The population-level impact of antiretroviral treatment on HIV incidence depends on the clustering of ART patients in sexual networks

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Word count:

- Body of the text (excluding tables and figures): 3031
- Abstract: 267

Abstract

Antiretroviral treatment (ART) reduces HIV transmission, but its impact on HIV incidence may be offset by changes in sexual networks during the course of ART scale-up. Concerns about “risk compensation” (i.e., increases in individual risk behaviors due to perceptions that HIV is no longer lethal or transmissible) have largely been dispelled in empirical studies. But other emerging patterns of sexual networking may modify the effects of ART on HIV incidence. We used a mathematical model to show that ART homophily - a tendency among ART patients to preferentially form new relationships with other ART patients – can lead to the clustering of ART patients in sexual networks. These cluster have large and complex effects on the effectiveness of ART for HIV prevention, depending on the level of HIV prevalence, coverage of HIV testing and ART, and adherence to ART. ART homophily should be measured empirically and incorporated into models used to plan and evaluate ART programs.

Key words: HIV; antiretroviral therapy; treatment as prevention; homophily; sexual networks;

Introduction

Early initiation of antiretroviral therapy (ART) significantly improves the survival of persons living with HIV (PLWH) and reduces HIV transmission to uninfected partners by more than 90% (1-3). Some mathematical models suggest that treatment-as-prevention (TasP) programs could lead to HIV elimination, even in some of the most severely affected settings (4, 5). PEPFAR and other international organizations (e.g., UNAIDS) have thus placed ART scale-up at the center of their approach to achieving an "AIDS-free generation" (6, 7).

But the clinical efficacy of ART in preventing HIV transmission may not translate to real-life settings (8). This will depend in large part on the capacity of HIV programs to engage and retain PLWH on a "HIV treatment cascade", i.e., a series of clinical steps PLWH must go through to achieve viral suppression. In particular, for TasP programs to be effective, a high proportion of PLWH must 1) be diagnosed, 2) be linked to care, 3) remain in care, and 4) adhere to ART. An ambitious program of implementation science now seeks to improve each step of the HIV treatment cascade (9-16).

The effects of ART on HIV incidence may also depend on changes in sexual networking dynamics during the course of ART scale-up. In some settings, increasing ART availability may foster changes in sexual networking patterns that limit the extent of contact between PLWH and susceptible HIV-negative individuals, thus further increasing the beneficial effects of ART on HIV incidence. In other instances however, changes in sexual networking patterns may also lead to more contacts between PLWH and susceptible individuals, thus reducing – and potentially even offsetting - its expected impact on HIV incidence.

The Health Belief Model (17) suggests that "risk compensation" is one

mechanism through which such negative feedback loops between ART and HIV incidence may emerge (figure 1). Risk compensation occurs when people increase their individual risk behaviors in response to the increased availability of preventive interventions (18-22). If they perceive that HIV is less often fatal and/or may be less likely to be transmitted during sexual intercourse when ART becomes more available, then they may acquire new partners or engage in concurrent relationships. If it occurs, risk compensation can then significantly increase the density and reach of the sexual networks, which connect susceptibles and PLWH. Ultimately, it may reduce the effects of ART on HIV incidence. Empirical studies of risk compensation have however generally concluded that there was limited risk compensation after ART. Neither ART patients, nor HIV-negative individuals living in communities where ART becomes available, seem to increase the number of their sexual partners, for example (23-25).

[FIGURE 1 ABOUT HERE]

ART homophily in sexual networks

Even if ART does not lead to risk compensation, other feedback loops may emerge in the complex causal system linking ART scale-up and HIV incidence. In particular, increasing ART availability may affect the process of partnership selection/dissolution through which sexual networks are formed (figure 1). For example, during the course of ART scale-up, ART patients may increasingly form new relationships with other ART patients. Similarly, relationships between two ART patients may be less likely to dissolve than other relationships in which only one of the two partners is an ART patient. We call these sexual networking dynamics “ART homophily”, i.e., a tendency of ART patients to preferentially engage in, and maintain, sexual relationships with other PLWH who are also on ART.

Qualitative studies have documented several psychosocial mechanisms, which may lead to such dynamics. For an ART patient, ART homophily may indeed reduce fear for further HIV transmission (26) and ease anxiety about HIV status disclosure (27). ART homophily also gives patients direct access to emotional support (28) and facilitates sharing of coping strategies during episodes of drug-induced side effects or HIV treatment fatigue (29). In addition, ART patients may share common life histories, e.g., being widowed or having lost a previous partner. Finally, in a number of ART programs, ART patients frequently interact with each other during dedicated ART clinics, in support groups or in various income-generating activities (30). This increased social proximity may lead to emotional closeness, and may provide additional opportunities to form new sexual partnerships with others who are also ART patients.

ART homophily and other mechanisms of network formation

ART homophily has not been considered in existing investigations of sexual networking during the course of ART scale-up. Instead, most mathematical models of TasP have considered that sexual networks were formed either at random, or by mixing between different pre-defined risk groups (e.g., 4, 31, 32, 33). Empirical investigations of sexual networks have focused on documenting socioeconomic homophily (34-40), i.e., preferences for partners of the same age, gender, educational level or ethnic group, for example. In some populations (e.g., Men who have sex with men), another form of homophily called “serosorting” has also been extensively investigated (41-49). This is a behavioral strategy in which individuals preferentially select partners of the same HIV serostatus as them, so as to limit HIV transmission risks while possibly enabling unprotected sex.

ART homophily may overlap with some of these mechanisms of network formation in specific contexts. For example, in populations where there are marked

socioeconomic inequalities in access to ART, then both socioeconomic and ART homophily may lead to a higher than expected number of relations between ART patients. Similarly, in populations where all PLWH are receiving ART, then ART homophily and serosorting would be undistinguishable. In other contexts however, ART homophily is a distinct mechanism of network formation, which interacts with these other processes in a complex manner.

The emergence of ART clusters in sexual networks

ART homophily is particularly important for understanding and projecting the effects of ART on HIV incidence, because it may lead to profound changes in the distribution of PLWH within sexual networks. This is the case even when the underlying individual risk behaviors (e.g., number of partners) remain constant, i.e., when there is no risk compensation. Let us consider how ART homophily affects sexual networks in a fictitious population with 3 ART patients, 1 untreated PLWH and 4 HIV-negative individuals, where all individuals have between 1 and 3 sexual partnerships. In the absence of ART homophily (figure 2, panel a), then all 8 individuals are connected in one single sexual network. In the presence of ART homophily however (figure 2, panel b), ART patients now form a separated “ART cluster”, which is separated from the rest of the sexual network. Even in situations where ART patients do not solely form relationships with other ART patients, ART homophily may still lead to ART clusters within sexual networks, i.e., subsets of the sexual networks in which the density of ART patients is much higher than in the rest of the networks.

[FIGURE 2 ABOUT HERE]

When ART patients engage in ART homophily and ART clusters emerge, the rest of the sexual networks are affected by compensatory changes. Since ART patients are no longer available for relationships with untreated PLWH or with HIV-negative individuals, then these two groups must increasingly form relationships with each other if they want to maintain the number of sexual relationships they engage in constant. The sexual networking patterns of ART patients thus affect the partnerships formed by all other members of the sexual networks.

ART clusters and the effectiveness of treatment-as-prevention

In this context, the potential effects of ART clusters on the effectiveness of ART in preventing HIV transmission are complex. For a given level of ART coverage, they likely depend on a number of parameters such as HIV prevalence, ART adherence or the extent of serosorting, among others. In figure 2, we provide some intuition about these effects in the case of the same population comprising 3 ART patients, 1 untreated PLWH and 4 HIV-negative individuals. In the left panels of figure 2, sexual networks are formed at random with regards to ART status, whereas in the right panels of figure 2, sexual networks are formed on the basis of perfect ART homophily and thus include a fully disconnected ART cluster. In the upper panels of figure 2, ART patients are highly adherent to treatment, and thus are significantly less infective (e.g., due to suppressed HIV viral load). In the lower panels, some of the ART patients do not adhere to treatment, and thus remain infective. In all networks, the distribution of the number of partners across all individuals is similar (i.e., each individual has exactly the same number of partners in networks with and without ART clusters).

On the one hand, ART clusters may reduce the effect of ART on HIV incidence in situations where ART adherence is high (upper panels of figure 2). This is so because, whereas highly adherent ART patients “break” transmission chains in networks without ART clusters, they do not play that role in contexts with ART clusters. In panel a, where there are no ART clusters, individual A is protected from the risk of HIV acquisition because individual B adheres to ART and is thus unlikely to transmit HIV. In panel b, where ART clusters are present, individual A faces a much higher risk of HIV acquisition because he is now in direct contact with C, an untreated (and thus infective) PLWH.

On the other hand, in contexts where ART adherence is low, then the effects of ART clusters on the effectiveness of ART for HIV prevention may be reversed (lower panels of figure 2). In these contexts, ART patients likely remain infective because low ART adherence is associated with poor viral suppression. Then ART clusters withdraw a number of infective PLWH from the broader sexual networks, which also include susceptible individuals (figure 2, panels c and d). This reduces the number of opportunities for HIV transmission within sexual networks.

In rest of this paper, we incorporate the possibility of ART homophily into a mathematical model of the population-level effects of ART on HIV transmission. We identify the contexts in which the emergence of ART clusters in a sexual network could reduce versus enhance the population-level impact of ART on HIV incidence.

Methods

Model structure: We developed a static mathematical model of the population-level impact of ART on HIV incidence. There are 4 population groups: HIV-negative individuals, PLWH who are unaware of their infection (and thus are not treated and remain infective), PLWH who are aware of their infection but are not treated (and

thus remain infective), and ART patients. There are no differences in infectivity between PLWH who are aware or unaware of their treatment. The infectivity of ART patients depends on their level of adherence to ART (see below).

The main parameters of the model are the population prevalence of HIV (noted *h*), the fraction of PLWH who are aware that they are HIV-positive (*d*), the uptake of ART among PLWH who are aware of their infection (*a*) and the couple-level reduction in HIV transmission associated with ART (*r*). We define *r* as an incidence rate ratio, equal to HIV incidence in serodiscordant couples in which the infected partner has initiated ART divided by HIV incidence among serodiscordant couples in which the infected partner has not initiated ART. The coverage of ART, i.e. the proportion of all PLWH who are on ART is defined as *da*. The model also accounts for the average number of partners per time unit (*p*), the average number of unprotected sex acts per partnership (*s*), and the average HIV transmission probability per unprotected sex act (*i*).

The key parameters of interest are *n*, the degree of serosorting and *m,* the degree of ART homophily. Both parameters vary between 0 and 1. When $n=m=0$, relationships in the population are formed at random with respect to HIV status and ART status. When $n=1$ and $m=0$, diagnosed PLWH exclusively form partnerships with other diagnosed PLWH, but among those, PLWH who have initiated ART do not preferentially seek partners who are also on ART. Instead, partnerships between PLWH who are on and off ART are formed proportionately to the relative size of these groups. When $m=1$ and $n=0$, ART patients exclusively form partnerships with other ART patients, resulting in emergence of ART clusters that are completely separated from the rest of the sexual networks, as in panel B of Figure 1. This prompts compensatory changes in networking patterns among HIV-negatives and PLWH who are not ART, i.e., they increase the frequency at which they form partnerships with each other. When $0<n<1$, diagnosed PLWH have preferences for

being in relationships with other diagnosed PLWH, but still have a proportion of their relationships with other PLWH who are not yet aware of their status and with HIV-negative people. Likewise, when $0<m<1$, ART patients have preferences for being in relationships with other ART patients, but still have a proportion of their relationships with others who are not ART patients.

Assumptions: To simplify the analysis, we assumed that there is no risk compensation the modeled population: ART initiation does not lead to changes in the number of sexual partners individuals have, nor does it affect condom use or other aspects of the HIV transmission process within couples. We also assumed homogeneity in sexual activity: every member of the population has the same number of partners and each sexual partnership entails the same number of sex acts.

Model equations: In serodiscordant couples, when the HIV-positive partner is not on ART, the per-partnership probability of HIV transmission, noted t, is $1 – (1 - i)^s$. When the HIV-positive partner is on ART, this probability, noted t_{ART}, is equal to $1 – (1 – i)^{rs}$. The rates at which HIV-negative individuals form relationships with diagnosed PLWH on and off ART are $phda(m – 1)(n – 1)$ and $phd(1 – a)(1 – n)$, respectively. The rates of relationship formation with other HIV-negatives and undiagnosed PLWH are proportional to the size of the populations of HIV-negatives and undiagnosed PLWH: $1 – h$ and $h(1 – d)$, respectively. Taken together, these four rates sum to p, i.e., the number of partners individuals have in our model. The HIV incidence rate, noted I, can then be calculated from these rates of partnership formation and their associated per-partnership probabilities of HIV transmission (see Supplementary Material for more details on the model equations). Lastly, the

population-level impact of ART on HIV incidence, (I/I_{noART}) – 1, is defined as the relative change in the HIV incidence rate, associated with ART. In this formulation, I_{noART} is calculated as I except that none of the PLWH are on ART (a=0).

Values of model parameters: We considered three HIV prevalence levels (1%, 10% and 35%) in our analysis, representing the wide range of HIV prevalence levels observed worldwide. In these analyses, h=1% represents situations typical of concentrated epidemics, whereas h=35% represents situation common in certain hyperendemic, settings (50-53). Percentages of PLWH that are aware of their HIV status (d) and ART uptake among these diagnosed PLWH (a) ranged from 50% to envisioned future levels of 90%, under the assumption of immediate, unconditional access to ART, as currently being piloted in TasP trials (54-57). The range of values for the HIV incidence rate ratio associated with ART in serodiscordant couples (r) was derived from a recent systematic review of prospective studies (8). We let the parameters n and m vary between 0 and 1, where 0 represents no serosorting/ART-homophily and 1 represents perfect serosorting/ART-homophily.

Model analysis: First, we conducted a one-way analysis to assess how each model parameter relates to the population-level impact of ART under the assumption of random mixing with respect to HIV and ART status (m=n=0). Second, we explored how variations in m and n affect the impact of ART on HIV incidence for different levels of HIV prevalence (h), HIV diagnosis (d), ART uptake (a) and intra-couple effectiveness of ART (r). To facilitate further exploration of the behavior of the model and strengthen intuition for the model results, we developed an online app (https://artclustering.shinyapps.io/ModelExploration) that interactively illustrates how

the HIV prevention benefits of ART and the relationship dynamics between the model's four population subgroups change as a function of the model's parameters.

[TABLE 1 ABOUT HERE]

Results

One-way analysis: In sexual networks without serosorting and ART-homophily (m=n=0), the impact of ART on HIV incidence only depends on the proportion of PLWH who are aware of their infection (d), ART uptake (a) and the intra-couple ART effectiveness (r). The annual number of partners (p), the average number of unprotected sex acts per relationship (s) and the per sex act probability of HIV transmission (i) do not affect the impact of ART on HIV incidence in this model (Figure 3). Note that this does not mean that these parameters do not influence HIV incidence. Indeed, HIV incidence increases with increasing values of p, s and i, but the relative change in HIV incidence when comparing scenarios with and without ART is unaffected. Henceforth, these parameters were not included in the multi-way analysis.

[FIGURE 3 ABOUT HERE]

Does ART-homophily modify the impact of ART? we investigated the association between each model parameter and the modification factor associated with m, the relative increase/decrease in the impact of ART on HIV incidence that results from the presence of ART homophily (figure 4). We found that this modification factor was

associated with 1) HIV prevalence, 2) the fraction of PLWH aware of their status, and 3) adherence to ART (i.e., *r*). On the other hand, this modification factor did not depend on ART uptake among diagnosed PLWH, the average number of sexual partners, the number of sex acts per relationship and the average probability of transmission per sex act. It also did not depend on the level of serosorting within the population.

[FIGURE 4 ABOUT HERE]

In multi-way analyses, the interactions between ART clusters and other model parameters are complex (Figure 5). In populations with HIV prevalence ≈ 1%, ART-homophily increases the impact of ART on HIV incidence relative to a baseline without ART-homophily for virtually all combinations of model parameters. ART homophily however particularly improves the impact of ART on HIV incidence if ART patients do not strictly adhere to treatment. For example, in settings with low ART adherence among ART patients (i.e., $r = 0.34$), ART homophily increases the impact of ART on HIV incidence by close to 50%, regardless of other model parameters. On the other hand, if adherence is high (i.e., $r = 0.04$), then ART homophily only increases the impact of ART by 10% relative to a situation in which networks are formed at random.

[FIGURE 5 ABOUT HERE]

Similar results are obtained in populations with HIV prevalence ≈ 10%, but the potential effects of ART homophily on the population-level impact of ART vary more widely when HIV prevalence ≈ 35%. In such hyper-endemic populations, ART homophily may improve the impact of ART on HIV incidence when adherence to ART is low. On the other hand, if ART adherence is high, then the emergence of ART clusters reduces the expected impact of ART on HIV incidence. For example, in contexts with high proportions of PLWH aware of their infection, but low adherence to ART (upper right corner), then ART homophily increases the impact of ART by close to 50% relative to similar contexts in which networks would be formed at random. But when adherence to treatment is low among ART patients, the effects of ART homophily on the impact of ART vary. If large proportions of PLWH are aware of their infection, then ART homophily has virtually no effects on the impact of ART on HIV incidence. But if few PLWH are aware of their infection, then ART homophily may even reduce the impact of ART by close to 25% (lower left corner).

Discussion

We explored how ART clusters in sexual networks can influence the population-level impact of ART on HIV incidence. Unlike other sexual mixing patterns such as serosorting (43, 46-48) and mixing between and across subgroups with varying levels of sexual risk behaviors (5, 58), ART clusters in sexual networks have not previously been considered in mathematical models of the effectiveness of ART for HIV prevention. This is a significant gap since the ART status of potential partners often plays a significant role in relationship decisions among ART patients (26). Using a simple mathematical model, we showed that ART clusters may modify the prevention impact of ART in a complex manner, depending simultaneously on the

performance of HIV testing and treatment programs (fraction of PLWH that are aware of their HIV status, and ART adherence) and the epidemiological context (HIV prevalence).

In concentrated epidemics and in generalized epidemics where HIV prevalence is no more than 10%, ART clusters enhance the impact of ART on HIV incidence. On the other hand, the impact of ART clusters may be more complex in hyperendemic settings where the HIV prevalence among certain gender-age strata may reach or even exceed 35%.(50-53) In such settings, ART clusters also enhance the impact of ART on HIV incidence when HIV status awareness among PLWH(*d*), and therefore ART coverage (*da*) are high, and ART adherence are low. This is because ART patients who do not adhere to treatment remain infective. In that case, ART clusters provide indirect protection to HIV-negative individuals by limiting their contact with potential sources of HIV transmission.

In contrast, in hyperendemic settings where HIV status awareness (and hence ART coverage) is low but ART adherence is high, ART clusters may reduce the impact of ART on population-level HIV incidence. This is so because in such settings, highly-adherent ART patients (who are significantly less infective than other PLWH) would have helped interrupt chains of HIV transmission in sexual networks connected to HIV-negative individuals. Instead, because of ART clusters, HIV-negative individuals are more likely to come into contact with undiagnosed (and untreated) and thus more infective PLWH. Since the combination of high ART adherence and low ART coverage characterises most current ART programmes, ART may at the moment have a lower impact on HIV incidence than estimated by standard mathematical models without ART clusters.(59, 60)

Our analysis has several important limitations. Firstly, while our model provides qualitative insights into the effect of ART clusters on the prevention benefit of ART, empirical investigations of ART clusters (the value of *m*) in settings with low and high HIV prevalence are required to obtain a quantitative understanding of the effect size. Questions about the ART status of one's (prospective and current) partners should be included in studies of sexual behaviours conducted among ART patients, as is already the case in the MaxART study, an ongoing implementation study of early access to ART for all PLWH in Swaziland.(61) Secondly, our model only considered situations in which there was no risk compensation among ART patients. Future refinements of this model should investigate interactions between risk compensation and the emergence of ART clusters. Thirdly, our model did not include population heterogeneity in sexual risk behaviours, nor did it include the acute phase of HIV infection, during which PLWH have an elevated viral load and are highly infectious.(62, 63) These factors may modify the effects of ART clusters on HIV incidence in a complex manner. Fourthly, we only considered ART-related sexual mixing patterns. But partner choices could be more complex in the context of combination prevention, in which ART is scaled-up alongside other HIV prevention interventions such as medical male circumcision. Finally, we focused on the instant change in ART-associated reduction of HIV incidence as a result of an instant change in the ART clustering parameter. However, future models should investigate temporal trends in ART impact on HIV incidence as ART clusters emerge in dynamic sexual networks. This approach may help assess the potential of interventions that promote (or dissuade) ART-based partner selection as a complementary intervention in HIV combination prevention packages that include TasP.

While these limitations may limit the transferability of our numeric results to real-life settings, our analysis demonstrates the potential importance of ART clusters for

estimating the prevention benefits of ART. Consequently, our results suggest that the mathematical models that are being used to estimate the current and future impact of TasP programmes should be amended to take into account the possible emergence of ART clusters in sexual networks. This inclusion would yield a better representation of the range of HIV incidence reduction that can be expected after ART scale-up. Since ART clusters also potentially modify the population-level effect of ART on HIV incidence, they should also be considered when planning large-scale cluster-randomized trials of TasP. In some settings, they may indeed increase the statistical power of such trials, whereas in others they may lead to underpowered trials.

Acknowledgements

The authors are grateful to Hans-Peter Kohler for comments on an earlier draft of the model.

Authors and contributors:

The concept of this study was conceived by SH. both authors contributed to the study design. WD developed the mathematical model, conducted the modelling analysis and wrote the first draft of the paper. Both authors contributed to the analysis, discussion of the results, and writing of the manuscript.

Disclose funding received for this work:

WD received funding from the Canadian International Development Agency (CIDA) and the Dutch Postcode Lottery through the *Max*ART programme (Maximizing ART for Better Health and Zero New HIV Infections). SH received funding from the National Institutes of Health through grant R03HD0177722 (PI: Helleringer).

Conflicts of interest

There are no conflicts of interest.

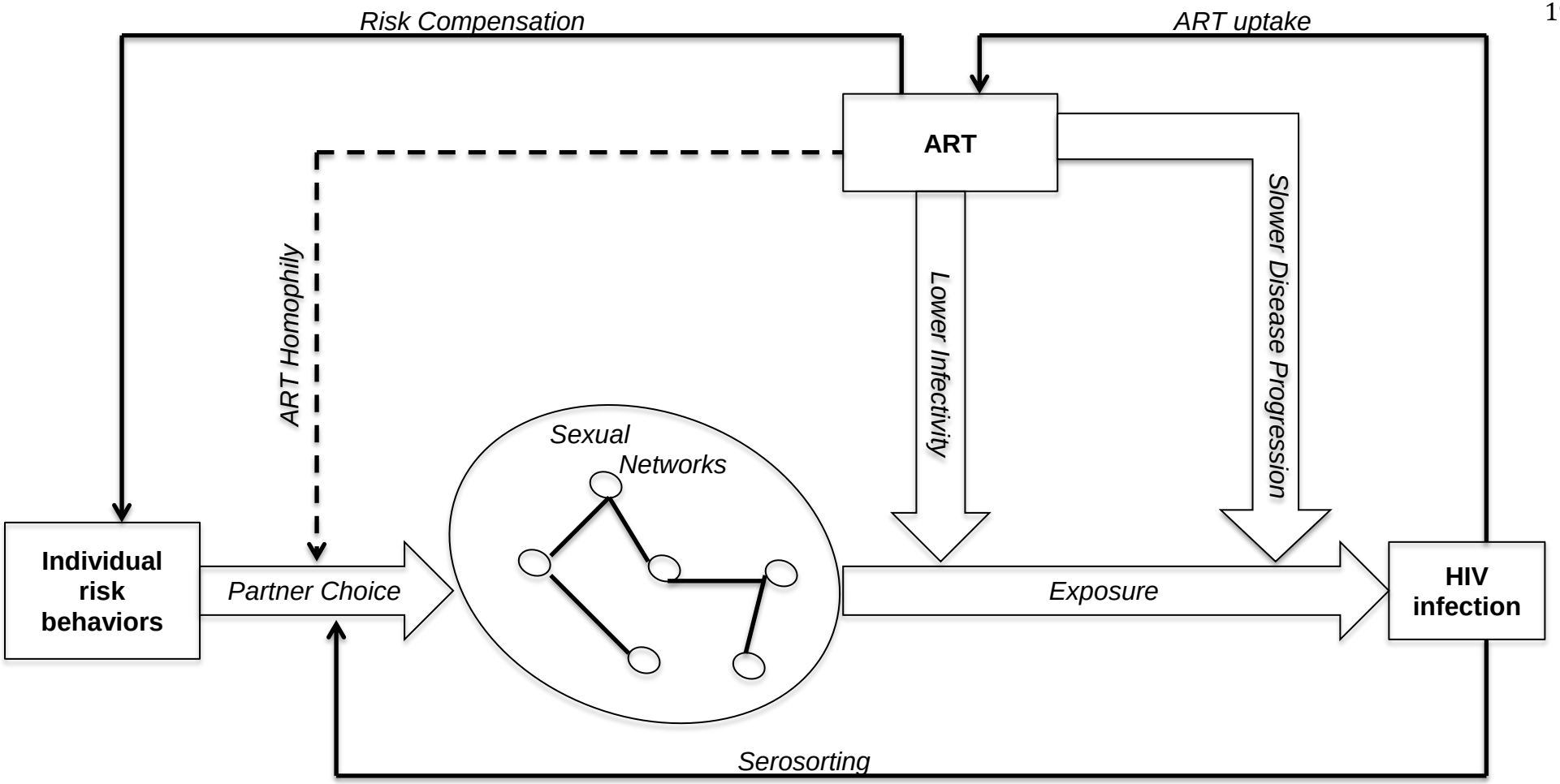

Figure 1: Causal pathways linking the availability of ART to HIV incidence within a population
Notes: wide arrows represent direct pathways, whereas solid narrow arrows represent feedback loops that have been considered in the literature on treatment-as-prevention. The dotted arrow represents ART homophily, another causal feedback loop that has not been considered in the literature on treatment-as-prevention.

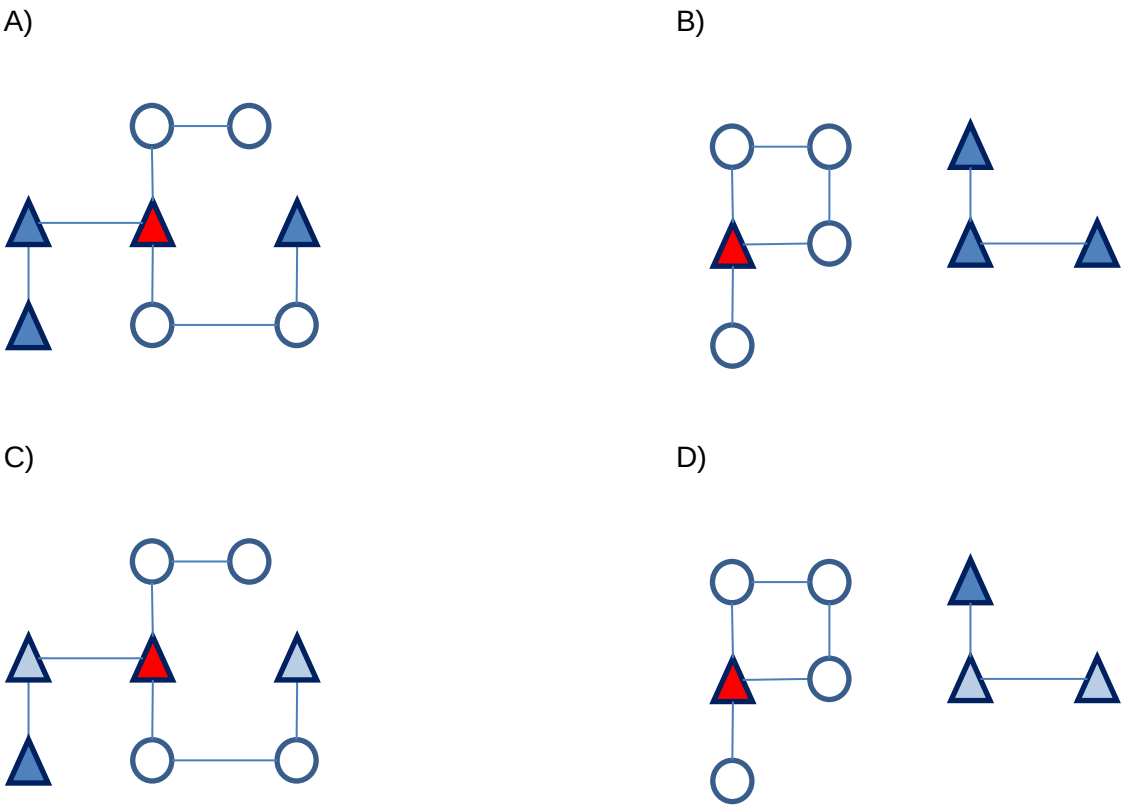

Figure 2. Illustration of the effects of ART clusters on HIV exposure in a population. HIV-negative individuals appear in empty circles, while people living with HIV (PLWH) are represented by triangles. ART patients appear in blue triangles, whereas other (untreated) PLWH appear in red triangles. In panels A) and C) the network is formed at random, in panels B) and D) the network is formed based on ART homophily: all HIV-negative individuals are connected only to the one PLWH not on ART, and the 3 ART patients are connected together in an ART cluster. The level of adherence to ART is represented by shades of blue: light blue indicates ART patients who are not adherent to ART, whereas darker blue indicates ART patients who are adherent to ART.

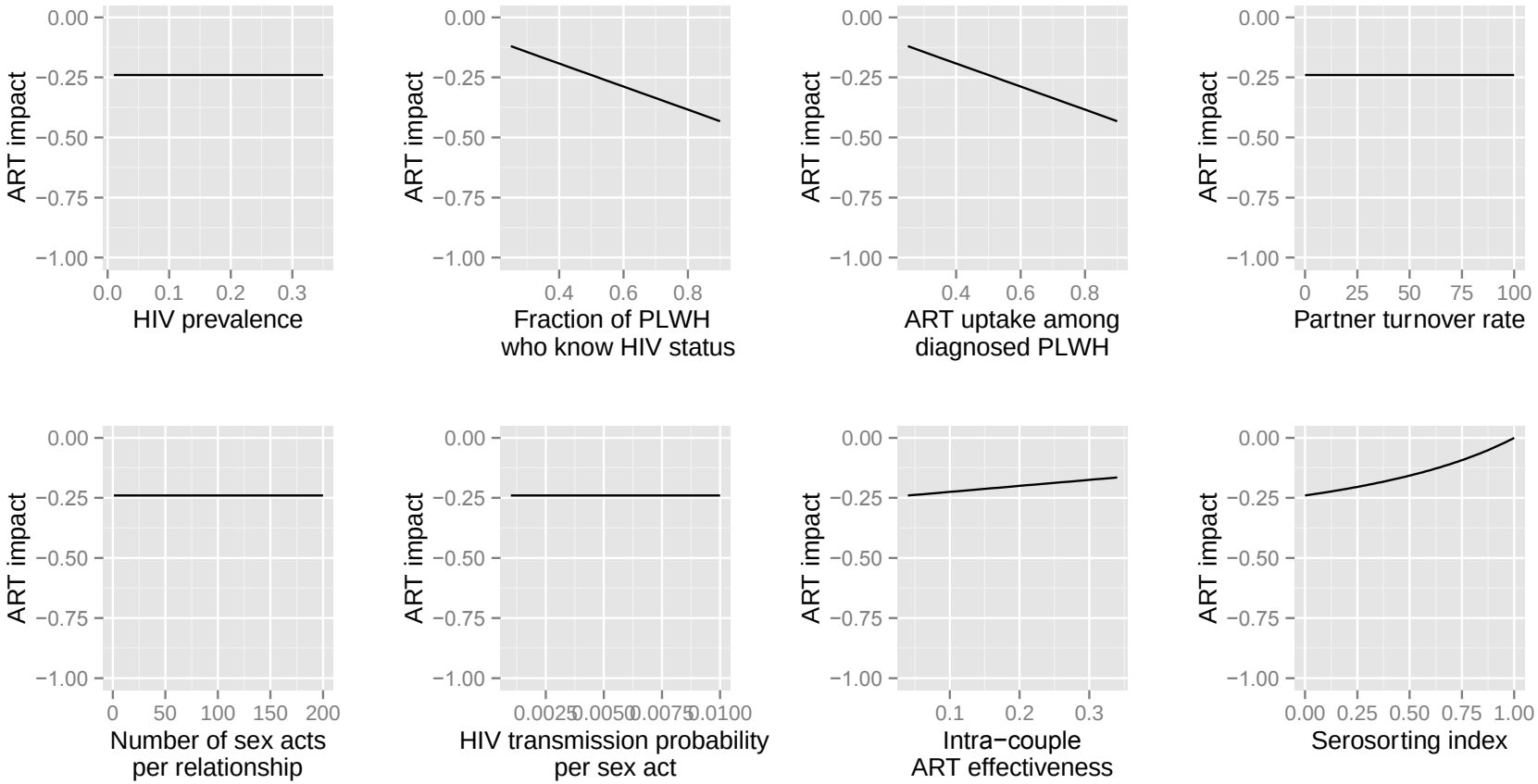

Figure 3: effect of model parameters on the impact of ART on HIV incidence. In each of these panels, we have set the level of ART homophily to m = 0.

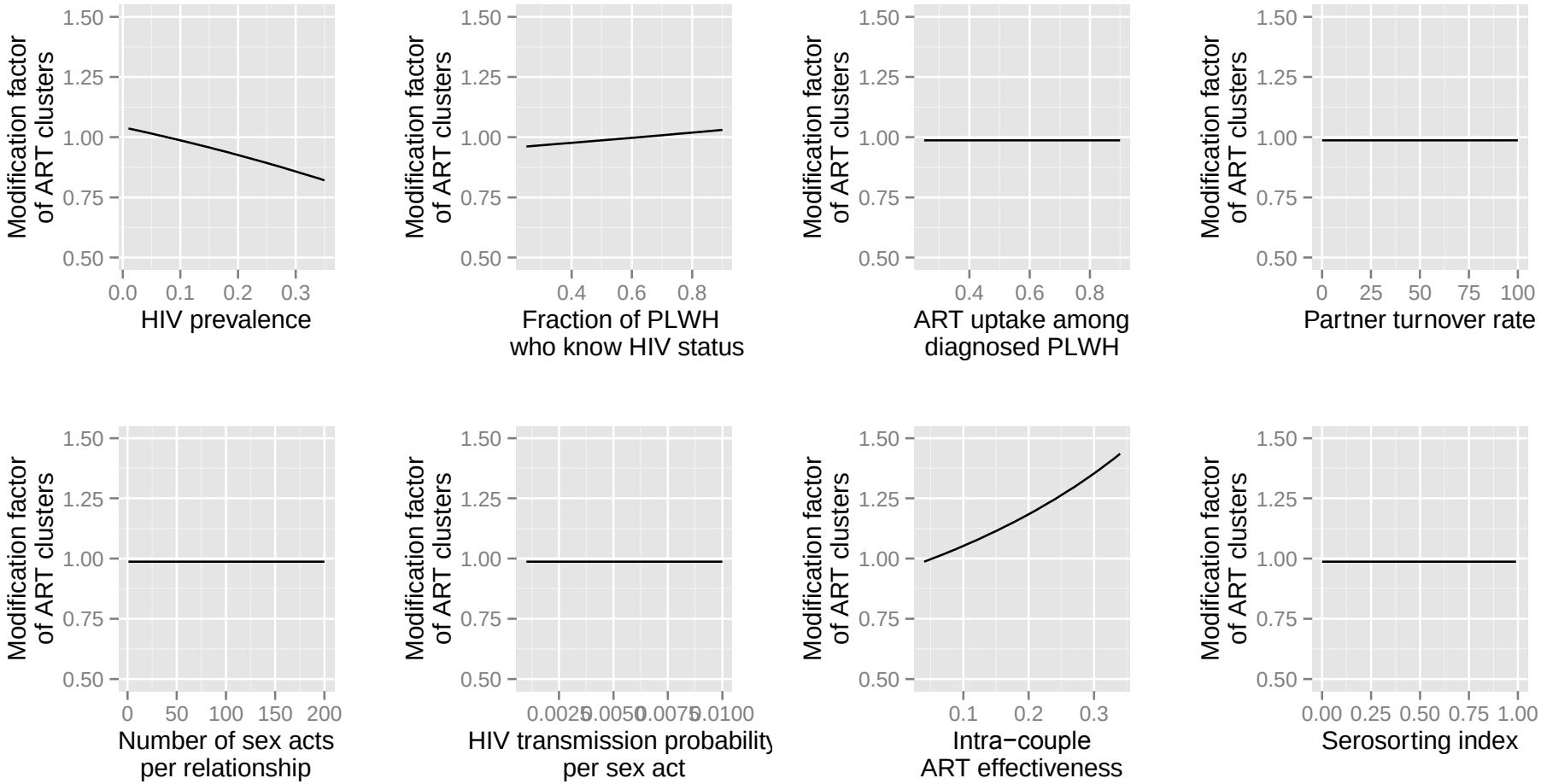

Figure 4: effect of model parameters on the modification factor associated with ART homophily. The modification factor is the ratio of the impact of ART when m = 1 to m = 0.

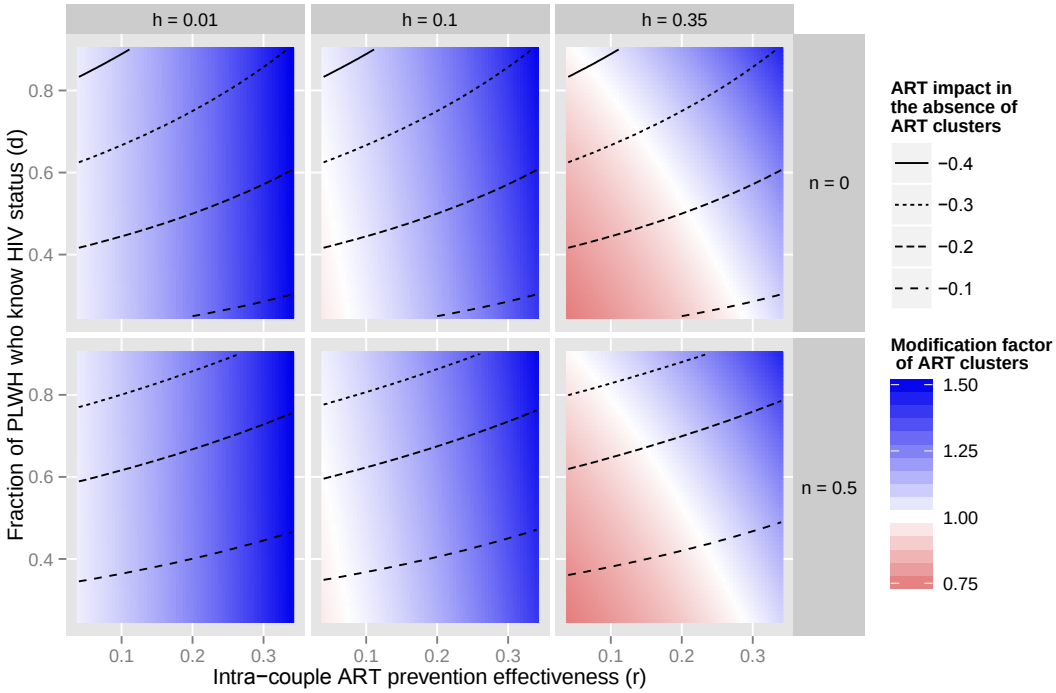

Figure 4. The effect of ART clusters and serosorting on the population-level impact of ART on HIV incidence, by levels of HIV prevalence (*h*), Fraction of PLWH who are aware of their HIV status (*d*) and intra-couple effectiveness of ART (*r*). Contour lines indicate the impact of ART on HIV incidence in the absence of ART clusters (*m*=0). Colour coding indicates the modification factor of ART clusters, i.e., the factor by which the ART impact on HIV incidence increases (>1 in blue) or decreases (<1 in red) when comparing the case of *m*=1 to the case of *m*=0. For example, in the darkest blue areas, the impact of ART on HIV incidence is 50% greater in the presence of perfect ART homophily (i.e., m=1) than it would have been if networks were formed at random (i.e., m = 0). The uptake of ART among diagnosed PLWH (a) was fixed at 50% in all model scenarios shown.

Parameter	Description	Range (baseline) in one-way analysis	Values in multi-way analysis
h	HIV prevalence	1% – 35% (10%)	1%, 10% and 35%
d	Diagnosed PLWH	25% – 90% (50%)	25% – 90%
a	ART uptake*	25% – 90% (50%)	50% and 90%
p	Partner turnover rate	0.05 – 100 (0.5)	0.5
s	Number of unprotected sex acts per relationship	1 – 500 (200)	200
i	Per sex act HIV transmission probability	0.001 – 0.01 (0.005)	0.005
r	Incidence rate ratio among serodiscordant couples on and off ART	0.04 – 0.34 (0.04)	0.04 – 0.34
m	ART assortativity index	0 – 1 (0)	0 – 1
n	HIV serosorting index	0 – 1 (0)	0 – 1

Table 1: Range of parameters values explored.

Supplementary Material

A. Deriving the probability of HIV transmission per sex act when the HIV-positive partner is on ART (t_{ART}) from the incidence rate ratio (r) in serodiscordant couples on vs off ART.

The risk of HIV transmission per sex act in the absence of ART, i, can be viewed as the result of a continuous force of infection f, maintained for a short period of time delta_i:
$i = 1 - \exp(-f \text{ delta\_i})$

Likewise, the risk of HIV transmission per sex act while the HIV positive partner is on ART, i_{ART}, is the result of a reduced force of infection. The incidence rate ratio, r, expresses the relative reduction in this force of infection:
$i_{ART} = 1 - \exp(-fr \text{ delta\_i})$

Hence:
$\ln(1 - i) = -f \text{ delta\_i}$
$\ln(1 - i_{ART}) = -fr \text{ delta\_i}$
$\ln(1 - i_{ART}) = \ln(1 - i)r$
$1 - i_{ART} = (1 - i)^r$
$i_{ART} = 1 - (1 - i)^r$

Probability of transmission per relationship (s unprotected sex acts):
$t_{ART} = 1 - (1 - i_{ART})^s = 1 - ((1 - i)^r)^s$
$t_{ART} = 1 - (1 - i)^{rs}$

B. Calculation of the population-level impact of ART on HIV incidence in the case of random mixing (m=0, n=0)

If sexual mixing is random with respect to HIV status and ART status (i.e., m=0 and n=0), then the fraction of relationships formed by HIV-negative people with PLWH on and off ART is equal to hda and $h(1 - da)$, respectively.

In the absence of any ART programme, the HIV incidence rate at the population level, I, is simply $-\log(1 - t)ph$. If some PLWH are on ART (da>0), the HIV incidence rate becomes:
$I = -\log(1 - t_{ART})phda - \log(1 - t)ph(1 - da)$

The population-level impact of ART on HIV incidence, $I/I_{noART} - 1$, is defined as the relative change in the HIV incidence rate, associated with ART, whereby I_{noART} follows the same calculation as I except that this time no one is on ART (a=0).

C. Calculation of population-level impact of ART on HIV incidence in the case of serosorting (n>0) and ART clustering (m>0).

If some degree n of serosorting is introduced, PLWH who know their HIV status will form more relationships with other diagnosed PLWH. If some degree m of ART clustering is also introduced, the subset of PLWH on ART will still have the same fraction of their relationships with other diagnosed PLWH as diagnosed PLWH not on ART, but in addition, they will disproportionally favour PLWH who are also on ART, when forming new relationships.

These relative shifts in relationship preferences for diagnosed PLWH and PLWH on ART subgroups, lead to compensatory shifts for HIV-negative people. The fraction of their total number of relationships that are formed with PLWH on ART is no longer hda but $hda(1-n)(1-m)$, and the fraction with PLWH who are diagnosed but not on ART is $hd(1-a)(1-n)$.

To compensate for the reduced availability of diagnosed PLWH off ART as a result of serosorting and the reduced availability of diagnosed PLWH on ART as a result of serosorting and ART clustering, HIV-negative people will form more relationships with other HIV-negative people and undiagnosed PLWH, proportional to their respective subpopulation group size.
The total fraction of their relationships with diagnosed PLWH is:
$hda(1-n)(1-m) + hd(1-a)(1-n) = hd(1-n) - hda(1-n)m$

Of all people in the population, the respective fractions $h(1-d)$ and $1-h$ are undiagnosed PLWH and HIV-negative people. Hence, the fraction of HIV-negative people's relationships formed with undiagnosed PLWH is:
$h(1-d)/(h(1-d) + (1-h))(1-(hd(1-n) - hda(1-n)m))$, while the fraction of HIV-negative people's relationships formed with other HIV-negative people is:
$(1-h)/(h(1-d) + (1-h))(1-(hd(1-n) - hda(1-n)m))$.

The HIV incidence rate can now be calculated as:

$$\begin{aligned} I = {} & -\log(1-t_{ART})phda(1-n)(1-m) + \\ & -\log(1-t)phd(1-a)(1-n) + \\ & -\log(1-t)p[h(1-d)/(h(1-d) + (1-h))(1-(hd(1-n) - hda(1-n)m))] \end{aligned}$$

As was the case for random mixing with respect to HIV status and ART status, the population-level impact of ART on HIV incidence, $I/I_{noART} - 1$, is defined as the relative change in the HIV incidence rate, associated with ART, whereby I_{noART} follows the same calculation as I except that this time no one is on ART (a=0).

$$\begin{aligned} I_{noART} = {} & -\log(1-t)phd(1-n) + \\ & -\log(1-t)p[h(1-d)/(h(1-d) + (1-h))(1-hd(1-n))] \end{aligned}$$

From the equations above, we see that both the incidence, I, and the population-level impact of ART on HIV incidence, $I/I_{noART} - 1$, change linearly with m, but the

direction in which they change depends on h, d and r (because r determines how different t_{ART} is from t.

The parameter m subtracts m times $-\log(1 - t_{ART})phda(1 - n)$ from the incidence, but also adds m times $-\log(1 - t)\ \ h(1 - d)/(h(1 - d) + (1 - h))\ \ phda(1 - n)$. After removing the scaling factor $phda(1 - n)$, we see that only t, t_{ART}, h and d remain. Since $-\log(1 - t_{ART})$ is r times smaller than $-\log(1 - t)$, the question becomes: is $h(1 - d)/(h(1 - d) + (1 - h))$ smaller or larger than r? We can also find the turning point, by expressing one parameter as a function of the other two: when $h(1 - d)/(h(1 - d) + (1 - h)) = r$ then $d = (h - r)/(h - hr)$. For instance, when the HIV prevalence is 35% and the incidence rate ratio associated with ART among serodiscordant couples is 0.04, it is sufficient that less than 92% of PLWH are aware of their status for ART clustering to have an impeding effect on the prevention benefits of ART. For the same ART incidence rate ratio but a background prevalence of 10%, status awareness among PLWH needs to drop below 62% before ART begins to weaken the impact of ART on HIV incidence.

In other words, ART clustering will weaken the prevention benefits of ART if the subpopulation of undiagnosed PLWH is more than r times larger than the sum of the subpopulations of HIV-negative people and undiagnosed PLWH. Conversely, ART clustering will augment the impact of ART on HIV incidence if the opposite is the case. From this, it follows that the strongest synergistic effect of ART clustering on the impact of ART on HIV incidence is achieved when r is very large, h is small and d is large, while ART clustering can reduce the prevention benefits of ART if it occurs in a context of high HIV prevalence where not many PLWH are diagnosed (small d), but treatment effectiveness is excellent (small r).

Serosorting results in a smaller fraction of relationships being formed between HIV-negative people and PLWH, regardless of all the other parameters. Because PLWH on ART are by definition aware of their HIV status, and therefore subject to a level n of serosorting, serosorting results in a reduced incidence rate ratio between the ART and no ART scenario. In the limit of n=1, all contacts that HIV-negative people have with PLWH are necessarily in the absence of ART, such that the impact of ART drops to zero. Note that an analogy with the case of perfect ART clustering (m=1) cannot be drawn, by definition, because for ART clustering to be possible, there must be at least some level of ART uptake (da>0).

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