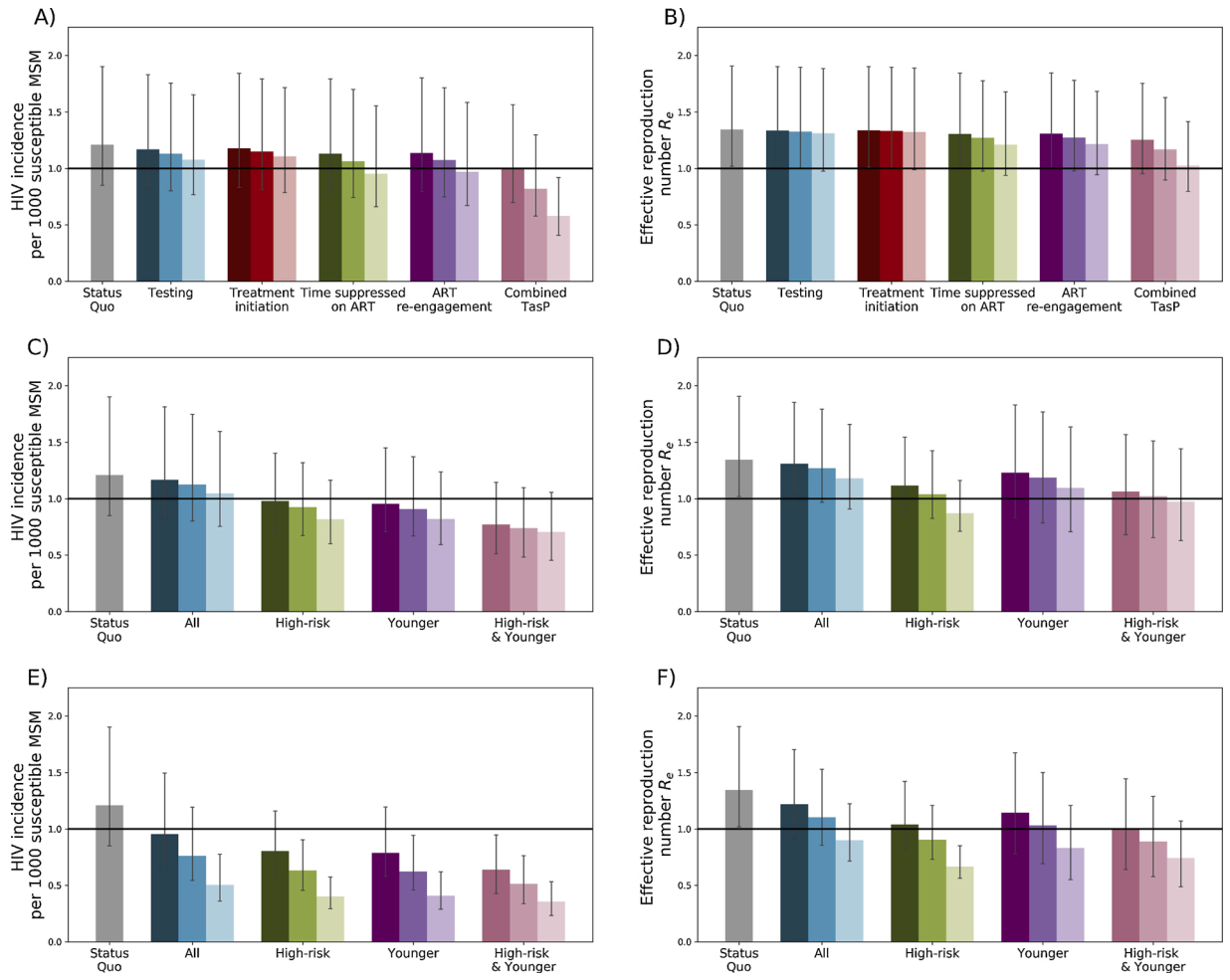

Fig. 2. Impact of interventions on HIV incidence rate and effective reproduction number (R_e): (A & B) TasP interventions; (C & D) PrEP interventions; and (E & F) combination of TasP and PrEP interventions. Bars go from Low to High scenarios as per Table 1.

rates of acute infection among susceptible individuals on PrEP ($\overrightarrow{\lambda}_{pa}$ and $\overrightarrow{\lambda}_{o}$) depend on the infection rate $\overrightarrow{\lambda}$ and the effectiveness of PrEP. Based on the guidance for PrEP use in BC, HIV testing is required every three months, which indicates that the number of acute infections moving to the undiagnosed compartments is negligible (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020c). Although PrEP is dispensed based on set guidelines, participants in the program can choose to take PrEP in many different ways. Therefore, it is hard to determine with 100% certainty the way PrEP is being taken by some participants, and due to this limitation, we named these compartments as mentioned before.

We incorporated multiple data sources to estimate demographic and behavioural parameters: BC population data from Statistics Canada, BC MSM population data from BC Centre for Disease Control, HIV surveillance data from the Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) program and prospective cohort survey data from the Momentum Health Study (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a; The Centre for Gobal Public Health - University of Manitoba, 2016; Statistics Canada, 2017, 2018; Moore et al., 2016). We calibrated the model based on the Monte Carlo filtering method (Rose et al., 1991). We uniformly sampled 2,500,000 combinations of initial conditions of the model in 2010 and plausible parameter values, by the Latin Hypercube sampling method, ran simulations for the period 2010–2015, and kept 1039 sets with simulations that fell into the ranges of: (1) the estimates of HIV prevalence among the MSM population in BC from the Public Health Agency of Canada (available in 2011 and 2014, as shown in Table S7); (2) the estimated HIV incidence in 2011 and 2014 (Table S7); (3) surveillance data including HIV diagnoses, treatment initiation and virologic suppression (viral load <200 copies/mL) from the STOP HIV/AIDS program (starting from 2012, to account for the impact of the TasP strategy in BC, as shown in Supporting Information Table S6) (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020a; Public Health Agency of Canada, 2018). In the model, PrEP was introduced in 2016 and we assumed that there were approximately 500 MSM on PrEP by the end of 2017 (as MSM were paying out-of-pocket). Starting from 2018, we assumed that the PrEP enrollment rate was a sigmoid function, with an estimation of 5620 MSM enrolled by the end of 2019 following what was observed in BC's PrEP program (Toy et al., 2019; British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020b). We used the 1039 parameter sets to run the model for the period 2016–2019 and validated the model by comparing the model estimates to the estimated HIV prevalence in 2016 and the number of new HIV infections in 2016 and 2018 from the Public Health Agency of Canada (as shown in Supporting Information Fig. S2).

The numerical and analytical aspects were coded in Python™, and the numerical simulations were done using the NUMPY and SCIPY libraries (Jones and Peterson, 2001). The detailed model description, along with all parameter estimations and model calibration, can be found in the Supporting Information.

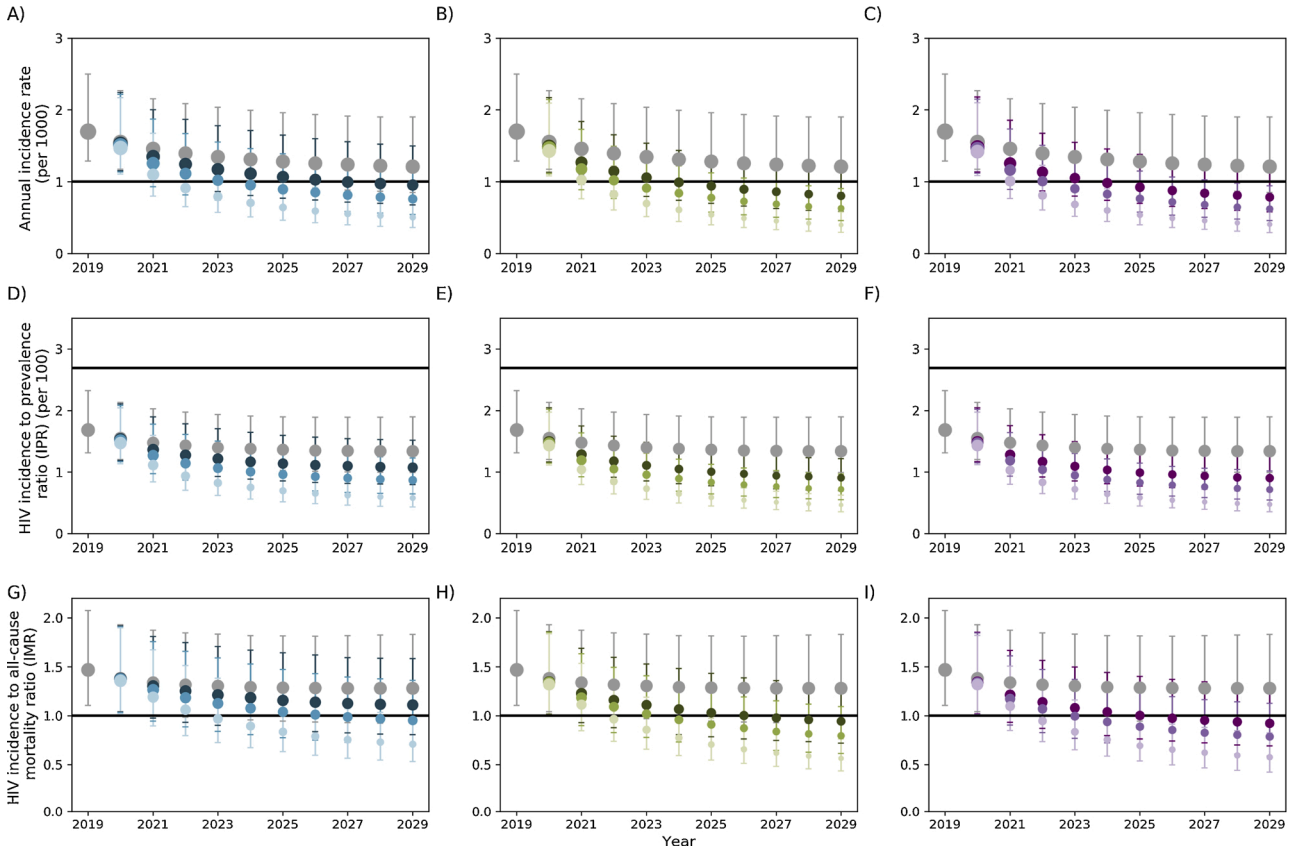

Fig. 3. Impact of TasP and PrEP interventions on the annual HIV incidence rate, HIV incidence to prevalence ratio (IPR) and HIV incidence to mortality ratio (IMR) targeting all MSM (blue), high-risk MSM (green) and younger MSM (purple). Each of the four curves represent the Status Quo, Low, Medium, High scenarios, respectively, as per Table 1 (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2.2. Modeling scenarios

Under the Status Quo scenario, we kept all the parameters the same as those in 2019. We assessed the effect of different TasP interventions with 10% (Low), 20% (Medium) and 40% (High) improvement from the Status Quo scenario (Table 1): (1) improving testing by increasing the diagnosis rates for all CD4 categories; (2) improving treatment initiation by increasing the ART initiation rates for all CD4 categories (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2015); (3) increasing time suppressed on ART by increasing the average time on ART (process from T_4 to T_0) before disengagement; and (4) improving ART re-engagement by increasing the ART re-initiation rate. In addition, we examined the effect of combined TasP interventions (1)-(4). We chose interventions (3) and (4) since in many ART programs there is a cyclical process of engagement, disengagement and re-engagement of patients in HIV care. This process, also known as "churn", is highly heterogeneous among patients and they vary in duration, and it has direct individual and public health implications (Wang et al., 2017). We used a sigmoid function for each parameter changing from Status Quo level to full uptake within one year. We assessed the effect of PrEP assuming a 10% (Low), 20% (Medium) and 40% (High) improvement from the Status Quo scenario (Table 1). We simultaneously increased the average time on presumed-appropriate PrEP use, the transition rate from other types of PrEP use to presumed-appropriate PrEP use, the average time on PrEP before discontinuation, and the PrEP enrollment rate by the end of 2029. We also targeted different subgroups for PrEP enrollment, by: (1) keeping the same distribution of PrEP in 2019 in all subgroups; (2) focusing only on high-risk subgroups; (3) focusing only on younger subgroups; (4) focusing only on the high-risk and younger subgroup. Additionally, we assessed the impact of combining TasP and PrEP according to the Low, Medium, and High scenarios as outlined in Table 1. More detail on PrEP allocation can be found in the Supporting Information.

2.3. Main outcomes

Under each scenario, model simulations were done for 1039 different parameter sets for the period 2020–2029. We estimated the following outcomes at the end of 2029: HIV point prevalence; HIV incidence (cumulative number of cases and rate per 1000 susceptible MSM); and all-cause mortality (cumulative number of cases and rate per 1000 HIV-positive MSM), in the form of median (2.5^{th}-97.5^{th} percentiles). For some outcomes, we also calculated the percent change in relation to the Status Quo scenario. In addition, we provided the extra number needed to be on ART/PrEP (NNT) to avert one new HIV infection in comparison to the Status Quo scenario, as a measure for intervention efficiency (Jenness et al., 2016). The NNT was the extra person-time on ART (T_i, $i = 0,..,4$) or on PrEP (P_{pa} and P_o) divided by the averted number of new HIV infections under the intervention scenario.

To assess whether TasP and PrEP can reduce the public health impact of the HIV epidemic in BC, by 2029, we used three longitudinal metrics: (1) the WHO HIV incidence threshold of <1 HIV new case per 1000 susceptible MSM (also known as the goal to achieve disease elimination as a public health concern); (2) the HIV incidence to prevalence ratio (IPR) of <0.027, where the threshold is the reciprocal of the number of years a person living with HIV survives, which was estimated based on the median age at which MSM becomes infected with HIV and the life expectancy of MSM on ART in BC (as shown in Section 2 of the Supporting Information); and (3) the HIV incidence to all-cause mortality ratio (IMR) of <1 (Ghys et al., 2018; Granich et al., 2009). Additionally, we assessed whether these interventions can lead to disease elimination by means of the effective reproduction number (R_e). R_e was estimated

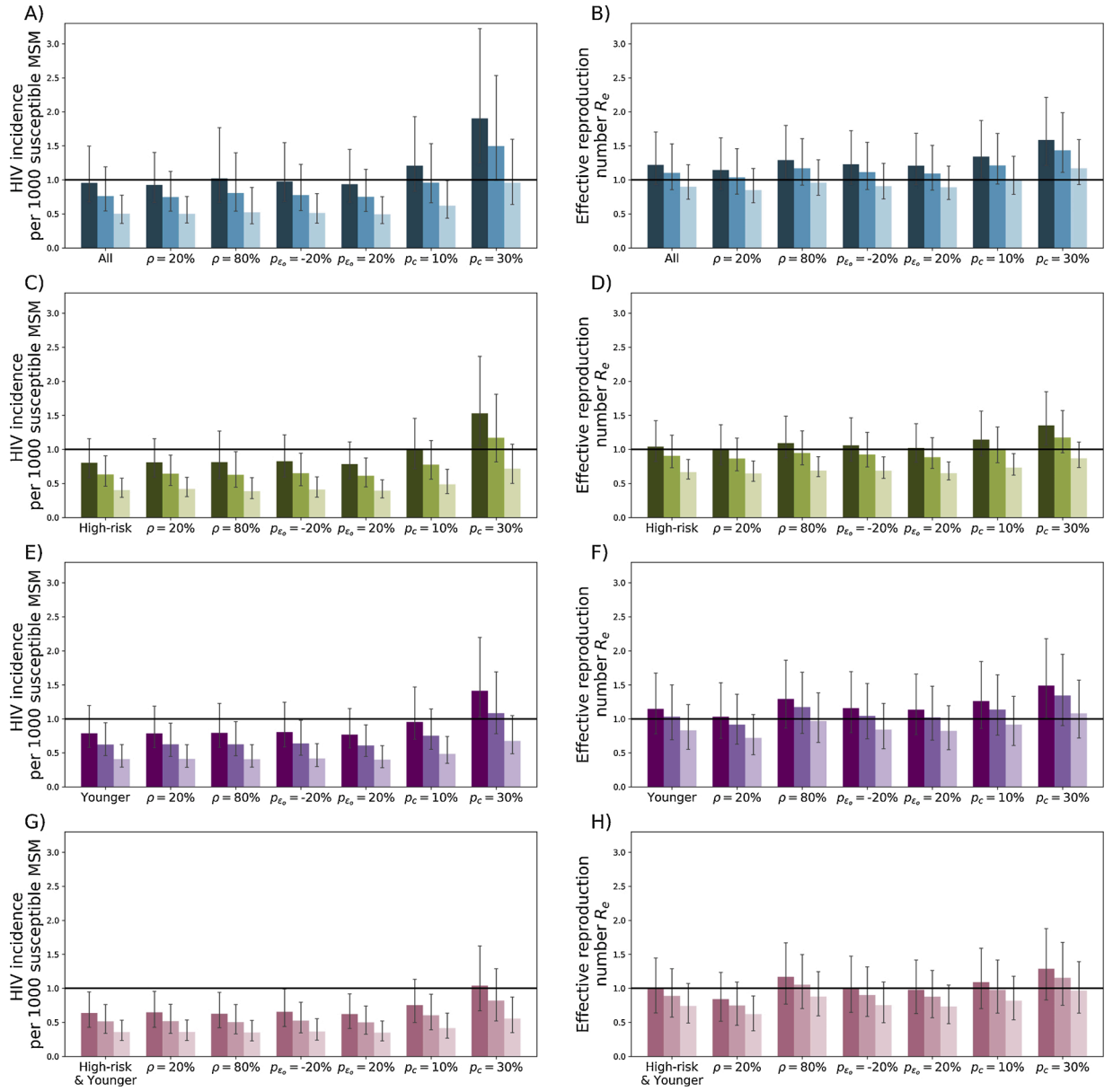

Fig. 4. Sensitivity analysis for HIV incidence rate (A. targeting all MSM, C. targeting high-risk MSM, E. targeting younger MSM, and G. targeting high-risk and younger MSM) and effective reproduction number (B. targeting all MSM, D. targeting high-risk MSM, F. targeting younger MSM and H. targeting high-risk and younger MSM) by varying: the percentage of sexual contacts reserved for the same subgroup (ρ); the percent change on the effectiveness of other types of PrEP use (p_{ε_o}); and the percent increase on the average number of partners with unprotected anal sexual intercourse contacts in each subgroup (p_c). Each of the three bars represent TasP and PrEP under the Low (darker colour), Medium, High (lighter colour) scenarios, respectively.

based on the Next Generation Matrix method (Diekmann et al., 2010; van den Driessche and Watmough, 2002). This quantity measures the average number of secondary new infections caused by a typical infectious individual, in consideration of interventions. If $R_e < 1$ under a certain scenario, it means that disease elimination will happen in the foreseeing future, but not necessarily by the end of the simulation period. We assumed that the goal is achieved when 97.5% of simulated outcomes are below the corresponding threshold. In addition, we assumed that the goal of disease elimination is achieved when both 97.5% of the simulated incidence rate and R_e are below their thresholds.

2.4. Sensitivity analysis

We conducted sensitivity analyses based on the HIV incidence rate and R_e under the combined TasP and PrEP intervention scenarios, taking into account possible behaviour changes among the MSM population in BC, by: (1) varying the percentage of sexual contacts within the same subgroup (i.e., sexual mixing) (ρ) from 40% and 60% under Status Quo scenario to 20% and 80%; (2) varying the effectiveness of other types of PrEP use (ε_o) by $\pm$ 20%; (3) increasing the average number of partners with CAI acts in each subgroup (c) by 10% and 30%, under the assumption that ART optimism will likely increase HIV risk behaviour. We also performed univariate sensitivity analyses by estimating the univariate sensitivity coefficients for the HIV incidence rate, R_e, HIV prevalence, and all-cause mortality rate under the Status Quo for the top ten parameters (i.e., with the highest coefficients) at the end of 2029. These sensitivity coefficients measure the relative change in the outcome with respect to the relative change in a model parameter (Rozada et al., 2016). Positive coefficients occur when changes (i.e., an increase or a decrease) in a parameter are positively associated with changes in the outcome. Negative coefficients occur when changes in a parameter are inversely associated with changes in the outcome. The

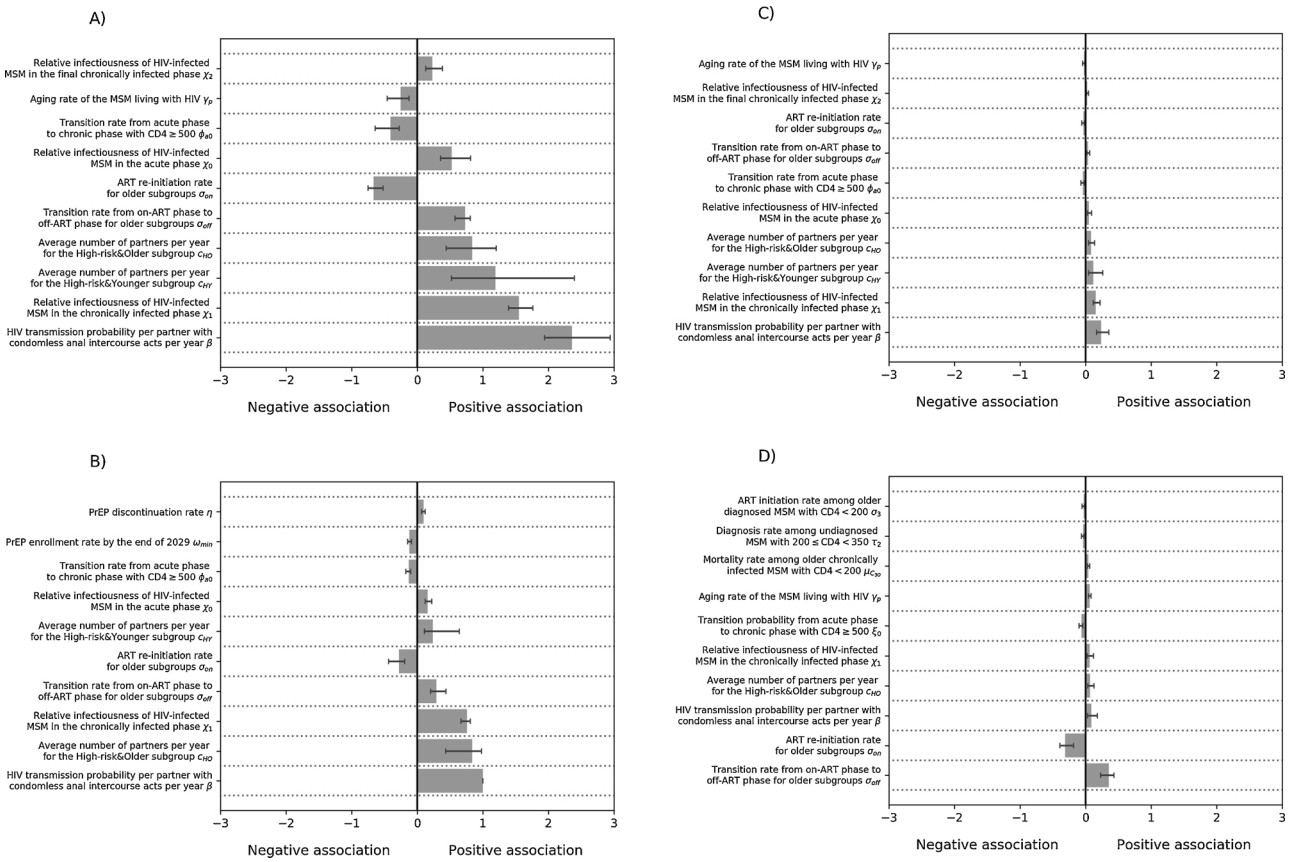

Fig. 5. Univariate sensitivity analyses under the Status Quo scenario for (A) HIV incidence rate, (B) effective reproduction number, (C) HIV prevalence, and (D) mortality rate among MSM living with HIV for the top ten parameters with the highest sensitivity coefficients.

magnitude of the sensitivity coefficient also reflects how sensitive the outcome is to changes in each parameter. In addition, we conducted sensitivity analyses regarding the following assumptions which could potentially impact the results under the intervention scenarios: (1) a 75% reduction in the number of partners with CAI acts for those diagnosed with HIV before ART initiation; (2) we assumed that 35% of susceptible MSM and 52% of MSM diagnosed with HIV will practice sero-adaptive practices; (3) MSM in older subgroups on PrEP will have a higher number of partners to reflect the behaviour of younger MSM; and (4) MSM in older subgroups on PrEP will have fewer partners to reflect the behaviour of older MSM (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020b; Card et al., 2018; Vallabhaneni et al., 2013). The last two sensitivity analyses were done to assess if we missed important HIV transmission dynamics due to the assumed broad age groups in our model. Details of model modification can be found in the Supporting Information.

2.5. Ethics

The linkage and usage of administrative databases were approved and performed by data stewards in each collaborating agency and facilitated by the BC Ministry of Health. This study received approval from the University of British Columbia ethics review committee at the St Paul's Hospital, Providence Health Care site (H08-02095, H18-00949). The Momentum Health Study received approval from the same University of British Columbia ethics review committee (H11-00673), from the Simon Fraser University (2011s0691) and the University of Victoria (11-459).

3. Results

3.1. Status quo

By the end of 2019, the model showed that there were 4921 (2.5^{th}–97.5^{th} percentile 4713–5196) MSM living with HIV, 94.7% (92.2%–96.2%) of which were HIV diagnosed, 91.3% (88.1%–93.3%) initiated ART, and 78.1% (74.3%–81.9%) were virologic suppressed. The incidence rate was 1.7 (1.3–2.5) per 1000 susceptible MSM, and the mortality rate was 11.5 (9.3–13.9) per 1000 HIV-positive MSM.

Under the Status Quo scenario, with an extra 6552 MSM ever enrolled on PrEP from 2020 to 2029, the model predicted that there would be 700 (514–1041) HIV incident cases and 538 (428–667) deaths over a 10-year period. The HIV point prevalence, at the end of 2029, was estimated at 8.2% (7.6%–9.2%) of all MSM in BC (5083 (4739–5637) out of 61,814 (59,681–63,847) MSM). The HIV continuum of care for MSM in 2029 was estimated to be 96.7% (94.8%–97.7%) HIV diagnosed, 94.8% (92.3%–96.1%) initiated ART, and 81.1% (77.2%–85.0%) were virologic suppressed (Supporting Information Table S8). Additionally, the model estimated that the HIV incidence rate in 2029 would be 1.2 (0.9–1.9) per 1000 susceptible MSM, representing a 28.9% reduction from 2019, and the mortality rate would be 10.6 (8.3–13.0) per 1000 HIV-positive MSM, representing a 7.8% reduction from 2019 (Table S8). Results for the impact of TasP and PrEP interventions, separately and combined, on different model outcomes, at the end of 10 years, can be found in Supporting Information Tables S8-S10.

3.2. Conditions for the elimination of the HIV epidemic

Fig. 2 shows the estimated HIV incidence rate in 2029, and the effective reproduction number R_e under each intervention scenario. The WHO incidence threshold can be achieved by all targeting strategies by improving TasP and PrEP at least by the Medium scenario, except when PrEP does not target any particular MSM subgroup (Fig. 2E). The WHO incident threshold can also be achieved by improving TasP by the High scenario and can almost be achieved by providing PrEP to the high-risk and younger subgroup (Fig. 2C). The estimates of R_e indicate that the HIV epidemic among the MSM population can be eventually eliminated if given to the high-risk group based on the High scenario (Fig. 2F). Notable reductions of R_e with wide credible intervals were observed under the High TasP scenario and High PrEP scenarios targeting high-risk subgroups, younger subgroups, and the high-risk and younger subgroup (Fig. 2B&D). The efficiency of strategies by improving TasP and PrEP by the Medium scenario, estimated as NNT, was 36 (22–53) if targeting high-risk subgroups, 40 (23–59) if targeting younger subgroups, and 29 (14-50) if targeting the high-risk and younger subgroup.

In Fig. 3, we explored the combined longitudinal effect of TasP and PrEP on the annual HIV incidence, IPR and IMR. As shown in this figure, we have already achieved the IPR goal (<0.027) for all scenarios investigated (Fig. 3 D-F). For the HIV incidence goal (<1 HIV new case per 1000 susceptible MSM), we noticed that by scaling-up both interventions targeting the high-risk or younger MSM subgroups, under the High scenario, we can reach this goal as early as 2024 (Fig. 3 A-C). Focusing on the IMR goal (<1), if both TasP and PrEP are scaled-up to the High scenario, focusing on the high-risk or younger MSM subgroups, we can reach this goal by 2025 (Fig. 3 G-I).

3.3. Sensitivity analyses

Based on the previous results, we estimated the impact of varying behavioural parameters and the effectiveness of other types of PrEP use on the HIV incidence rate in 2029, and the effective reproduction number R_e under the combined TasP and PrEP scenarios (Fig. 4). Changing the sexual mixing pattern between subgroups (ρ) or the effectiveness of other types of PrEP use (p_{ε_o}) did not have a large influence on the HIV incidence rate for all scenarios. The percent increase on the average number of partners with CAI acts in each subgroup (p_c) was the parameter that influenced the most these outcomes. Similar impact can be seen for R_e. In addition, reducing the mixing parameter ρ to 20% if PrEP was prioritized to high-risk and younger MSM can achieve R_e <1. Estimates for all combinations of TasP and PrEP scenarios can be found in the Supporting Information Table S14.

Secondly, we performed univariate sensitivity analyses by estimating the sensitivity coefficients on the HIV incidence rate, R_e, HIV prevalence and mortality rate in 2029 under the Status Quo scenario. The top ten parameters with highest coefficients are shown in Fig. 5. The most sensitive parameter was the HIV transmission probability per partner with CAI acts per year (β) for HIV incidence rate, R_e and HIV prevalence, while the all-cause mortality rate was most sensitive to the parameters corresponding to ART interruption (σ_{off} and σ_{on}).

We tested the robustness of the impact of combining TasP and PrEP interventions on HIV incidence rate and effective reproduction number, by varying risk-taking behaviour of MSM after HIV diagnosis (Fig. 6. A-B), taking into account sero-adaptive practices among MSM (Fig. 6. C-D), and varying risk-taking behaviour of MSM on PrEP among older subgroups (Fig. 6. E-F). The WHO incidence threshold can still be achieved by improving TasP and PrEP by the High scenario, and R_e <1 can be achieved by provision of PrEP to high-risk MSM.

4. Discussion

Our results demonstrate that to achieve the goal of HIV elimination required the optimization of all aspects of TasP and the simultaneous provision of PrEP to high-risk MSM (reduction in HIV incidence rate by as much as 67%, R_e as low as 0.67). Providing PrEP to younger MSM or high-risk and younger MSM could achieve comparable results with incidence rates below 1/1000 susceptible MSM (WHO threshold), however with wide credible intervals for R_e that crossed one. Of note, TasP was uniquely able to significantly decrease both HIV incidence and all-cause mortality. The most influential aspect of TasP in this regard was increasing time suppressed on ART. On the other hand, PrEP was most effective in reducing HIV incidence rate when given to those in the high-risk and younger subgroup.

Our results are consistent with previous modeling and empirical studies demonstrating the preventive effect of PrEP when taken daily by MSM at high risk of HIV infection (McCormack et al., 2016; Okano et al., 2016; Punyacharoensin et al., 2016; Zablotska et al., 2018). Still, questions remain on how to best expand the population health use of PrEP for MSM in BC. First, we showed that PrEP is most effective when given to MSM at high-risk of HIV infection. Consistent with current eligibility guidelines in BC (British Columbia Centre for Excellence in HIV/AIDS (BC-CfE), 2020c), we expect that a substantial proportion of MSM will be eligible to receive PrEP, as seen in the United States (Smith et al., 2015). Thus, it is vital that we develop and scale-up cost-effective strategies to deliver PrEP to these individuals. Second, even though combining TasP and PrEP could be effective in reducing new HIV infection, the impact would be compromised by increased number of partners with CAI acts possibly due to declining condom use. Third, in the model, as we did not have information on the number of partners with CAI acts per year in order to stratify risk-taking behaviour among MSM, we estimated this parameter by model calibration and, therefore, we should be cautious to directly implement the calibrated value as the criteria for high-risk MSM. Other ways to identify MSM at high-risk of HIV infection (e.g., based on history of prior rectal sexually transmitted infections) should be explored. On the other hand, we showed that targeting younger MSM was almost as effective as targeting high-risk group, which indicates a simple way to deliver PrEP without stigmatizing individuals based on their risk-taking behaviour. Last, we should acknowledge that the success of targeted PrEP and TasP rests critically on identifying MSM at risk of HIV infection, and those already living with HIV but not diagnosed and retained on ART treatment. Cohort studies, like the Engage Study, can be used to better understand the key barriers to PrEP and TasP access among MSM across Canada (The Engage Team, 2017).

Our model also has important implications and limitations. First, even though many studies have been conducted using risk-stratified compartment models (Okano et al., 2016; Punyacharoensin et al., 2016; Luz et al., 2018; Gilmour et al., 2020), we further developed the model to describe the HIV epidemic among MSM incorporating age-risk stratification, so that it better reflects the heterogeneity of the MSM population in BC. In addition, our model is based on data derived from two population-based registries for PrEP and ART delivery, in a setting with universal healthcare, where there is no financial barrier to access any of these programs. This model is quite intricate because it requires a large number of parameters estimated, and while most parameters were based on empirical data, behaviour related parameters were susceptible to a high degree of uncertainty. Our sensitivity analyses showed how different outcomes were influenced by the values used for these parameters. Second, we did not model the effect of different comorbid conditions (e.g., drug- and alcohol-related harms, mental illnesses and sexually transmitted infections) known to significantly modify the risk

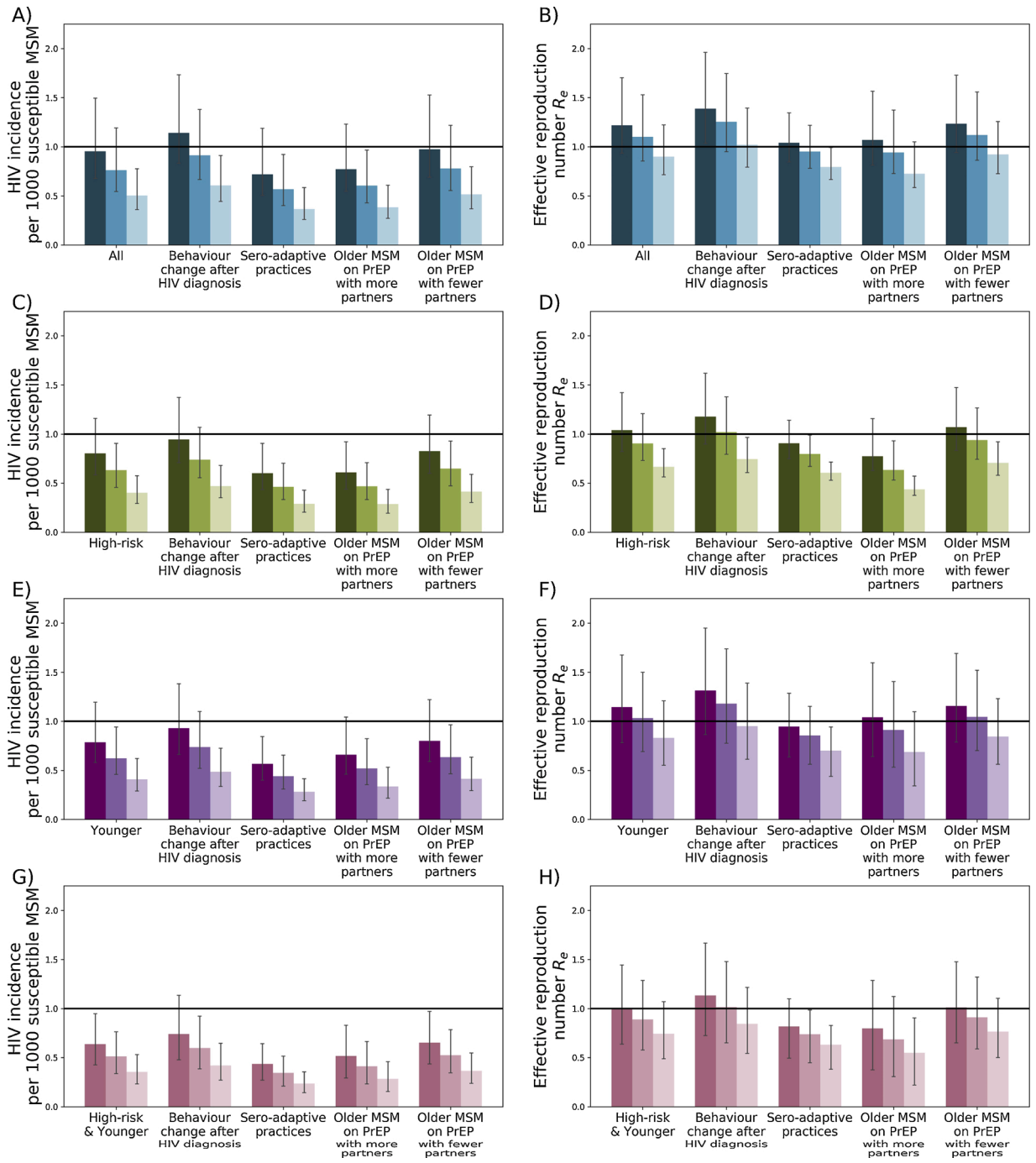

Fig. 6. Sensitivity analysis for HIV incidence rate (A. targeting all MSM, C. targeting high-risk MSM, E. targeting younger MSM, and G. targeting high-risk and younger MSM) and effective reproduction number (B. targeting all MSM, D. targeting high-risk MSM, F. targeting younger MSM and H. targeting high-risk and younger MSM) by: change of risk-taking behaviour after HIV diagnosis; sero-adaptive practices among MSM; older MSM on PrEP with more partners; and older MSM on PrEP with fewer partners. Each of the three bars represent TasP and PrEP under the Low (darker colour), Medium, High (lighter colour) scenarios, respectively.

of HIV transmission (Ward and Ronn, 2010; Safren et al., 2010; Santos et al., 2013). Although these conditions are important determinants of transmission in this population, modeling their effect would greatly increase the model complexity and is beyond the scope of this study. Third, this model does not explicitly model migration of MSM to and from BC, given that these data are not available. Last, although we assessed the effect of different degrees of sexual mixing between the different risk groups, we did not model the complexities that exist in the sexual networks of these individuals.

In conclusion, our model provides important results to inform the development of public health policies to address the HIV epidemic among MSM in BC and in other similar settings. Based on both the WHO threshold for disease elimination and R_e, further optimizing TasP and providing PrEP to high-risk MSM can achieve the goal of HIV elimination in BC.

Disclaimer

All inferences, opinions, and conclusions drawn in this model simulation are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Author contribution

The author's contributions were as follows: Initial study concept and design: VDL, JZ; Acquisition of data: VDL, JZ, NJL, JSGM; Data analysis: JZ, VDL; Mathematical model design: JZ, VDL, NJL; Drafting of the manuscript: JZ, VDL; VDL, JZ, KGC, NJL, GCP, ZW, JSGM revised the manuscript critically for important intellectual content and approved the final version submitted for publication.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2021.100461.

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