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Research Paper

The potential impact of initiating antiretroviral therapy with integrase inhibitors on HIV transmission risk in British Columbia, Canada

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ABSTRACT

Background: Available agents within the integrase strand-transfer inhibitor (INSTI) class have been shown to lead to a faster decay in viral load than other regimens. Therefore, we estimated the potential reduction in HIV transmission risk among antiretroviral-naïve individuals initiating on INSTI-based antiretroviral therapy (ART), focusing on the gay, bisexual and other men who have sex with men (gbMSM) population and various degrees of sexual activity.
Methods: Using two mathematical models that estimate the HIV transmission risk corresponding to different viral loads, we estimated the average probability of HIV transmission per risky contact for gbMSM during the six months post-ART initiation, stratified by stage of HIV infection, viral load at ART initiation and type of first-line ART (i.e., INSTI or non-INSTI-based ART). This study focused individuals who initiated ART between 2011 and 2016 with at least one year of follow-up in British Columbia, Canada.
Findings: Time to first virologic suppression for INSTI-based regimens was 21.4 days (95% credible interval (CI) 19.9–23.2), compared to 58.6 days (95% CI 54.1–62.2) for non-INSTI regimens. We showed that INSTI-based regimens could reduce the HIV transmission risk by at least 25% among those with viral load ≥5 $\log_{10}$ copies/mL at ART initiation.
Interpretation: Initiating ART on INSTI-based regimens has the potential to reduce HIV transmission risk among individuals with high baseline viral load levels, especially among those with high levels of sexual activity.
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1. Introduction

The natural history of HIV infection is characterized by a high degree of heterogeneity in plasma HIV-1 RNA (hereafter referred to as viral load) levels over time [1]. It has long been established that the rate of HIV transmission is strongly associated with viral load levels [2–4]. As such, the early and late stages of HIV disease are linked to high risk of transmission due to elevated viral load [1,5]. It is estimated that for each 10-fold increase in viral load among people living with HIV/AIDS (PLWH), the risk of transmission increases by 2.5 times [4]. However, virologic suppression due to the consistent use of antiretroviral therapy (ART) has been shown to significantly reduce to zero the risk of sexual HIV transmission [6,7]. Thus, ART induced virologic suppression represents an effective mechanism to prevent forward transmission of HIV [6,8].

The scaling-up utilization of modern ART has led to a dramatic reduction in HIV-related morbidity and mortality [9,10]. Studies have shown that people who initiated ART at high CD4 cell counts were more likely to achieve virologic suppression at nine months [11]. Although most ART regimens may lead to virologic suppression, studies have shown that the rates of viral load decline vary between ART regimens due to the presence of drug resistance (transmitted or acquired) and sub-optimal adherence to ART [12]. Recently, studies have shown that PLWH initiating ART on integrase strand-transfer inhibitor-based (INSTI) regimens achieve virologic suppression more rapidly compared to other frequently used first-line regimens [13]. Therefore, INSTI-based

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Panel: Research in context

Evidence before this study

We searched for articles from PubMed and abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Society (IAS) and AIDS conferences. We included combinations of the terms "integrase strand-transfer inhibitors", "INSTI", "Treatment as Prevention", "TasP", "HIV transmission", "gay, bisexual and other men who have sex with men", "gbMSM", "men who have sex with men", "MSM", "efficacy", "effectiveness", "risky sexual behaviour", "mathematical models", and "transmission probability". These studies have shown that Treatment as Prevention is still the most efficacious intervention to prevent onward HIV transmission in the gbMSM group. Additionally, it showed that INSTIs are currently the most efficacious antiretrovirals in achieving fast virologic suppression.

Added value of this study

To the best of our knowledge, this study is the first to use mathematical modeling to explore the potential impact of initiating gbMSM on INSTIs, as opposed to other antiretrovirals, in preventing HIV onward transmission among these individuals. We conducted this longitudinal cohort study in a setting with universal healthcare, where there are no financial barriers to access antiretroviral therapy. In this study, we also highlighted that this strategy is best suited for gbMSM presenting for treatment with high viral load, or during acute infection, and involved in risky sexual behaviour.

Implications of all the available evidence

In the TasP and U = U eras, there are still some population subgroups at a high risk of transmitting HIV, and thus not fully benefiting from modern antiretroviral therapy. The evidence provided in this study showed that for these strategies to be successful, treatment programs should focus on initiating gbMSM on INSTIs to lead to fast viral suppression and prevent onward HIV transmission.

regimens have the potential to further reduce HIV transmission during the first months on ART.

However, it is also well known that viral load is not the sole factor determining the risk of HIV transmission [14]. In the gay, bisexual and other men who have sex with men (gbMSM) population, studies have shown that increasing risk of HIV acquisition is evident among those with high frequency of virus exposure, i.e., high frequency of condomless anal intercourse with sero-discordant partners [15,16]. In British Columbia (BC), the epidemic among the gbMSM population has been comparatively less responsive to the positive effects of ART (when used for treatment and not prophylaxis) in reducing transmission than other populations (mainly people who inject drugs (PWID)), even though this is the population that experiences the least attrition in the HIV care continuum due to a higher engagement into care and treatment response [17]. Therefore, we conducted the present study to estimate the potential reduction in HIV transmission risk among antiretroviral-naïve individuals initiating on INSTI-based antiretroviral therapy, focusing on the gbMSM population and various degrees of sexual activity.

2. Methods

2.1. Study data

Since 1992, the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program (DTP) has been responsible for the provision of free-of-charge ART, HIV medical care and laboratory monitoring services for all PLWH residing in BC as per the BC's HIV therapeutic guidelines [18]. This study was conducted using data from the HAART Observational Medical Evaluation and Research (HOMER) cohort of the DTP [19]. To include all individuals with INSTI-based regimen as first-line ART (raltegravir started in 2011, elvitegravir in 2013, and dolutegravir in 2014), those included in the analysis were ART-naïve adults (aged ≥19 years) who initiated treatment between January 1, 2011 and December 31, 2016. Individuals were followed for at least one year, determined by the end of the study period (December 31, 2017), the last contact date (i.e., the last available laboratory test date, the last filled ART prescription refill date or physician visit date), or the date of death (all-causes). Additionally, individuals enrolled in the study must have had a CD4 count and a viral load measurement within six months before ART initiation. CD4 cell counts were measured by flow cytometry, followed by fluorescent monoclonal antibody analysis (Beckman Coulter, Inc., Mississauga, Ontario, Canada). As CD4 tests are performed in different laboratories across BC, the DTP captures approximately 85% of all CD4 tests in BC. All viral load determinations in BC, performed using HIV-1 TaqMan Assay v2.0 (Roche Molecular Diagnostics, Laval, Quebec, Canada), are done at the St Paul's Hospital virology laboratory and automatically included in the DTP database. In BC, treatment guidelines recommend HIV drug resistance testing at baseline using Sanger sequencing, so a fully active ART regimen is prescribed. For regimen eligibility, ART was initiated with two nucleoside reverse transcriptase inhibitors (NRTI) as backbone, plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (bPI), or an INSTI; non-backbone classes were held constant within one year since ART initiation. Ingredients within the INSTI class were analyzed together and separately. We did not include a small number of acutely infected individuals who initiated on INSTI and bPI simultaneously since we would not be able to differentiate between the effect of INSTI and of bPI.

2.2. Statistical methods

The following variables measured at ART initiation were investigated: age (19–29, 30–39, 40–49, and ≥50), self-reported gender (male; female), self-reported HIV risk group (gbMSM; PWID; gbMSM/PWID; other; and unknown), CD4 cell count (<200, 200–349, 350–499, and ≥500 cells/mm [3]), and $\log_{10}$-transformed viral load (<4, 4–5, and ≥5 $\log_{10}$ copies/mL). We also considered the time from ART initiation to virologic suppression (1 month, 1–3 months, 3–-6 months, and over 6 months or never suppressed). Virologic suppression was defined by two consecutive viral loads <200 copies/mL since ART initiation. Individuals with a single viral load <200 copies/mL within six months were considered virologic suppressed if their next viral load was also <200 copies/mL. This threshold of suppression was chosen since a recent study showed no linked transmissions among gbMSM with a viral load <200 copies/mL [8]. The date of virologic suppression was determined by the date in which the first viral load was <200 copies/mL.

We compared the time from ART initiation to virologic suppression (1 month, 1–3 months, 3–6 months, and over 6 months or never suppressed) by INSTI type and other variables using Pearson's Chi-squared test or Fisher's exact test depending on the cell size [20]. We modeled the change in viral load ($\log_{10}$ transformed) for the first six months since ART initiation using Generalized Additive Models

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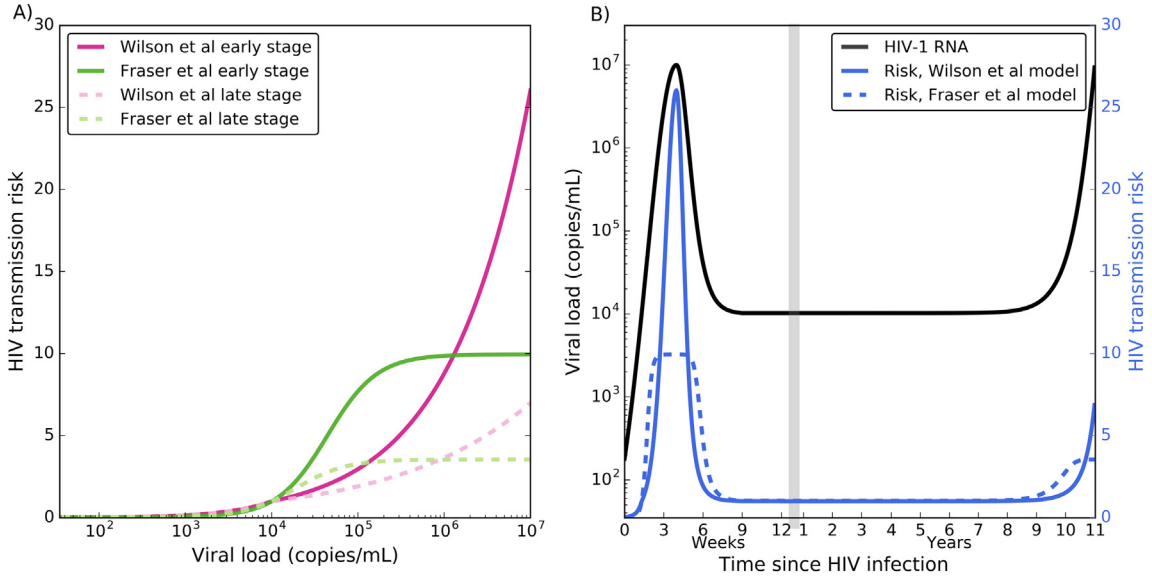

Fig. 1. Comparison of the Wilson et al. and Fraser et al. models. A) Transmission risk function based on viral load for both Wilson et al. and Fraser et al. models. The area under the Fraser et al. curve was optimized to match the area under the Wilson et al. curve for both the early stage and late stage scenarios. B) The simulated viral load along the natural history of HIV infection (black curve, left y-axis), and the associated risk of HIV transmission, for the Wilson et al. and the Fraser et al. models (solid and dashed blue curves, right y-axis). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(GAM), with a cubic spline basis [21]. Associated 95% Bayesian credible intervals (CI) were obtained based on the posterior predictive distribution. Estimation of the GAM occurred via a penalized likelihood approach that automatically determines a balance between goodness-of-fit and smoothness by penalizing excessive curvature in the fitted function [21]. Goodness-of-fit was assessed using R^2, the percentage of the deviance explained, and the sum of the deviance residuals. All reported *P*-values are two-sided, and the level of significance was set at 5%. All statistical analyses were performed using R version 3.2.3, and GAM fitting was done using the mgcv library (functions gam, summary, gam.check, and residuals.gam).

2.3. Mathematical models

The relationship between viral load and HIV transmission risk, independently of the transmission probability across different risk

Table 1
Demographic and clinical characteristics of people living with HIV in British Columbia who initiated antiretroviral therapy between 2011 and 2016, stratified by first regimen type.

Variables	Naive initiated ART	Initiated ART on INSTI		*P*-value
		Yes	No	
	N = 1459	N = 376	N = 1083	
Total viral load tests first year on ART	7725	1862	5863	
Age				<0.0001
19–29	266 (18.2%)	70 (26.3%)	196 (73.7%)	
30–39	419 (28.7%)	102 (24.3%)	317 (75.7%)	
40–49	441 (30.2%)	87 (19.7%)	354 (80.3%)	
≥50	332 (22.8%)	117 (35.2%)	215 (64.8%)	
Sex at birth				0.8509
Male	1208 (82.8%)	313 (25.9%)	895 (74.1%)	
Female	251 (17.2%)	63 (25.1%)	188 (74.9%)	
HIV risk group				<0.0001
PWID	272 (18.6%)	36 (13.2%)	236 (86.8%)	
gbMSM	436 (29.9%)	150 (34.4%)	286 (65.6%)	
gbMSM/PWID	54 (3.7%)	8 (14.8%)	46 (85.2%)	
Other	179 (12.3%)	73 (40.8%)	106 (59.2%)	
Unknown	518 (35.5%)	109 (21.0%)	409 (79.0%)	
CD4 cell count (cells/mm^3) at ART initiation				0.0718
<200	332 (22.8%)	79 (23.8%)	253 (76.2%)	
200–349	332 (22.8%)	80 (24.1%)	252 (75.9%)	
350–499	335 (23.0%)	78 (23.3%)	257 (76.7%)	
≥500	460 (31.5%)	139 (30.2%)	321 (69.8%)	
Viral load ($\log_{10}$ copies/mL) at ART initiation				0.5805
<4	309 (21.2%)	75 (24.3%)	234 (75.7%)	
4–5	683 (46.8%)	173 (25.3%)	510 (74.7%)	
≥5	467 (32.0%)	128 (27.4%)	339 (72.6%)	
Suppressed at 6 months				0.0020
Yes	1297 (88.9%)	351 (27.1%)	946 (72.9%)	
No	162 (11.1%)	25 (15.4%)	137 (84.6%)	

ART: antiretroviral therapy; PWID: people who inject drugs; gbMSM: gay, bisexual and other men who have sex with men; INSTI: integrase strand-transfer inhibitor-based regimen. Counts in each category were compared by Pearson's Chi-squared test.

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populations (e.g., heterosexuals, gbMSM), was adapted from two previously established mathematical models (Fig. 1A). The first model was developed by Wilson et al. which fits a linear trend in log-risk and log-viral load [2]. This model was scaled to match the observed reduction in transmission risk in virologically suppressed individuals [6], as well as the increase in transmission risk at high viral loads (i.e., up to 25 times higher risk in the early stage and up to six times higher risk in the late stage relative to the chronic stage) [22]. The second model was based on the work by Fraser et al., which fitted a Hill function to model the relationship between viral load and transmission risk [3]. This second model was calibrated to match the reduction in the relative transmission risk in virologically suppressed individuals, and the overall risk (showing as the area under the viral load-risk curve) in the Wilson et al. model for comparison purposes.

Fig. 1B shows the risk of HIV transmission corresponding to different viral load levels along the natural history of HIV infection. A simplified representation of the HIV natural history was constructed, divided into the following stages: (i) early stage, (ii) chronic stage, and (iii) late stage. The early stage, based on recent data from diagnosed hyper-acute individuals, lasts on average eight weeks, peaks four weeks after infection at approximately 10^7 copies/mL (or 7 $\log_{10}$ copies/mL), and stabilizes in the chronic stage at approximately 10^4 copies/mL (or 4 $\log_{10}$ copies/mL) [23,24]. The late stage begins approximately nine years after infection, with viral loads increasing from the chronic stage to approximately 10^7 copies/mL over the next two years [25]. The change in viral load in the early and late stages was simulated with logistic functions in $\log_{10}$-transformed viral load. The chronic stage was simulated as a constant viral load of 10^4 copies/mL in order to maintain a common baseline transmission risk across the Wilson et al. and the Fraser et al. models.

To assess the impact of ART initiation and fast viral load suppression on HIV transmission risk for different HIV acquisition risk groups, we introduced a quantitative measurement E, which was the product of the number of susceptible partners and the transmission probability for a given number of risky contacts per partner [2,26]. E represents the average number of new HIV infections from an individual living with HIV for a specified period of time, considering their risk behaviour, their stage of HIV infection, and the change in viral load during this period, given by:

$$E(T, viral\ load, I) = S(T)\cdot\left(1-\left(1-\overline{P}(viral\ load, T, I)\right)^{r(T)}\right),$$

where T is the time during which we measure the HIV transmission risk, $r(T)$ is the average number of risky contacts (e.g., condomless vaginal/anal sex and needle sharing acts) per partner during time T, $S(T)$ refers to the number of susceptible partners during time T, $\overline{P}(viral\ load, T, I) = \frac{\beta}{T}\int_0^T R(viral\ load(t), I)dt$ indicates the average HIV transmission probability per risky contact during time T, β is the transmission probability per risky contact, and $R(viral\ load(t), I)$ represents the risk of HIV transmission corresponding to the viral load and stage of HIV infection (I) at any time t, determined by the Wilson et al. and Fraser et al. models.

As stated, this study focused on the gbMSM population. We assumed that β, the transmission probability per risky contact, was 1.43% [27]. To provide a more complete picture of the potential impact of initiating gbMSM on INSTI-based regimens, we estimated the average number of new HIV infections from one individual during the first six months since ART initiation (i.e., T), based on different assumptions regarding: (1) $S(T)$, the number of susceptible partners having condomless anal sex: ranging from 0 to 20; (2) $r(T)$, the average number of condomless anal sex acts per partner in the last six months: ranging from 0 to 120; (3) viral load at ART initiation ($\log_{10}$ transformed): low (<4 $\log_{10}$ copies/mL), medium (4–5 $\log_{10}$ copies/mL), and high (≥5 $\log_{10}$ copies/mL); and (4) I, the stage of HIV infection at ART initiation: early, and chronic to late stages. Nonzero values of the number of susceptible partners and condomless anal sexual acts per partner were estimated from available literature [28–30]. Note that in these models, we did not change the degree of sexual activity by health status (e.g., CD4 level), as this information was not built into the model.

2.4. Sensitivity analysis

Since $R(viral\ load(t), I)$, $\overline{P}$ and E are related to each other, we performed univariate sensitivity analyses on $\overline{P}$ to show how the model can be affected by the uncertainty of parameters and model assumptions. The sensitivity analyses were done for the individual with high viral load (≥5 $\log_{10}$ copies/mL) at ART initiation, who has an average of 10 partners and 60 condomless anal sex acts per partner during six months. We varied the following parameters: (1) the risk of HIV transmission at the peak (i.e., highest viral load) of the early (from 26 to 12.6 and 56.6) and late (from 7 to 3.8 and 14.3) stages in the Wilson et al. and Fraser et al. models; (2) the viral load in the chronic stage was changed to 3.7 and 4.8 $\log_{10}$ copies/mL, in comparison to 4 $\log_{10}$ copies/mL in the original setting; and (3) the transmission probability per risky contact was changed from 1.43% to 0.48% and 2.85% based on the 95% confidence interval from the literature [22,27,31].

Table 2
Demographic and clinical characteristics of people living with HIV in British Columbia who initiated antiretroviral therapy between 2011 and 2016, stratified by time to virologic suppression.

	Time from ART initiation to first virologic suppression								*P*-value
	In 1 month since ART initiation		In 1–3 months		In 3–6 months		Over 6 months or never suppressed		
Total	263	18.0%	686	47.0%	348	23.9%	162	11.1%	
Regimen type									<0.0001
INSTI	148	39.4%	172	45.7%	31	8.2%	25	6.6%	
Non-INSTI	115	10.6%	514	47.5%	317	29.3%	137	12.7%	
INSTI ingredient									0.7193
Dolutegravir	85	40.3%	99	46.9%	15	7.1%	12	5.7%	
Elvitegravir	47	41.2%	47	41.2%	11	9.6%	9	7.9%	
Raltegravir	16	31.4%	26	51.0%	5	9.8%	4	7.8%	
Age									0.1422
19–29	57	22.8%	115	46.0%	47	18.8%	31	12.4%	
30–39	66	15.9%	199	48.1%	94	22.7%	55	13.3%	
40–49	74	16.9%	204	46.7%	114	26.1%	45	10.3%	
≥50	66	18.4%	168	46.9%	93	26.0%	31	8.7%	
Sex at birth									0.1440
Male	226	18.7%	563	46.6%	293	24.3%	126	10.4%	
Female	37	14.7%	123	49.0%	55	21.9%	36	14.3%	
HIV risk group									<0.0001
PWID	17	6.3%	121	44.5%	70	25.7%	64	23.5%	
gbMSM	102	23.4%	208	47.7%	101	23.2%	25	5.7%	
gbMSM/PWID	9	16.7%	20	37.0%	13	24.1%	12	22.2%	
Other	39	21.8%	90	50.3%	35	19.6%	15	8.4%	
Unknown	96	18.5%	247	47.7%	129	24.9%	46	8.9%	
CD4 cell count (cells/mm^3) at ART initiation									<0.0001
<200	20	6.0%	168	50.6%	92	27.7%	52	15.7%	
200–349	57	17.2%	144	43.4%	89	26.8%	42	12.7%	
350–499	62	18.5%	163	48.7%	82	24.5%	28	8.4%	
≥500	124	27.0%	211	45.9%	85	18.5%	40	8.7%	
Viral load at ART initiation ($\log_{10}$ copies/mL)									<0.0001
<4	108	35.0%	143	46.3%	39	12.6%	19	6.1%	
4–5	126	18.4%	349	51.1%	142	20.8%	66	9.7%	
≥5	29	6.2%	194	41.5%	167	35.8%	77	16.5%	

ART: antiretroviral therapy; PWID: people who inject drugs; gbMSM: gay, bisexual and other men who have sex with men; INSTI: integrase strand-transfer inhibitor-based regimen.

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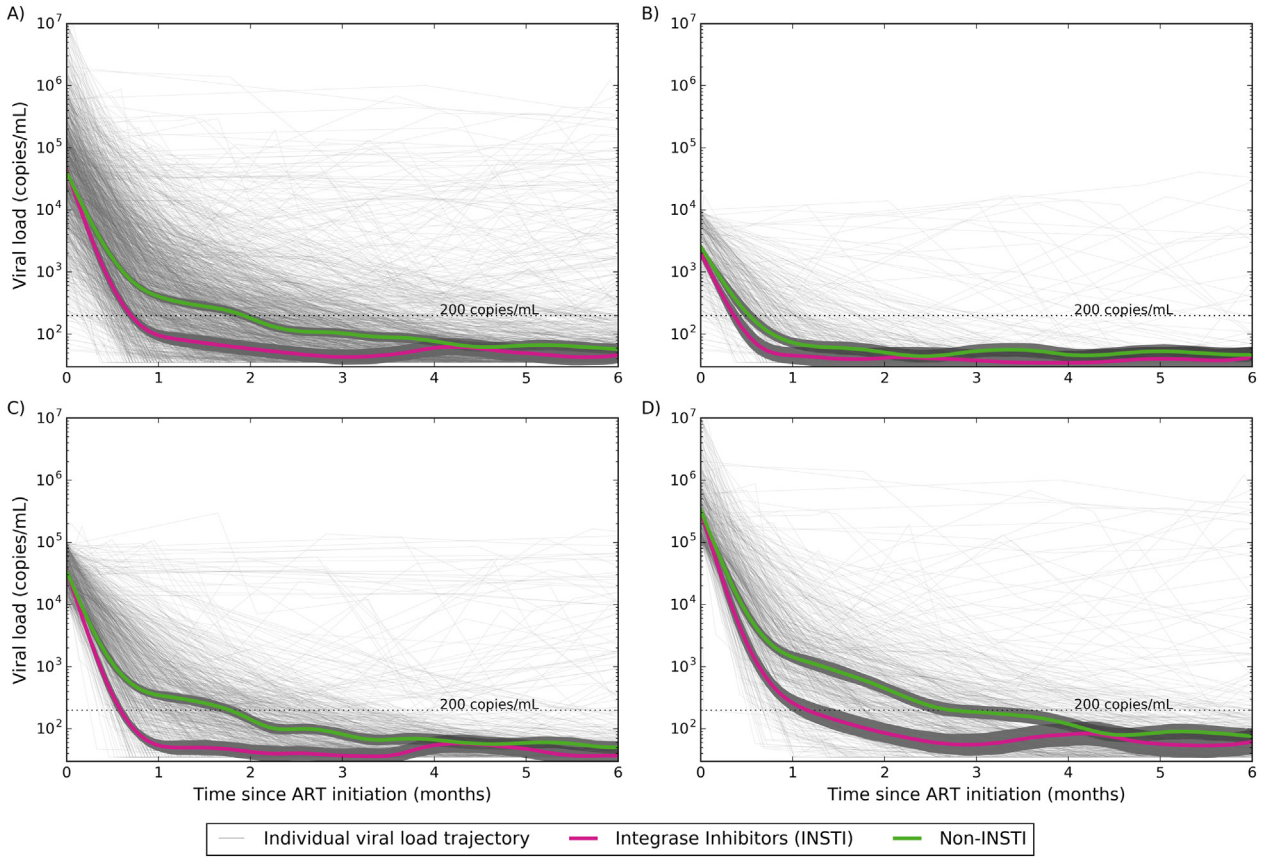

Fig. 2. Trajectory in the mean $\log_{10}$-transformed viral load, and associated 95% Bayesian credible interval for the mean (grey area around each trajectory), from ART initiation to six months of follow-up. Individual viral load trajectories are shown in the background. A) All individuals included; B) including those with low viral load level (<4 $\log_{10}$ copies/mL) at ART initiation; C) including those with medium viral load level (4–5 $\log_{10}$ copies/mL) at ART initiation; D) including those with high viral load level (≥5 $\log_{10}$ copies/mL) at ART initiation.

2.5. Ethics

This study was approved by the University of British Columbia ethics review committee at the St Paul's Hospital, Providence Health Care site (H18-00949). This study included secondary-use data where informed consent was not obtained, and it was approved by the research ethics board that reviewed the application.

3. Results

3.1. Study population characteristics

Overall, 1459 ART-naïve individuals initiated treatment in BC between January 1, 2011 and December 31, 2016. Among these, 83% were male, 30% were gbMSM, 59% were age between 30 and 49 years, 46% presented to treatment with <350 CD4 cells/mm^3, 32% presented to treatment with viral load ≥5 $\log_{10}$ copies/mL, 26% started treatment with INSTI-based regimens, and 89% achieved virologic suppressed at six months (Table 1). The median number of viral load tests, during the first year, among those starting on INSTI and non-INSTI based ART was 5 (25th–75th percentile: 4–6; range 2–13) and 5 (25th–75th percentile: 4–6; range 1–15), respectively. In bivariable analyses, individuals aged 50 years or older, those who self-identify as gbMSM and in the Other category, and individuals who achieved viral suppression within six months were more likely to initiate ART on INSTI-based regimens (Table 1).

3.2. Characteristics by time to virologic suppression

Table 2 summarizes the characteristics of the 1459 individuals by time from ART initiation to virologic suppression, if applicable. Those

Table 3
Average probability of HIV transmission per condomless anal sex act during the first six months since ART initiation, estimated by two mathematical models (Wilson et al. and Fraser et al.), stratified by the viral load at ART initiation ($\log_{10}$ transformed) and stage of HIV infection.

Viral load at ART initiation ($\log_{10}$ copies/mL)	Stage of infection	Average probability of HIV transmission per act (multiplied by 100) during the first six months since ART initiation (95% CI)			
		Wilson et al.		Fraser et al.	
		INSTI	Non-INSTI	INSTI	Non-INSTI
<4	Early stage	0.025 (0.019, 0.033)	0.035 (0.029, 0.041)	0.056 (0.055, 0.057)	0.058 (0.057, 0.059)
	Chronic & late stages	0.025 (0.019, 0.033)	0.035 (0.029, 0.041)	0.055 (0.054, 0.057)	0.058 (0.056, 0.059)
4–5	Early stage	0.087 (0.076, 0.099)	0.126 (0.111, 0.143)	0.143 (0.128, 0.160)	0.166 (0.149, 0.186)
	Chronic & late stages	0.081 (0.072, 0.092)	0.119 (0.106, 0.135)	0.123 (0.114, 0.134)	0.146 (0.133, 0.160)
≥5	Early stage	0.257 (0.217, 0.307)	0.381 (0.334, 0.432)	0.500 (0.437, 0.573)	0.664 (0.593, 0.744)
	Chronic & late stages	0.192 (0.165, 0.225)	0.294 (0.261, 0.329)	0.280 (0.252, 0.313)	0.374 (0.339, 0.412)

ART: antiretroviral therapy; INSTI: integrase strand-transfer inhibitor; 95% CI: 95% Bayesian credible intervals.

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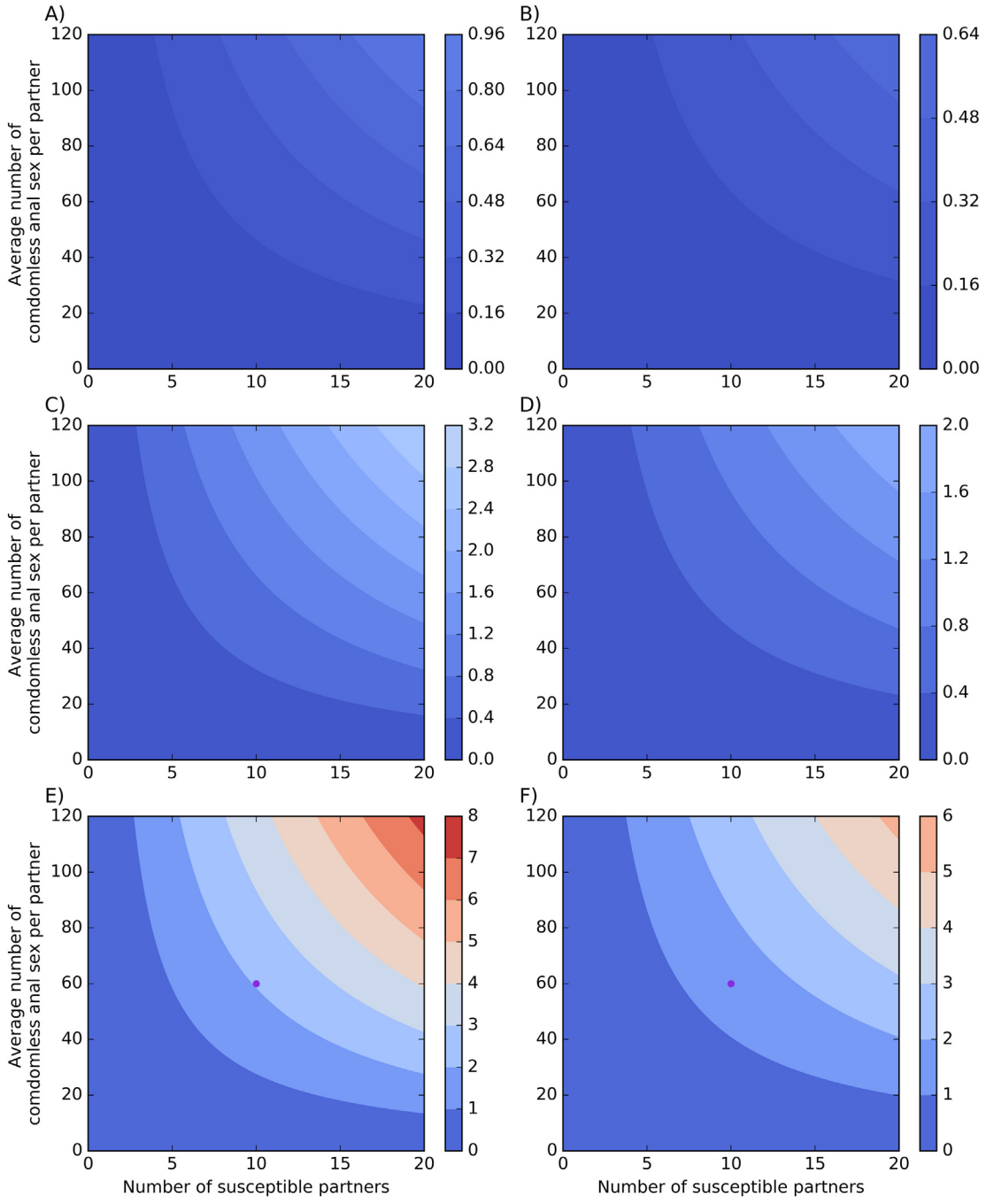

Fig. 3. Average number of new HIV infections during the first six months since ART initiation, for a gbMSM experiencing the early stage of HIV infection, estimated by the Wilson et al. model, stratified by the viral load at ART initiation (log_{10} transformed) and ART regimen type: viral load <4 log_{10} copies/mL on non-INSTI (A) and on INSTI (B) regimens; viral load 4–5 log_{10} copies/mL on non-INSTI (C) and on INSTI (D) regimens; viral load ≥5 log_{10} copies/mL on non-INSTI (E) and on INSTI (F) regimens. Different colours (blue to red) indicate different levels of transmission risk (low to high). The purple dot in (E) and (F) indicates the average number of new HIV infections from a gbMSM with 10 susceptible partners and 60 condomless anal sex per partner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

who initiated ART on INSTI-based regimens were more likely to achieve virologic suppression within three months since ART initiation in comparison to other regimens, regardless of the specific INSTI ingredient. For other variables, please see Table 2.

Fig. 2 shows the estimated trajectory in viral load (log_{10} transformed) during the first six months since ART initiation in our entire cohort. Overall, the average time to virologic suppression for individuals who initiated ART on INSTI-based regimens was 21.4 days (95% CI 19.9–23.2) relative to 58.6 days (95% CI 54.1–62.2) for those who initiated on non-INSTI regimens (Fig. 2A) (*P*-value for difference < 0.0001). In comparison, the average time to virologic suppression for individuals with low viral load at ART initiation (<4 log_{10} copies/mL) was much shorter: 11.0 days (95% CI 9.5–13.2) for those on INSTI regimens and 16.1 days (95% CI 13.9–18.4) for those on non-INSTI regimens (Fig. 2B) (*P*-value <0.0001). Additionally, for those who initiated ART with high viral load (≥5 log_{10} copies/mL), the average time to virologic suppression was much longer: 35.2 days (95% CI 29.8–45.7) for those on INSTI regimens and 83.0 days (95% CI 73.7–110.4) for those on non-INSTI regimens (Fig. 2D) (*P*-value for difference < 0.0001).

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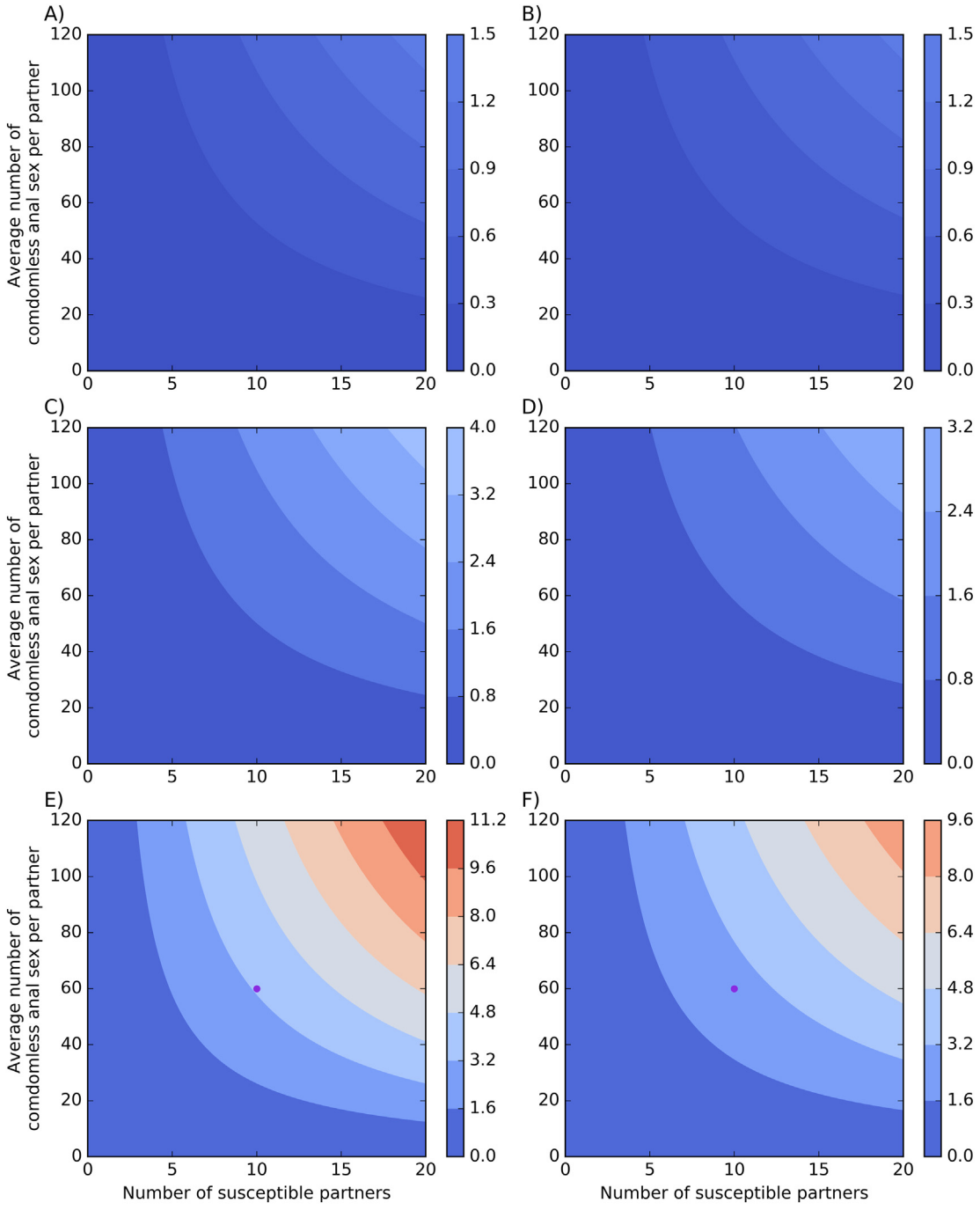

Fig. 4. Average number of new HIV infections during the first six months since ART initiation, for a gbMSM experiencing the early stage of HIV infection, estimated by the Fraser et al. model, stratified by the viral load at ART initiation ($\log_{10}$ transformed) and ART regimen type: viral load <4 $\log_{10}$ copies/mL on non-INSTI (A) and on INSTI (B) regimens; viral load 4–5 $\log_{10}$ copies/mL on non-INSTI (C) and on INSTI (D) regimens; viral load ≥5 $\log_{10}$ copies/mL on non-INSTI (E) and on INSTI (F) regimens. Different colours (blue to red) indicate different levels of transmission risk (low to high). The purple dot in (E) and (F) indicates the average number of new HIV infections from a gbMSM with 10 susceptible partners and 60 condomless anal sex per partner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. HIV transmission risk among gbMSM

Next, we estimated the average probability of HIV transmission per condomless anal sex act (multiplied by 100) during the first six months since ART initiation ($\overline{P}$) utilizing the two mathematical models previously defined (Table 3). Under the assumption of the Wilson et al. model, the impact of INSTI-based regimens on the referred probability was significant for medium and high viral loads (i.e., the 95% CI does not cross each other). For example, if the individual was diagnosed in the early stage of HIV infection with a viral load ≥5 $\log_{10}$ copies/mL, by initiating ART on INSTI-based regimen instead of other regimens, the average probability of HIV transmission would be reduced from 0.381 (95% CI 0.334–0.432) to 0.257 (95% CI 0.217–0.307) (33% reduction). Under the assumption of Fraser et al., the impact of INSTI-based regimens was significant only for high viral load levels, with 25% of reduction in the average probability regardless of the stage of HIV infection.

Fig. 3 (Wilson et al.) and Fig. 4 (Fraser et al.) show the average number of new HIV infections for a gbMSM experiencing the early stage of HIV infection during the first six months since ART initiation, taking into consideration different levels of sexual behaviour risk, viral load at ART initiation and the type of initial ART regimen. Based on the

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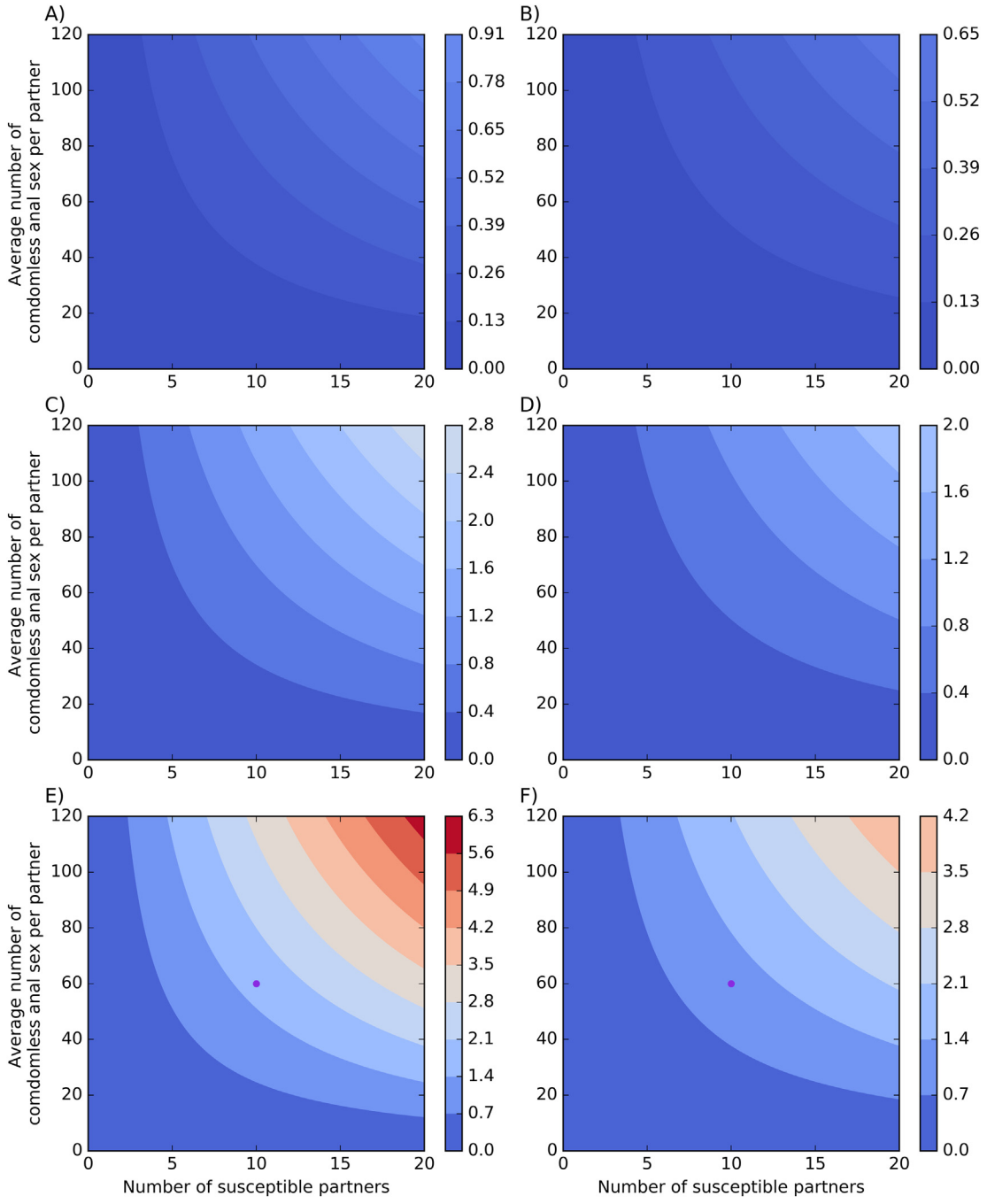

Fig. 5. Average number of new HIV infections during the first six months since ART initiation, for a gbMSM experiencing the chronic and late stage of HIV infection, estimated by the Wilson et al. model, stratified by the viral load at ART initiation (log_{10} transformed) and ART regimen type: viral load <4 log_{10} copies/mL on non-INSTI (A) and on INSTI (B) regimens; viral load 4–5 log_{10} copies/mL on non-INSTI (C) and on INSTI (D) regimens; viral load ≥5 log_{10} copies/mL on non-INSTI (E) and on INSTI (F) regimens. Different colours (blue to red) indicate different levels of transmission risk (low to high). The purple dot in (E) and (F) indicates the average number of new HIV infections from a gbMSM with 10 susceptible partners and 60 condomless anal sex per partner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Wilson et al. model, for example, the purple dot in Fig. 3 (E) and (F) represents the average number of new infections for a gbMSM with 10 susceptible partners and an average of 60 condomless anal sex acts per partner during the six months. In this case, if the gbMSM starts ART with a viral load ≥5 log_{10} copies/mL, this person can generate on average 2.0 new infections if on a non-INSTI initial regimen, and it drops to 1.4 if on an INSTI regimen (30% reduction). If we use the Fraser et al. model, this same person can generate on average 3.3 new infections if on a non-INSTI initial regimen and it drops to 2.6 if on an INSTI regimen (21% reduction) (Fig. 4 (E) and (F)). The results for the chronic and late stages are presented in Figs. 5 and 6.

3.4. Sensitivity analysis

We performed sensitivity analyses on the average probability of HIV transmission per condomless anal sex act (multiplied by 100) during

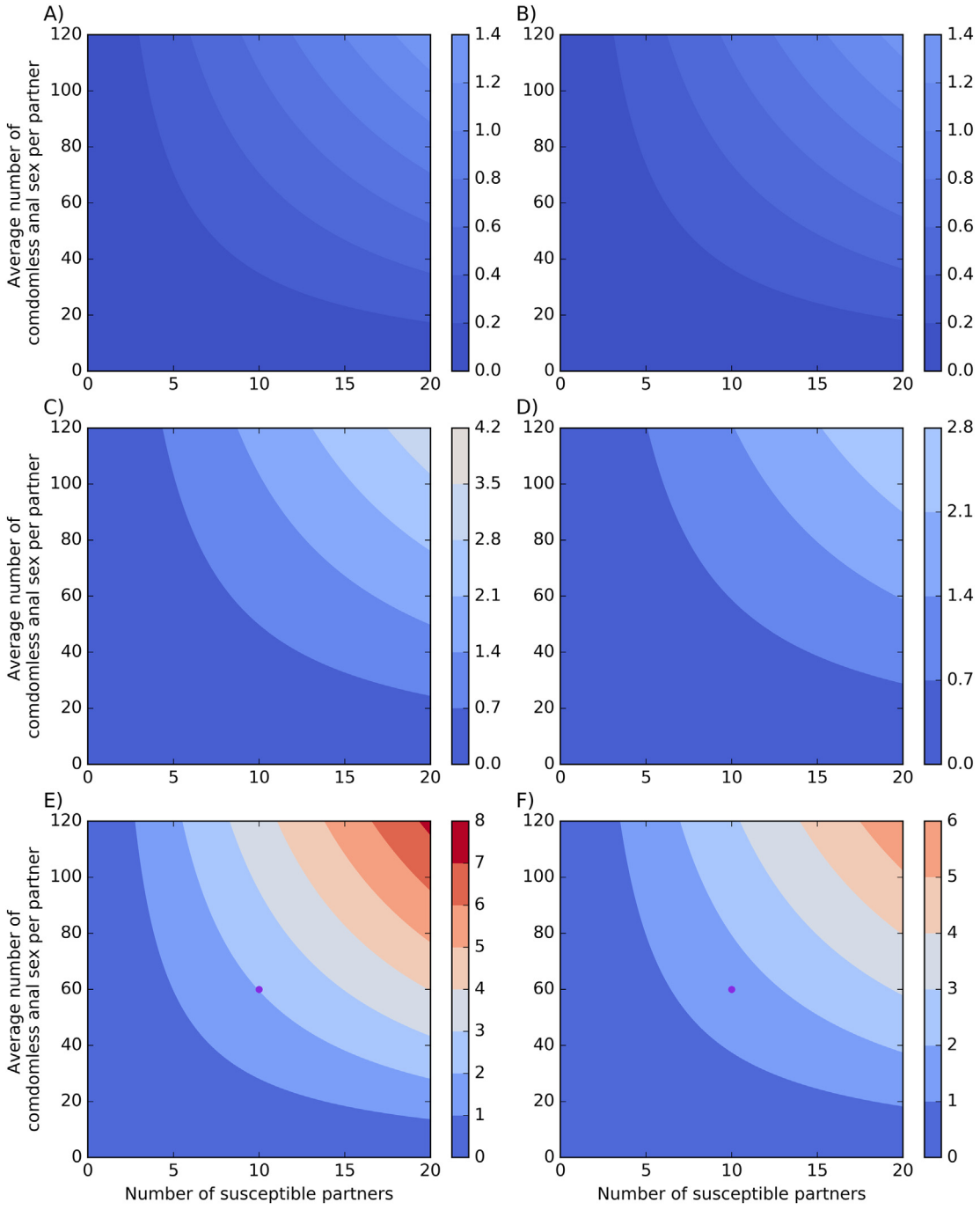

Fig. 6. Average number of new HIV infections during the first six months since ART initiation, for a gbMSM experiencing the chronic and late stage of HIV infection, estimated by the Fraser et al. model, stratified by the viral load at ART initiation ($\log_{10}$ transformed) and ART regimen type: viral load <4 $\log_{10}$ copies/mL on non-INSTI (A) and on INSTI (B) regimens; viral load 4–5 $\log_{10}$ copies/mL on non-INSTI (C) and on INSTI (D) regimens; viral load ≥5 $\log_{10}$ copies/mL on non-INSTI (E) and on INSTI (F) regimens. Different colours (blue to red) indicate different levels of transmission risk (low to high). The purple dot in (E) and (F) indicates the average number of new HIV infections from a gbMSM with 10 susceptible partners and 60 condomless anal sex per partner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the first six months since ART initiation ($\overline{P}$) by varying the HIV transmission probability at the peak viral load (i.e., 7 $\log_{10}$ copies/mL), the viral load in the chronic stage, and the transmission probability per risky contact for gbMSM population (Table 4). We found that regardless of the stage of HIV infection, the type of regimen and the type of model, the parameter most sensitive in the model was the assumed transmission probability per risky contact. However, the benefit of initially using INSTI-based regimens, especially among gbMSM with high initial viral load, did not change based on these results.

4. Discussion

This combined modeling and population cohort-based study shows that initiating ART with INSTI-based regimens can potentially reduce HIV transmission risk significantly when compared to non-INSTI regimens. However, this was highly dependent on viral load at ART initiation and the individual's risk level, and to a lesser extent on the stage of HIV infection. Our large population-based analysis confirmed previous studies showing faster virologic suppression following the initiation

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Table 4
Sensitivity analysis on the average probability of HIV transmission per condomless anal sex act (multiplied by 100) during the first six months since ART initiation for Wilson et al. and Fraser et al. models at the (A) early stage infection and (B) chronic-late stage infection.

		Wilson et al.		Fraser et al.	
		INSTI	Non-INSTI	INSTI	Non-INSTI
(A)					
Status Quo	–	0.257 (0.217, 0.307)	0.381 (0.334, 0.432)	0.500 (0.437, 0.573)	0.664 (0.593, 0.744)
HIV transmission risk (at 26 in Status Quo)	12.6	0.217 (0.185, 0.256) −16%	0.328 (0.290, 0.369) −14%	0.358 (0.318, 0.404) −28%	0.476 (0.429, 0.528) −28%
	56.6	0.315 (0.261, 0.380) 22%	0.457 (0.398, 0.524) 20%	0.728 (0.622, 0.851) 46%	0.967 (0.853, 1.098) 46%
Viral load in chronic stage (at 4 $\log_{10}$ copies/mL in Status Quo)	3.7	0.317 (0.269, 0.375) 23%	0.479 (0.422, 0.545) 26%	0.531 (0.462, 0.610) 6%	0.705 (0.628, 0.792) 6%
	4.8	0.139 (0.116, 0.167) −46%	0.200 (0.176, 0.227) −48%	0.413 (0.364, 0.469) −17%	0.548 (0.492, 0.611) −17%
Transmission probability per risky contact (at 1.43% in Status Quo)	0.48%	0.086 (0.073, 0.103) −66%	0.128 (0.112, 0.145) −66%	0.168 (0.147, 0.192) −66%	0.223 (0.199, 0.250) −66%
	2.85%	0.513 (0.432, 0.611) 99%	0.759 (0.666, 0.862) 99%	0.997 (0.871, 1.142) 99%	1.323 (1.181, 1.484) 99%
(B)					
Status Quo	–	0.192 (0.165, 0.225)	0.294 (0.261, 0.329)	0.280 (0.252, 0.313)	0.374 (0.339, 0.412)
HIV transmission risk (at 7 in Status Quo)	3.8	0.171 (0.148, 0.199) −11%	0.266 (0.237, 0.297) −10%	0.224 (0.204, 0.248) −20%	0.303 (0.276, 0.332) −19%
	14.3	0.224 (0.190, 0.264) 16%	0.336 (0.297, 0.379) 14%	0.379 (0.336, 0.429) 35%	0.503 (0.453, 0.560) 35%
Viral load in chronic stage (at 4 $\log_{10}$ copies/mL in Status Quo)	3.7	0.223 (0.194, 0.261) 16%	0.354 (0.315, 0.400) 21%	0.296 (0.265, 0.331) 5%	0.393 (0.356, 0.434) 5%
	4.8	0.124 (0.106, 0.146) −35%	0.180 (0.161, 0.202) −39%	0.239 (0.216, 0.265) −15%	0.321 (0.292, 0.352) −14%
Transmission probability per risky contact (at 1.43% in Status Quo)	0.48%	0.065 (0.055, 0.075) −66%	0.099 (0.088, 0.111) −66%	0.094 (0.085, 0.105) −66%	0.126 (0.114, 0.138) −66%
	2.85%	0.383 (0.329, 0.448) 99%	0.586 (0.520, 0.657) 99%	0.559 (0.502, 0.624) 99%	0.745 (0.676, 0.821) 99%

INSTI: integrase strand-transfer inhibitor-based regimen. The columns in each regimen-model scenario show the point estimate, the 95% Bayesian credible interval, and the percent change of each sensitivity scenario with respect to the corresponding Status Quo scenario.

of INSTI-based ART relative to those who initiate with other frequently used first-line regimens [13]. Combining this result with an estimation of viral load-dependent probability of HIV transmission focusing on the gbMSM population, we found that the average probability of HIV transmission during the first six months after ART initiation can be reduced by at least 25% for a person with high viral load level if INSTI-based ART regimens could be used. We also estimated the average number of new HIV infections during the first six months since ART initiation accounting for different levels of risky sexual behaviour. Our results showed that the highest impact of initiating ART on INSTI-based regimens was among gbMSM with a high viral load at ART initiation and with considerable high-risk behaviour, regardless of the stage of HIV infection.

To the best of our knowledge this is the first study comparing the HIV transmission risk of individuals on INSTI-based regimens to other first-line used regimens, during the period between ART initiation and virologic suppression, using a modeling approach. By estimating the average number of new HIV infections, which incorporated the relationship among HIV transmission, viral load and sexual risky behaviours, we quantitatively measured the impact of INSTI-based regimens on the reduction of HIV transmission risk, which is not negligible within the first months of ART initiation. Our results suggest that a significant amount of transmission risk can be averted simply by the choice of initial ART regimen in specific settings, particularly for high risk individuals.

Our results have potentially important implications. From a public health perspective, controlling the HIV pandemic has become a critical priority for the global community. This was formally confirmed by the adoption of the UN resolution entitled “Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030” at the UN General Assembly in June 2016 [32]. Despite the recent global decline in new HIV infections, the current pace may not be sufficient to meet the UN Target, thus potentially jeopardizing the goal of ending the AIDS epidemic by 2030 [33]. Within this context, our results present potential opportunities to further prevent new HIV infections by reducing HIV transmission risk from newly diagnosed individuals. Indeed, it was recently announced that at least one of the INSTI class agents will be made available to low and middle income countries at a substantially reduced cost, making it possible to offer INSTI-based regimens as a first line option in such settings [33]. However, our results also demonstrated that besides the stage of HIV infection and viral load levels, the transmission risk was affected by other factors, such as risky sexual behaviours among the gbMSM population, which indicated that the impact of INSTI-based regimens should be assessed separately among groups with different risk exposures, such as heterosexual individuals or PWID.

This study has some limitations. First, to account for the uncertainty in the relationship between HIV transmission risk and viral load level, we utilized two very different mathematical models and conducted univariate sensitivity analyses on multiple parameters. Under both models, our results were consistent, especially for high viral loads. Second, we were unable to account for time-varying behaviour change due to factors such as ART optimism and use of pre-exposure prophylaxis by their negative partners. However, by estimating the average number of new HIV infections for different risky sexual behaviours, we could provide boundaries of transmission risk if sexual behaviour changes over time. Third, since we only considered ART naïve individuals in our analysis, we did not take into consideration the trajectories of individuals who failed on other regimens and started on INSTI-based regimens. We believe that by concentrating on ART naïve individuals, we eliminated some biases that may have played a role in explaining the trajectories of the non-naïve individuals. Finally, confounder by indication may have played a role in this study. Being older may be associated with a lower number of sexual acts in comparison to younger individuals, and these individuals are

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more likely to be prescribed INSTI-based regimens to minimize the risk of adverse drug reactions due to their comorbid conditions. However, our model is an average model and we present a range of sexual activity, and thus, we believe that this effect did not affect our results.

In conclusion, our results confirm that individuals on INSTI-based regimens can achieve faster virologic suppression than other commonly used first-line ART regimens, and there is the potential to avert onward HIV transmission, especially among individuals with high viral load partaking in high risk behaviour.

Author contributions

JZ and VDL designed the study, interpreted the results and wrote the first draft of this manuscript; JZ, IR, JD did all the coding and mathematical analyses. DM, SG, RB, and JSGM provided scientific support for the design of the study; RB, SG, DM and JSGM provided access to the data and some of the parameters for our model; VDL supervised the analysis and provided administrative support; and all authors approved the final version of the manuscript.

Declaration of Competing Interest

We have the following conflicts of interest: JSGM has received limited unrestricted funding, paid to his institution, from Gilead Sciences, Merck, and ViiV Healthcare. The remaining authors do not have conflicts to declare.

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