Mathematical modelling of the influence of serosorting on the population-level HIV transmission impact of pre-exposure prophylaxis

Linwei Wang[a],*, Nasheed Moqueet[a],*, Anna Simkin[a], Jesse Knight[a,b], Huiting Ma[a], Nathan J. Lachowsky[c], Heather L. Armstrong[d,e], Darrell H.S. Tan[a,f,g], Ann N. Burchell[a,h,i], Trevor A. Hart[i,j], David M. Moore[d,k], Barry D. Adam[l], Derek R. Macfadden[f], Stefan Baral[m] and Sharmistha Mishra[a,b,f,g]

Objectives: HIV pre-exposure prophylaxis (PrEP) may change serosorting patterns. We examined the influence of serosorting on the population-level HIV transmission impact of PrEP, and how impact could change if PrEP users stopped serosorting.

Design: We developed a compartmental HIV transmission model parameterized with bio-behavioural and HIV surveillance data among MSM in Canada.

Methods: We separately fit the model with serosorting and without serosorting [counterfactual; sero-proportionate mixing (random partner-selection proportional to availability by HIV status)], and reproduced stable HIV epidemics with HIV-prevalence 10.3–24.8%, undiagnosed fraction 4.9–15.8% and treatment coverage 82.5–88.4%. We simulated PrEP-intervention reaching stable pre-specified coverage by year-one and compared absolute difference in relative HIV-incidence reduction 10 years post-intervention (PrEP-impact) between models with serosorting vs. sero-proportionate mixing; and counterfactual scenarios when PrEP users immediately stopped vs. continued serosorting. We examined sensitivity of results to PrEP-effectiveness (44–99%; reflecting varying dosing or adherence levels) and coverage (10–50%).

Results: Models with serosorting predicted a larger PrEP-impact than models with sero-proportionate mixing under all PrEP-effectiveness and coverage assumptions [median (interquartile range): 8.1% (5.5–11.6%)]. PrEP users' stopping serosorting reduced PrEP-impact compared with when PrEP users continued serosorting: reductions in PrEP-impact were minimal [2.1% (1.4–3.4%)] under high PrEP-effectiveness (86–99%); however, could be considerable [10.9% (8.2–14.1%)] under low PrEP effectiveness (44%) and high coverage (30–50%).

Conclusion: Models assuming sero-proportionate mixing may underestimate population-level HIV-incidence reductions due to PrEP. PrEP-mediated changes in serosorting

[a]MAP-Centre for Urban Health Solutions, St. Michael's Hospital, Unity Health Toronto, [b]Institute of Medical Sciences, University of Toronto, Toronto, Ontario, [c]School of Public Health and Social Policy, University of Victoria, Victoria, [d]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada, [e]School of Psychology, University of Southampton, Southampton, UK, [f]Department of Medicine, [g]Institute of Health Policy, Management, and Evaluation, [h]Department of Family and Community Medicine, [i]Dalla Lana School of Public Health, University of Toronto, [j]Department of Psychology, Ryerson University, Toronto, Ontario, [k]Department of Medicine, Division of Infectious Disease, University of British Columbia, Vancouver, British Columbia, [l]Department of Sociology, Anthropology, and Criminology, University of Windsor, Windsor, Ontario, Canada, and [m]Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA.

Correspondence to Sharmistha Mishra, MD, MSc, PhD, MAP-Centre for Urban Health Solutions, St. Michael's Hospital, Unity Health Toronto, University of Toronto, 209 Victoria St, Toronto, ON M5B 1T8, Canada.

Tel: +1 416 864 5746; e-mail: sharmistha.mishra@utoronto.ca

* Linwei Wang and Nasheed Moqueet contributed equally to this study.

could lead to programmatically important reductions in PrEP-impact under low PrEP-effectiveness. Our findings suggest the need to monitor sexual mixing patterns to inform PrEP implementation and evaluation.

Introduction

Sexual mixing patterns ('who has sex with whom') influence the population-level transmission dynamics of sexually transmitted infections (STIs) such as HIV [1]. Mixing influences how HIV may spread and persist, and thus how interventions may fare at a population-level [1]. However, the influence of mixing on estimated population-level impact of HIV prevention tools, such as HIV pre-exposure prophylaxis (PrEP), has been little studied.

PrEP with oral antiretrovirals has potential for large population-level impact, especially when impact includes the indirect prevention benefits accrued by individuals not on PrEP [2]. Most transmission models of PrEP impact include heterogeneity in HIV-risk via heterogeneity in number of sexual partners [3,4], while some include assortative sexual mixing by attributes such as sexual activity level [3], age (2−4) and race/ethnicity (2).

In the context of HIV epidemics among MSM, sexual mixing patterns also include seroadaptive behaviours such as serosorting [5]. Serosorting refers to preferential formation of partnerships between individuals of the same perceived HIV status [5]. Data from behavioural surveys in high-income settings suggest that both HIV-positive and HIV-negative MSM practice serosorting as an HIV-prevention measure [5,6]. However, across 15 transmission models of PrEP impact among MSM in high-income settings (Appendix-1 Table S1.1, http://links.lww.com/QAD/B1000), only three included serosorting [2−4]. With the roll-out of PrEP across North America and Europe, data are emerging about potential changes in serosorting among MSM, as PrEP may reduce stigma and anxiety around sex in serodiscordant partnerships [6,7]. Empirical data of MSM in Montréal, Canada, demonstrate less population-level serosorting among HIV-negative MSM on PrEP than those not on PrEP [6].

Mathematical models of PrEP impact among MSM have studied individual-level behaviour changes among those on PrEP, often referred to as 'risk compensation'. The models examined increases in partner numbers [3,8], and reductions in condom use [2−4,8], and predicted that realistic changes would not fully offset, but could weaken, PrEP's impact on reducing HIV transmission [2−4,8]. No

models have explored the influence of serosorting on the population-level HIV transmission impact of PrEP, or how PrEP impact could change if PrEP changes serosorting patterns.

We developed a mathematical model of HIV transmission among MSM in Canadian urban settings. First, we compared the impact of PrEP under simulated-epidemics with serosorting to that under comparable simulated-epidemics with sero-proportionate mixing. Second, under simulated-epidemics with serosorting, we compared the impact of PrEP under scenarios when PrEP-users stopped vs. continued serosorting after starting PrEP.

Materials and methods

Overview

We developed a deterministic compartmental model of HIV transmission to reproduce the epidemiologic features of stable HIV epidemics among MSM living in the three largest Canadian cities (Montréal, Toronto and Vancouver). The model includes five compartments defined by HIV status, HIV diagnosis and the use of PrEP or antiretroviral treatment (ART) (Appendix-2 Figure S2.1, http://links.lww.com/QAD/B1000). Individuals enter the model in the susceptible health-state at onset of sexual activity and exit the model due to death or cessation of sexual activity.

We sourced city or province-specific HIV surveillance reports and bio-behavioural surveys of MSM in Canada for estimates of HIV prevalence (year 2005−2017) [6,9,10], annual new HIV diagnoses (2013−2016) [11−13] and treatment parameters (2013−2018) [6,14,15]. We obtained sexual behavioural parameters from publicly available behavioural surveys of MSM in Canada [6,9,10]. Appendix-3 and 4.2, http://links.lww.com/QAD/B1000 describes details of data parameterization.

Our model was restricted to transmission via anal sex in keeping with our research question (rationale described in Appendix-2.2, http://links.lww.com/QAD/B1000). The probability of HIV acquisition for a susceptible

individual (force of infection) depended on per–act transmission probability of condomless anal sex; condom effectiveness; number of concurrent sex partners; probability the sex partner is living with HIV and not virally suppressed; number and type of anal sex acts per partnership; and condom use (Table 1, Appendix-2.2, http://links.lww.com/QAD/B1000). We assumed 86% of MSM on ART achieved viral suppression (Table 1) [14]; those virally suppressed could not transmit HIV.

Heterogeneity in HIV transmission risk was modelled via two sexual activity levels to capture individuals at a higher risk of infection [16]. We operationalized the difference between two activity groups via the number of concurrent sexual partners: the high activity group had six times as many sexual partners as the low activity group, and comprised 6−12% of the MSM population [17,18]. We applied the same condom use, number of sex acts, serosorting patterns in both groups and proportionate

Table 1. Model parameter values.

Parameters	Parameter range[a] (calibrated) or value (fixed)	Reference	Notes (details of evidence synthesis)
Entry and exit rate			
Baseline entry rate (per person per year)	1/50	NA	Assumption: the same as baseline exit rate.
Baseline exit rate (per person per year)	1/50	NA	Assumption: 1/duration of sexual activity (15−64 years)
Population annual growth rate (per year)	0.01	[32]	Direct estimate[b]: average annual population growth rate in Canada in the past 5 years (2013–2017).
All-cause mortality			
No HIV infection (per person per year)	0.0026	[33]	Direct estimate[b]: assumed to be the same as general male aged 15−64 years
HIV infected, not on ART (per person per year)	0.0893	[34]	Direct estimate[b]: inverse of the median duration of survival (1/11.2 years).
HIV infected, on ART (per person per year)	0.0114	[35]	Direct estimate[b]: chose lower bound of mortality estimate in the reference paper Table 2 to account for potential decline in mortality in recent years compared with 2000−2007 when estimate was drawn.
Sexual behavioural parameters			
Number of concurrent sexual partners for low sexual activity MSM (per person per year)	4	[9,18,36,37]	Indirect estimate[c]: weighted average across 4 studies of the 'low' activity group as those reporting 0–5 partners in the previous 6 months, for an average of two partners in the past 6 months; thus 4 per year.
Ratio: number of partners for high sexual activity MSM to number of partners for low sexual activity MSM	6	[17]	Triangulated estimate[d]: to reproduce an incidence ratio of 6 between the high vs. low activity groups; informed by incidence ratio between MSM with a HIRI score ≥25 vs. <25 (See Appendix 3.2.2, http://links.lww.com/QAD/B1000).
Proportion of high sexual activity MSM	[0.06, 0.12]	[18]	Indirect estimate[c]: informed by the HIRI score distribution among MSM attending Hassle Free clinics in Toronto (see Appendix 3.2.3, http://links.lww.com/QAD/B1000).
Number sex acts (per partnership per year)	13	[38]	Direct estimate[b]: MSM reported having anal sex for a median of one day in the preceding week.
Proportion of insertive anal sex acts, seroconcordant partnerships	0.5	NA	Assumption: would expect 50 : 50 as there is no need for sero-position in seroconcordant partnerships.
Proportion of insertive (HIV-negative perspective) anal sex acts, serodiscordant partnerships	0.77	[36]	Indirect estimate[b]: 27% of HIV-negative individuals report sero-position; these 27% can be used to represent the 'excess' fraction.
Condom use in serodiscordant partnerships	[0.36, 0.70]	[9,22]	Indirect estimate[b]: lower estimate obtained from the perspective of HIV-positive MSM in Momentum study; Upper estimate obtained from the perspective of HIV-negative MSM using the M-track data and weighted by main and casual partners.
Relative condom use in sero-concordant vs. discordant partnerships	[0.3, 1]	[21,22]	Indirect estimate[b]: captured discrepancy (thus uncertainty) in estimates reported by HIV-positive (0.3) vs. HIV-negative individuals (0.95).
Condom efficacy	80%	[39,40]	Direct estimate[b]: systematic review
Sexual mixing parameters			
Model 1 -serosorting	[0−1]	NA	0 indicates fully assortative mixing and 1 indicates proportionate mixing. Calibrated to produce epidemics with empirical levels of seroconcordance (Appendix 4.2.4, http://links.lww.com/QAD/B1000).

Table 1 (*continued*)

Parameters	Parameter range[a] (calibrated) or value (fixed)	Reference	Notes (details of evidence synthesis)
Model 2 – sero-proportionate mixing	1	NA	0 indicates fully assortative mixing and 1 indicates proportionate mixing. Calibrated to produce epidemics with empirical levels of seroconcordance (Appendix 4.2.4, http://links.lww.com/QAD/B1000).
Per act HIV transmission probability			
Insertive sex act (per anal sex act)	0.0022	[41]	Direct estimate[b]: estimate which did not distinguish when ejaculation occurred.
Receptive sex act (per anal sex act)	0.0073	[41]	Direct estimate[b]: estimate which did not distinguish when ejaculation occurred.
Testing, treatment, PrEP parameters			
Rate of HIV testing (per person per year)	[0.23, 0.78]	[42–44]	Triangulated estimate[d]: using provincial data (Ontario and British Columbia) of HIV testing among MSM to approximate urban settings in Canada.
Rate of ART initiation (per person per year)	[0.52, 0.84]	[14,45–48]	Triangulated estimate[d]: using regional data (Vancouver Coastal Health Authority) of ART initiation among MSM to approximate urban settings in Canada.
Rate of ART drop-out (per person per year)	0.08	[14,45–48]	Triangulated estimate[d]: using regional data (Vancouver Coastal Health Authority) of ART dropout among MSM to approximate urban settings in Canada.
Proportion of viral suppression among individuals on ART	86%	[14]	Direct estimate[b]: using regional data (Vancouver Coastal Health Authority) of viral suppression among MSM to approximate urban settings in Canada: average viral suppression between years 2014–2018. In the referenced data source [14], viral suppression was defined as having no detectable plasma viral load over a period $\geq$3 months in duration within the calendar year [49]. The definition of non-detectable was based on the viral load testing technology available at the time of measurement, which was $\leq$50 copies/ml for the period of 2014–2018.
PrEP coverage	50%	NA	Assumption: varied between 10 and 50% in sensitivity analysis.
Rate of PrEP initiation (per person per year)	>0	NA	Initiation rates were adjusted (instantaneously) to achieve defined PrEP coverage in 1 year.
PrEP effectiveness in reducing HIV transmission	86%	[23,29,50]	Direct estimate[b]: varied between 44 and 99% in sensitivity analysis to reflect various adherence levels.

ART, antiretroviral therapy; HIRI, HIV Incidence Risk Index; MSM, men who have sex with men; NA, not applicable; PrEP, HIV pre-exposure prophylaxis.
[a]Assumed uniform distribution.
[b]Estimates which could be directly extracted from (without additional calculation or with very basic calculations based on the notes) the reference.
[c]Estimates which were pooled (to derive either the average or the range) across multiple sources; or extracted from a single source with adjustments.
[d]Estimates which were triangulated from several other parameters obtained from various sources and under certain assumptions.

mixing by sexual activity level. The details of the parameterization of sexual activity groups are provided in Appendix 3.2, http://links.lww.com/QAD/B1000. We also applied the same rates of HIV testing and ART initiation in both groups.

We modelled sexual mixing by HIV status via a parameter $\in$, which controls the degree of assortative mixing (0 indicates fully sero–assortative mixing; 1 indicates sero–proportionate mixing) (Appendix-2.2.2, http://links.lww.com/QAD/B1000) [19]. We calibrated the value of $\in$ within the range of 0 to 1 to fit to the empirical estimates of the population-level sexual mixing patterns by HIV status (details below).

Calibration
We simulated and calibrated models separately under two assumptions: with serosorting vs. with sero–proportionate mixing (details in Appendix-4, http://links.lww.com/QAD/B1000).

Model-1: serosorting
We sampled 2000 sets of priors of the fitted parameters using Latin hypercube sampling [20], and calibrated the model to an equilibrium (Table 1, Appendix-4.3.1, http://links.lww.com/QAD/B1000): HIV prevalence 10.3–30.7% [6,9,10]; annual number of new HIV diagnoses 194–909 per 100 000 MSM [11–13]; and ART coverage 81–98% [6,14,15]. We simultaneously

calibrated our model to empirical estimates of two population-level seroconcordance values (Appendix-4.2.4, http://links.lww.com/QAD/B1000): proportion of seroconcordant partnerships (including HIV-negative and undiagnosed HIV) by self-perceived HIV-negative individuals (including individuals with undiagnosed HIV) 83.3–95.1% [6,21]; and proportion of seroconcordant partnerships by HIV-positive individuals 33.9–76.5% [6,22]. We assumed that all true HIV-negative individuals would self-perceive as HIV-negative. We assumed that a proportion of HIV-positive individuals would self-perceive as HIV-negative if undiagnosed, and have the same partnership distribution by HIV status as those who were true HIV-negative. We retained 320 sets of calibrated posteriors.

Model-2: sero-proportionate mixing
We set the value of $\in\ =1$ in *Model-2* reflecting sero-proportionate mixing. We re-fit the two condom use parameters (condom use between perceived serodiscordant partnerships; and relative condom use in perceived seroconcordant vs. discordant partnerships) within their prior ranges in Table 1. For *Model-1* and *2* to generate the same HIV prevalence, something else must compensate for the difference in population-level HIV transmission risk changes in the absence vs. presence of serosorting. We selected condom use because of uncertainty surrounding its estimates, and because condom use can be considered a proxy for risk. We calibrated the two condom use parameters to fit *Model-2* to the matched (<2% relative difference) equilibrium values of HIV prevalence, HIV new diagnoses rate and ART coverage generated by *Model-1* using an optimization algorithm (Appendix-4.3.2, http://links.lww.com/QAD/B1000) and obtained 244 sets of calibrated posteriors.

Pre-exposure prophylaxis intervention
Scenario-1: pre-exposure prophylaxis did not modify sexual mixing patterns
After model calibration, we introduced PrEP intervention to both *Model-1* and *2*. We applied uniform access and uptake of PrEP by sexual activity level, with a linear increase in PrEP coverage until 30% coverage among HIV-negative individuals was achieved 1-year post-implementation. We varied coverage (10–50%) in sensitivity analyses (Appendix-3.6.2, http://links.lww.com/QAD/B1000). PrEP coverage remained stable thereafter, and we did not include PrEP discontinuation for model simplification. We used PrEP effectiveness of 86% in our primary analysis, as per the IPERGAY [23] and the PROUD studies [24], and 44–99% in sensitivity analyses (Appendix-3.6.1, http://links.lww.com/QAD/B1000).

Scenario-2: pre-exposure prophylaxis mediated changes in serosorting
We introduced changes in serosorting following PrEP initiation under the model with serosorting (*Model-1*),

while maintaining other elements of the PrEP intervention as with *scenario-1*. We assumed that individuals stopped serosorting (sero-proportionate) when they initiated PrEP; men not on PrEP adapted accordingly when forming partnerships with PrEP users to balance partnerships; and men not on PrEP maintained the pre-intervention level of serosorting when forming partnerships with other men not on PrEP. Appendix-2.3.3, http://links.lww.com/QAD/B1000 details the mathematical solutions to balancing partnerships given above assumptions.

Analyses
Influence of serosorting
We calculated the absolute difference in the population-level PrEP impact between *Model-1* with serosorting and *Model-2* with sero-proportionate mixing, under the scenario when PrEP did not change sexual mixing patterns (*Scenario-1*). We quantified the population-level impact by the relative HIV incidence reduction 10 years after intervention, a measure often referred to as relative risk reduction in epidemiological studies to quantify individual-level efficacy of an intervention [25]. Appendix-5, http://links.lww.com/QAD/B1000 demonstrates the detailed calculations.

Influence of pre-exposure prophylaxis mediated changes in serosorting
We used simulated-epidemics generated by *Model-1 with serosorting* to estimate the absolute difference in the population-level PrEP impact between two scenarios: individuals on PrEP stopped vs. continued serosorting, and impact was measured by the relative HIV incidence reduction ten-years after intervention (Appendix-5, http://links.lww.com/QAD/B1000).

Sensitivity analyses
To examine the influence of HIV epidemic features (prevalence, fraction of undiagnosis and ART coverage), and levels of serosorting on the results, we performed bivariate analyses using scatter plots and multivariable analyses using partial rank correlation coefficient (PRCC) to identify the most influential factors [26]. We also examined a range of PrEP effectiveness (44–99%, reflecting various dosing and/or adherence levels) and coverage (10–50%) to identify the intervention conditions under which serosorting and PrEP-mediated changes in serosorting would have the largest influence on PrEP impact.

Results

Calibration
Model-1 with serosorting reproduced the observed range of epidemics with respect to HIV prevalence (10.3–24.8%), annual HIV diagnoses per 100 000 (391–904)

and ART coverage (82.5−88.4%). By calibrating to empirical estimates of population-level seroconcordance measures, the posterior values of ∈ ranged from 0.29 to 0.81, reflecting various levels of serosorting. The estimated HIV incidence at equilibrium ranged from 0.51 to 1.8 per 100 person-years (2.3−9.6, and 0.38−1.6 per 100 person-years for high and low sexual activity groups, respectively), HIV undiagnosed fraction ranged from 4.9 to 15.8%, and all-cause mortality among individuals living with HIV ranged from 2.4 to 3.5 per 100 person-years. We present the distributions of all calibrated posteriors in Appendix-6 Figure S6.1, http://links.lww.com/QAD/B1000.

Model-2 with sero-proportionate mixing reproduced similar values of HIV prevalence, new diagnosis rate and ART coverage as Model-1 with serosorting. To achieve this, the models needed a similar force of infection pre-intervention, and thus, the calibrated posteriors of condom use were higher in Model-2 than in Model-1 (Appendix-6 Figure S6.2, http://links.lww.com/QAD/B1000). Condom use had to be higher in Model-2 because − given relatively low level of undiagnosed HIV (4.9−15.8%) − simulated-epidemics with serosorting mean fewer partnerships wherein transmission could occur compared with simulated-epidemics with sero-proportionate mixing. For example, HIV-positive partners comprised 4.9−16.7% of partnerships by HIV-negative individuals under serosorting vs. 14.1−31.6% under sero-proportionate mixing (Appendix-6 Figure S6.2, http://links.lww.com/QAD/B1000). Thus, for Models 1 and 2 to produce comparable simulated-epidemics, the per-partnership transmission probability had to be higher in Model-1 with serosorting as reflected by lower condom use posteriors (Appendix-6 Figure S6.2, http://links.lww.com/QAD/B1000), compared with Model-2 with sero-proportionate mixing.

Influence of serosorting
Model-1 with serosorting predicted a larger population-level PrEP impact compared with Model-2 with sero-proportionate mixing. The difference in PrEP impact in models with vs. without serosorting increased over time (Fig. 1). As shown for one simulated-epidemic (HIV prevalence 16.2%, undiagnosed fraction 7.9%; representing the median values of HIV prevalence and undiagnosed fraction among all simulated-epidemics) in Fig. 1a, at 86% PrEP effectiveness and 30% coverage, the relative reduction in incidence 2 years after intervention was 36.7% under serosorting, and 32.3% under sero-proportionate mixing, reflecting an absolute difference of 4.4% in relative incidence reduction; the difference in impact between two models increased over time and plateaued by year-ten. By year-ten, the relative reduction in incidence was 57.7% under serosorting and 44.7% under sero-proportionate mixing, reflecting an absolute difference of 13.0% in relative incidence reduction. Across all simulated-epidemics, the 10-year absolute

difference in relative incidence reduction ranged from 2.0 to 21.7% (median: 9.5%; interquartile range: 6.7−12.5%) when comparing serosorting to sero-proportionate mixing (Fig. 1b). Higher level of serosorting was correlated with a larger difference in PrEP impact between simulated-epidemics with and without serosorting (Appendix-6 Figure S6.3, http://links.lww.com/QAD/B1000).

The findings could be explained by the synergetic effect of multiple risk reduction strategies/interventions. Both condom use and PrEP use directly influence the per-partnership transmission risk, whereas serosorting influences the proportion of partnerships where transmissions could happen; each element contributes to the HIV force of infection. In simulated-epidemics with serosorting but lower condom use (Model-1), the pre-intervention per-partnership transmission risk was higher thus the marginal benefits of PrEP use in reducing per-partnership transmission risk was larger resulting in larger population-level impact, compared with simulated-epidemics without serosorting (Model-2).

For a given PrEP coverage, the influence of serosorting on the PrEP impact decreased as PrEP effectiveness increased (Fig. 2). This inverse relationship stems from a smaller marginal benefit at the individual-level from serosorting when individual-level PrEP effectiveness is high; thus, a smaller influence of serosorting at the population-level (Appendix-6 Figure S6.4A, http://links.lww.com/QAD/B1000). The influence of serosorting was the largest at 50% coverage when PrEP effectiveness was low (44%); and peaked at 30% coverage when PrEP effectiveness was high (86−99%) (Fig. 2). This is because the rate of relative HIV incidence reduction due to PrEP diminishes when PrEP coverage exceeds 30−50% (Appendix-6 Figure S6.4B, http://links.lww.com/QAD/B1000).

Influence of pre-exposure prophylaxis mediated changes in serosorting
When PrEP users stopped serosorting, there was a reduced impact of PrEP compared with scenarios when PrEP users continued serosorting (Fig. 3). For example, at 86% PrEP effectiveness and 30% coverage, the reduction in PrEP impact 10 years after intervention ranged from 1.1 to 7.2% (median: 3.6%; interquartile range: 2.6−4.7%) between scenarios with and without PrEP-mediated changes in serosorting across all simulated-epidemics (Fig. 3).

In sensitivity analyses, the following factors demonstrated a strong association with the influence of PrEP-mediated changes in serosorting on PrEP impact (Appendix-6 Table S6.1, http://links.lww.com/QAD/B1000): PrEP effectiveness (PRCC = 0.91), level of serosorting (PRCC = −0.76), PrEP coverage (PRCC = −0.68) and pre-intervention HIV prevalence (PRCC = −0.37).
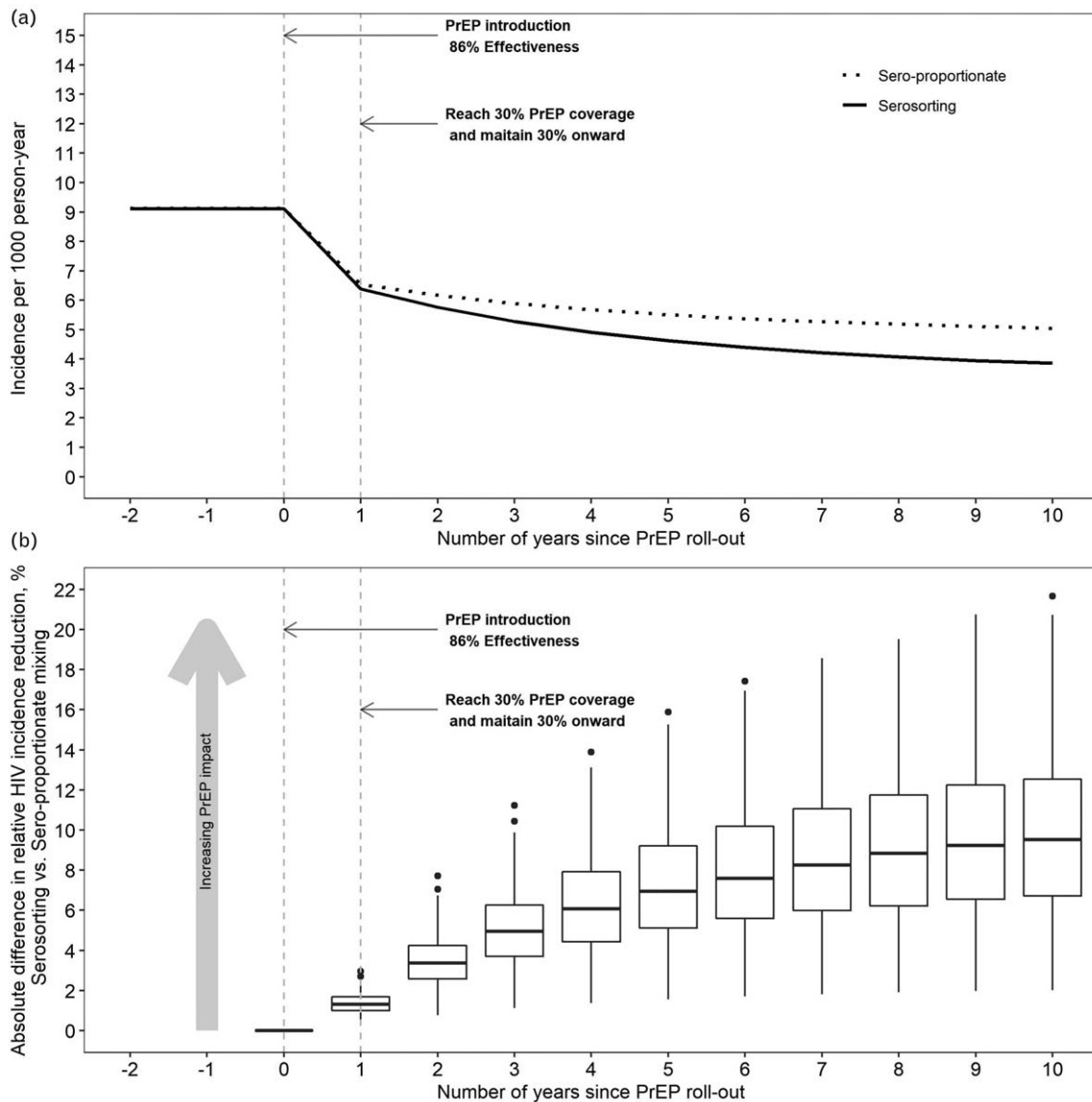
Fig. 1. Comparison of the population-level pre-exposure prophylaxis impact between models with serosorting vs. sero-proportionate mixing. (a) Incidence trajectory 10 years after PrEP introduction for one-example simulated-epidemic (HIV prevalence 16.2%; Undiagnosed HIV 7.9%). (b) Boxplots summary across 244 pairs of matched simulated-epidemics, where for each pair of matched simulated-epidemic, the absolute difference in the population-level PrEP impact over a ten-year period was calculated comparing serosorting to sero-proportionate mixing. PrEP, HIV pre-exposure prophylaxis.

−0.37). As shown in Fig. 4, when PrEP effectiveness was low (44%), PrEP-mediated changes in serosorting were more likely to reduce the PrEP impact, especially in settings with higher pre-intervention HIV prevalence, higher level of serosorting and at higher PrEP coverage [for instance, the median reductions in PrEP-impact was 10.9% (interquartile range: 8.2−14.1%), under 44% PrEP effectiveness and 30−50% PrEP coverage]. However, when the effectiveness of PrEP was high (86−99%), the influence of PrEP-mediated changes in serosorting had minimal influence on the transmission impact of PrEP [median: 2.1%, interquartile range: 1.4−3.4)] (Fig. 4).

Mechanism underlying pre-exposure prophylaxis mediated changes in serosorting

We compared the partnership distribution 10 years after PrEP initiation between scenarios when PrEP users stopped vs. continued serosorting. When PrEP users no longer serosort, their sexual partnerships comprise a higher proportion of HIV-positive partners, and thus a lower proportion of HIV-negative (both on and not on PrEP) and undiagnosed partners (Appendix-6 Figure S6.5A,C, http://links.lww.com/QAD/B1000). Men not on PrEP (including HIV-negative not on PrEP, HIV-positive and undiagnosed) therefore also form
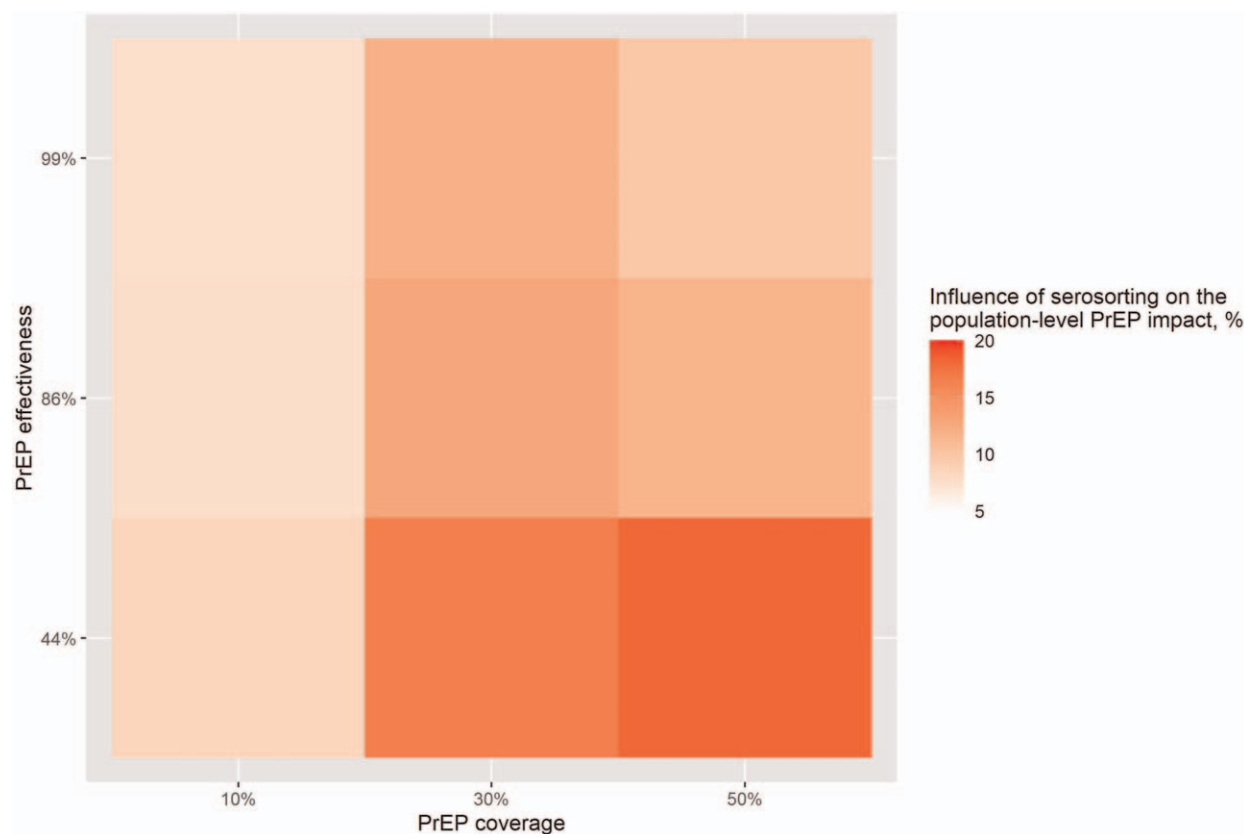
Fig. 2. Variations in the influence of serosorting on the population-level HIV transmission impact of pre-exposure prophylaxis, by PrEP coverage and effectiveness as demonstrated using one-example simulated-epidemic (HIV prevalence 16.2%; undiagnosed HIV 7.9%). Influence of serosorting on the PrEP impact was measured by absolute difference in the relative HIV incidence reduction 10 years after PrEP introduction between the model with serosorting vs. the model with sero-proportionate mixing. PrEP, HIV pre-exposure prophylaxis.

partnerships with PrEP users in a sero–proportionate manner, in order to balance partnerships (proofs shown in Appendix-2.3.3, http://links.lww.com/QAD/B1000). Consequently, the proportion of partnerships formed with PrEP users decreases for HIV-negative and undiagnosed individuals not on PrEP, and increases for HIV-positive individuals (Appendix-6 Figure S6.5A, http://links.lww.com/QAD/B1000). Under the assumption that men not on PrEP continue to serosort when forming partnerships with other men not on PrEP, our findings support that the proportion of partnerships formed between HIV-positive and perceived HIV–negative (including undiagnosed) individuals not on PrEP remained the same between both scenarios (Appendix-6 Figure S6.5A, http://links.lww.com/QAD/B1000; proofs shown in Appendix-2.3.3, http://links.lww.com/QAD/B1000). Finally, to satisfy partnership balancing overall, the proportion of perceived HIV-negative partners not on PrEP increases for perceived HIV-negative individuals not on PrEP, and the proportion of HIV-positive partners decreases for HIV-positive individuals (Appendix-6 Figure S6.5A, http://links.lww.com/QAD/B1000).

The difference in partnership distribution between two scenarios (PrEP users stopped vs. continued serosorting) meant that when we compared the number of incident infections 10 years into PrEP roll-out in the two scenarios, there were fewer infections within partnerships between PrEP-users and their undiagnosed partners; more infections within partnerships between PrEP-users and their HIV-positive partners; and more infections within partnerships between HIV-negative individuals not on PrEP and their undiagnosed partners (Appendix-6 Figure S6.5B, http://links.lww.com/QAD/B1000). Therefore, there were more infections overall when PrEP users stopped vs. continued serosorting.

Discussion

Using a dynamic HIV transmission model among MSM, we constructed counterfactual simulated-epidemics with and without serosorting. We found the impact of PrEP was higher in simulated-epidemics with serosorting, compared with comparable simulated-epidemics with
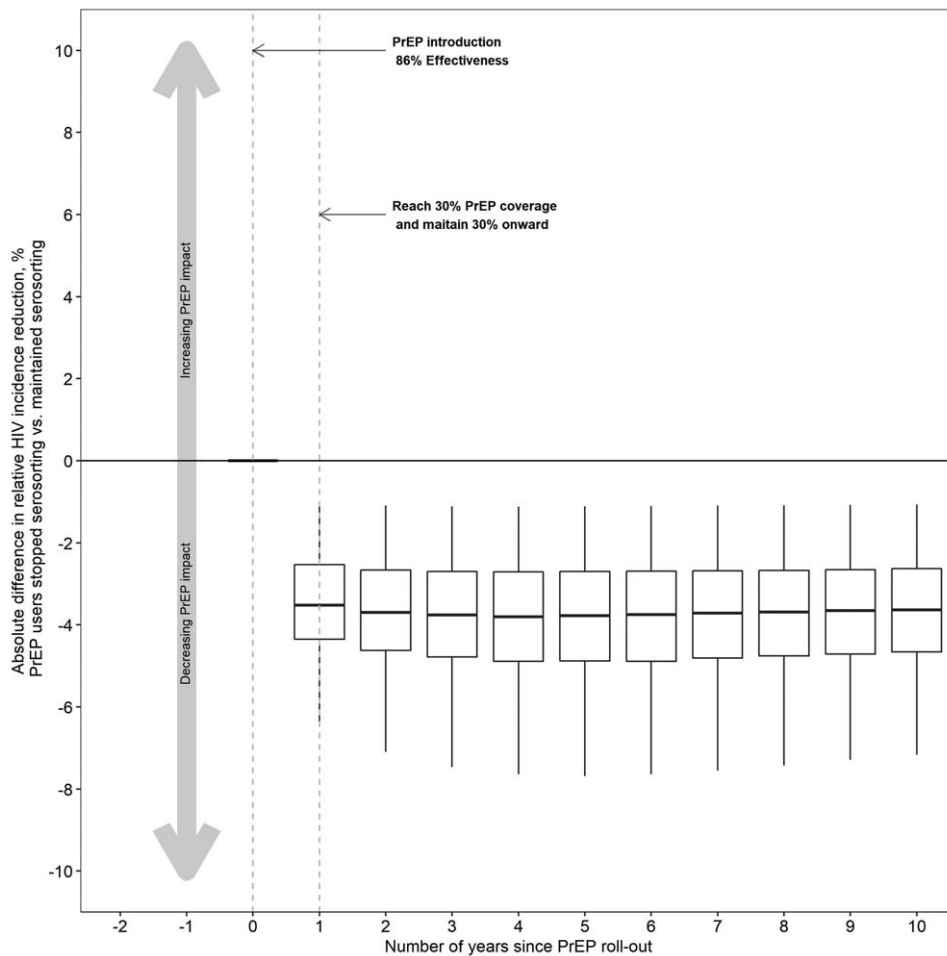
Fig. 3. Comparison of the population-level pre-exposure prophylaxis impact between scenarios when PrEP users stopped serosorting vs. continued serosorting. Boxplots summary across 320 sets of simulated-epidemics with serosorting, where for each simulated-epidemic, the absolute difference in the population-level PrEP impact over a ten-year period was calculated comparing scenarios when PrEP users stopped vs. continued serosorting. PrEP, HIV pre-exposure prophylaxis.

sero-proportionate mixing. We also compared two counterfactual scenarios: PrEP users' stopping serosorting reduced PrEP impact compared with scenarios when PrEP users continued serosorting; however, reductions in PrEP impact were minimal if PrEP effectiveness was high. Only in the context of low PrEP effectiveness and high PrEP coverage do PrEP-mediated changes in serosorting have the potential to programmatically meaningfully undermine the impact of PrEP.

Our findings suggest that in epidemic contexts where serosorting may reduce HIV transmission (i.e. settings with undiagnosed HIV <20% and ART coverage of >70%) [27], models that ignore serosorting patterns (i.e. assume sero-proportionate mixing) could underestimate the projected transmission impact of PrEP, or overestimate the PrEP coverage required to achieve a desired population-level incidence reduction goal. Therefore,

model-based evaluation of the impact of real-world PrEP implementation among MSM should incorporate serosorting patterns, especially in high-income settings wherein the epidemics are similar to those examined in the current study.

Our study is the first to our knowledge that directly examined the influence of PrEP-mediated changes in serosorting on the PrEP impact. Although PrEP-mediated changes in serosorting had minimal overall influence on population-level PrEP impact when PrEP effectiveness was high, they could result in a higher absolute number of incident HIV cases for HIV-negative individuals not on PrEP via transmissions from partners living with undiagnosed HIV. The modelled increase in infections was due to the downstream effects of PrEP-mediated changes in serosorting on the sexual network. Our findings highlight the importance of HIV testing to
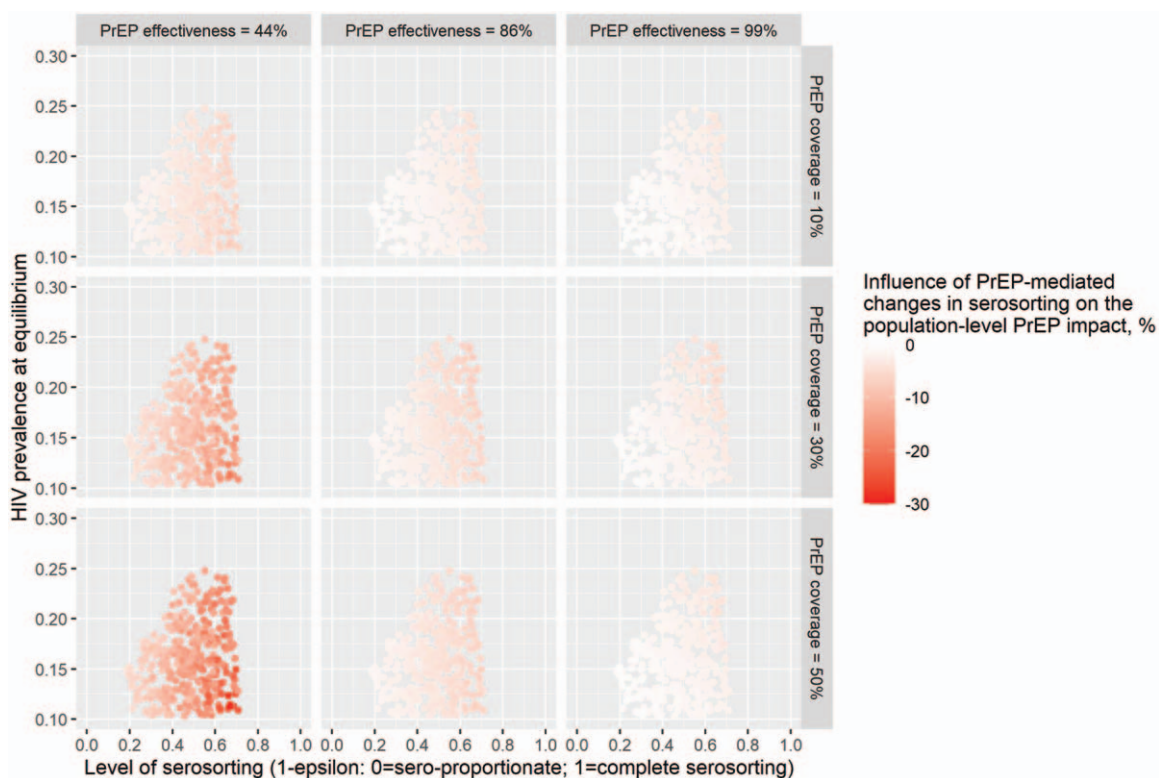
Fig. 4. Variations in the influence of pre-exposure prophylaxis mediated changes in serosorting on the population-level HIV transmission impact of PrEP by baseline level of serosorting, HIV prevalence at equilibrium, PrEP coverage and effectiveness. Influence of PrEP-mediated changes in serosorting on the PrEP impact was measured by absolute difference in the relative HIV incidence reduction 10 years after PrEP introduction, comparing scenarios in which PrEP users stopped serosorting vs. maintained serosorting. PrEP, HIV pre-exposure prophylaxis.

reduce the fraction or person–years of undiagnosed HIV in the population, especially after potential PrEP-mediated changes to sexual mixing.

PrEP-mediated changes in serosorting may considerably reduce PrEP impact if the PrEP effectiveness is low (44%) and as coverage reaches 30%. The influence of PrEP-mediated changes is relevant to the current state of PrEP roll-out in Canada, whereby 2017−2019, PrEP coverage in Canadian cities is between 11 and 23% [28]. Although early data suggest high PrEP adherence (>95%), participants may be 'early adopters' of PrEP whose high adherence may not represent the wider population of MSM [29]. Indeed, in USA cities with a longer history of PrEP roll-out, data suggest a high level of PrEP cessation in primary care settings [30], suggesting challenges to PrEP adherence in real-world implementation; therefore our lower bounds on 44% effectiveness is plausible when accounting for short-term adherence and long-term retention. Therefore, serosorting may continue to provide a synergetic benefit in combination HIV prevention with PrEP roll-out, especially with lower PrEP effectiveness (e.g. due to poor adherence) and under relatively low levels of undiagnosed HIV. Our findings support the need to monitor population-level sexual

mixing patterns in addition to individual-level behavioural changes following PrEP initiation.

To examine the causal mechanisms by which differences in PrEP impact may be attributable to changes in patterns of sexual mixing mediated by PrEP, we purposefully designed our experiments to exclude other behavioural changes due to PrEP (e.g. reduction in condom use). Future studies should further examine the relationship between multiple behavioural changes in PrEP users, and how they simultaneously influence the impact of PrEP.

Our study has several limitations. First, we examined a scenario wherein PrEP users stopped serosorting. Empirical data suggest less serosorting among PrEP users [6]; thus, our findings capture the maximum potential influence of PrEP-mediated changes in serosorting. Second, we simplified intervention scenarios (uniform access and uptake of PrEP by sexual activity level and stable PrEP coverage). Future analyses of PrEP-mediated changes in serosorting under different real-world PrEP intervention strategies is an important next step. For example, if PrEP were prioritized to higher-risk MSM, our findings from uniform PrEP implementation leading to a similar relative incidence reduction within each

group could translate to a larger difference in the absolute number of infections averted, compared with the uniform PrEP implementation, due to the higher baseline HIV incidence in the higher-risk group (Appendix-6 Table S6.2, http://links.lww.com/QAD/B1000). Third, we did not distinguish rates of HIV testing and ART initiation by sexual activity level due to lack of data; risk group-specific parameterization for these parameters might be important for studies evaluating risk group-targeted interventions. Fourth, we did not distinguish serosorting patterns and condom use by ART use or viral suppression, due to the lack of subgroup-specific empirical estimates. However, ART coverage and proportion virally suppressed in our simulated-epidemics were similar to the study samples from which we sourced average mixing and condom use estimates among HIV-diagnosed individuals (Appendix-4.2.4, http://links.lww.com/QAD/B1000). Fifth, we assumed proportionate mixing by sexual activity level due to limited local data. However, a study of a sample of MSM who visited an STI/HIV testing clinic in Sweden found a very moderate level of assortative mixing between high and low sexual activity groups in choosing casual partners (0.14, where the authors used value 0 to indicate proportionate mixing, and value 1 to indicate complete assortative mixing) [31]. Finally, as with many modelling studies, our findings are specific to the epidemiological context under study with PrEP interventions initiated at an epidemic equilibrium.

In summary, transmission models that do not consider patterns of serosorting may underestimate the effectiveness of PrEP programs. Moreover, PrEP-mediated changes in serosorting could lead to programmatically important reductions in PrEP impact. Our findings highlight the importance of monitoring sexual mixing patterns and their changes alongside the design and evaluation of PrEP implementation.

Conflicts of interest
There are no conflicts of interest to disclose.

Acknowledgements

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