Distinguishing sources of HIV transmission from the distribution of newly acquired HIV infections: why is it important for HIV prevention planning?

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ABSTRACT

Objective The term 'source of HIV infections' has been referred to as the source of HIV transmission. It has also been interpreted as the distribution of newly acquired HIV infections across subgroups. We illustrate the importance of distinguishing the two interpretations for HIV prevention planning.

Methods We used a dynamical model of heterosexual HIV transmission to simulate three HIV epidemics, and estimated the sources of HIV transmission (cumulative population attributable fraction) and the single-year distribution of new HIV infections. We focused an intervention guided by the largest transmission source versus the largest single-year distribution of new HIV infections, and compared the fraction of discounted HIV infections averted over 30 years.

Results The single-year distribution of newly acquired HIV infections underestimated the source of HIV transmission in the long term, when the source was unprotected sex in high-risk groups. Under equivalent and finite resources, an intervention strategy directed by the long-term transmission source was shown to achieve a greater impact than a distribution-directed strategy, particularly in the long term.

Conclusions Impact of HIV prevention strategies may vary depending on whether they are directed by the long-term transmission source or by the distribution of new HIV infections. Caution is required when interpreting the 'source of HIV infections' to avoid misusing the distribution of new HIV infections in HIV prevention planning.

INTRODUCTION

Estimating the source of HIV infections is a key step in the 'know your epidemic, plan your response' approach to HIV prevention,[1 2] and falls under the strategic planning phase of Programme Science.[3] Its importance stems from the rationale that if we identify the source of HIV infections, we can apply source-specific interventions to prevent onward transmission and reduce HIV incidence.[4 5]

However, in the context of disease dynamics, the term 'source of HIV infections' can be non-specific. It has been referred to as the source of HIV transmission, defined as the fraction of HIV infections that are due, or attributable, to specific risk behaviours or subgroups (eg, commercial sex)—that is, from whom infections are transmitted.[6–9] For example, the fraction of HIV infections attributable to sex during short-term migration was assessed in India, which then provided the basis for understanding the potential impact of condom-based interventions for migrants.[7] The term 'source of HIV infections' has also been interpreted as the distribution of newly acquired HIV infections across subpopulations—that is, in whom infections are acquired.[10–13] For example, appraisals of HIV epidemics have reported on the fraction of HIV infections acquired within serodiscordant couples, stable partnerships, or by high-risk groups as the current 'source of new HIV infections'.[10 11 13–15] Both interpretations involve estimating HIV incidence, but the subgroups in which infections originate may not always coincide with subgroups in which infections manifest. A single-year distribution of newly acquired HIV infections across subgroups will not necessarily equal the fraction of future infections due to behaviours within the same subgroups (source of transmission). As a result, HIV prevention strategies could vary depending on our interpretation of the 'source of HIV infections'.[16] In this paper, we explicitly distinguish between the source of HIV transmission and the distribution of newly acquired HIV infections, to illustrate how prevention strategies guided by one versus the other could influence the population-level impact of an intervention.

The static Modes of Transmission model (MOT) is commonly used to estimate the source of HIV infections.[13 17 18] The MOT predicts a single-year distribution of newly acquired HIV infections across subgroups, and therefore end-users of this model do not obtain information on the source of HIV transmission.[19 20] The source of transmission implies direct and indirect (or secondary) links between individuals, and reflects the number or proportion of HIV infections that could be prevented if individuals at the source who engaged in specific risk behaviours were protected from acquiring HIV.[6 7] The transmission source reflects the intended meaning of the term 'population-attributable fraction' in chronic disease epidemiology.[21] By contrast, the distribution of new HIV infections reflects the number or proportion of new infections predicted to occur in different subgroups.[19 20] The difference between the two interpretations of the 'source of HIV infections' may appear to be an issue of semantics, but the distinction becomes important when the distribution fails to identify the key transmission sources,[4 16] and the wrong 'source of HIV infections' is used to prioritise subgroups for HIV prevention. Correct identification of subgroups for targeted intervention is particularly important when

the transmission source corresponds to high-risk sex (commercial sex or multiple partnerships).[5 22]

In this paper, we use dynamical modelling to illustrate the distinction between a 1-year distribution of new HIV infections and the source of HIV infections in three representative epidemiologic contexts (concentrated, mixed and generalised epidemics). We then examine the discounted impact of HIV interventions guided by the long-term transmission source versus the single-year distribution of newly acquired HIV infections.

METHODS

Dynamical model

We used a dynamical model of heterosexual HIV transmission, as detailed in the web appendix. The model simulates an open population of four sexual activity groups (figure 1), and includes movement from high-activity to low-activity groups (eg, to represent retirement from sex work). A schematic of the dynamical model structure with the natural history of HIV (treated and untreated) is depicted in online supplementary figure A1.

Our objective was to conduct an illustrative examination of the distribution of new HIV infections versus source of HIV transmission, and not to predict potential intervention impact in a well-characterised regional epidemic. Nonetheless, to ensure these 'synthetic' epidemics reflected the use of plausible parameters, we used regional demographic, behavioural (including condom-use), and HIV prevalence data from Belgaum (South India), Lesotho, and Kisumu (Kenya), to simulate a concentrated (see online supplementary figure A2), generalised (see online supplementary figure A3), and mixed epidemic (see online supplementary figure A4), respectively.

Distribution of new HIV infections over 1 year

The distribution of new HIV infections ($DI_{2010–2011}$) is reported in keeping with published MOT reports,[17] and includes the predicted fraction of HIV infections acquired by the following subgroups in 2010:

A. Female sex workers (FSW) and clients (commercial sex)
B. Low-activity (main) partners of clients and FSWs
C. Individuals with multiple partners/year (MP group)
D. Low-activity (main) partners of MP group
E. Low-activity group (individuals with one partner/year), who are not classified as subgroups (b) or (d) between 2010 and 2011.

Source of HIV transmission

The source of HIV infections was calculated as the cumulative population attributable fraction (PAF) over time-horizon t_0-t_1:

A. From 1980 to 2010 ($PAF_{1980–2010}$)
B. From 2010 to 2011 ($PAF_{2010–2011}$)
C. From 2010 to 2040 ($PAF_{2010–2040}$)

The PAF is measure of the fraction of HIV infections in the total population due to a given risk factor or risk behaviour (eg, commercial sex), and was estimated from the dynamical model as follows:

$$PAF_{t_0-t_1}^{riskbehavior} = 100 \left(\frac{\int_{t_0}^{t_1} newHIVinfections_{total}^{riskbehavior} - \int_{t_0}^{t_1} newHIVinfections_{total}^{noriskbehavior}}{\int_{t_0}^{t_1} newHIVinfections_{total}^{riskbehavior}} \right)$$

Where, $newHIVinfections_{total}^{riskbehavior}$ refers to new HIV infections in the total population in the presence of the risk behaviour, and $newHIVinfections_{total}^{noriskbehavior}$ refers to new HIV infections in the total population in the absence of the risk behaviour.

We estimated the PAF from the dynamical model by setting the transmission probability within specific partnerships (or risk behaviour) to zero, from the start of each time-horizon (t_0).

Intervention impact

To illustrate the difference between interventions guided by the source of HIV infections versus the distribution of newly acquired HIV infections, we applied a targeted 'test and treat' programme, wherein HIV-positive individuals were initiated on combination antiretroviral treatment (cART) immediately following diagnosis.[23] The intervention was started in 2010, and cART is assumed to reduce per-act HIV transmission by 96%.[24] We assumed that acute HIV remained undiagnosed with standard testing, and therefore progressed untreated. Treatment was restricted to first-line cART, and patients did not resume cART after failing or discontinuing first-line drugs. cART reduced HIV-attributable mortality.

In all scenarios, we assumed that clinical cART delivery was scaled up after 2010, in accordance with the 2010 WHO recommendations to initiate cART at CD4 cell counts ≤350 cells/μL, and had achieved 40%/year treatment rates among eligible individuals in all subgroups by 2015 (baseline scenario, table 1).[25] We simultaneously allocated additional resources for the targeted 'test and treat' intervention by prioritising specific subgroups.

To compare strategies (table 1), we first applied a ceiling on the additional resources available for the 'test and treat' programme, at one person-years of intervention per adult population in the concentrated scenario (using the 2010 population estimate in Belgaum). Additional resources were capped at 10 person-years of intervention per adult population in mixed and generalised scenarios (based on the 2010 population estimate in Kisumu and Lesotho), because of their higher HIV prevalence. These additional resources were restricted to the additional person-years on cART for patients who began treatment under the 'test and treat' programme and were sexually active, and excluded efforts required for routine HIV testing. Second, we assumed that there was no resource ceiling, and that a 'test and treat' programme could achieve six-monthly cART initiation rates in the targeted subgroup irrespective of CD4 cell count beyond the acute stage.

For all scenarios, we assumed that condom use across subgroups was sustained at 2010 levels (see web appendix), such that resources for a targeted 'test and treat' programme were not diverted from existing HIV prevention programmes. We linearly increased the person-years of additional interventions (under a resource cap), or the cART initiation rates (under no resource cap) over 5 years, with sustained levels thereafter.

The 'test and treat' intervention strategies included the following (table 1):

A. *Intervention directed by the long-term source of HIV transmission*: A 'test and treat' programme targeted to a subgroup based on the largest long-term transmission source, as calculated by the $PAF_{2010–2040}$. Baseline cART for CD4≤350 cells/μL is maintained for all subgroups.
B. *Intervention directed by the single-year distribution of newly acquired HIV infections*: A 'test and treat' programme targeted to the subgroup which incurred the largest burden of new HIV infections in 2010. Baseline cART for CD4≤350 cells/μL is maintained for all subgroups.

We assumed that programmes could not reliably differentiate between low-activity individuals whose main partners are also

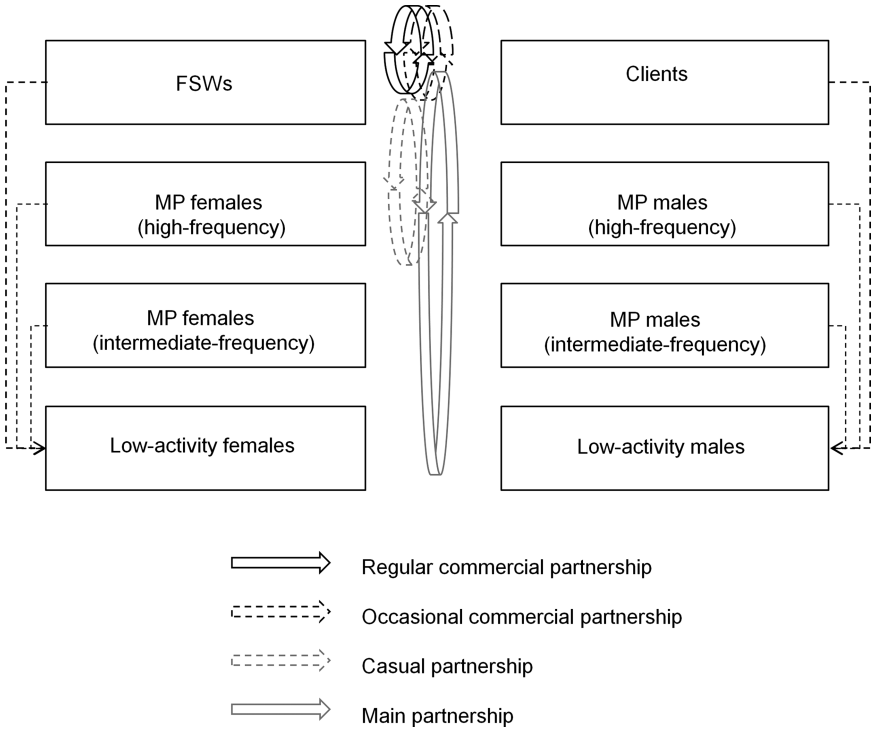

Figure 1 Schematic of the sexual structure of the dynamical model. The population is divided into different activity groups based on frequency of yearly partner change, and types of partnerships. There are four activity groups (female sex workers (FSWs) and clients, individuals who engage in multiple partnerships (MP) at a high frequency or intermediate frequency of yearly partner change rate, and currently low-activity individuals). There are four types of partnerships: commercial (occasional or regular), casual, or main. Individuals who engage in high-risk sex (commercial or casual sex) cease high-risk activity and enter into the low-activity population reflecting a turnover in each of the high-risk groups (black dashed lines).

low-activity, from low-activity individuals whose main partners engage in high-risk sex. Thus, if the low-activity subgroup was prioritised for the 'test and treat' programme, then all 'low-activity' individuals (including low-activity main partners of high-risk individuals) were included.

Intervention impact was measured as the cumulative fraction of discounted HIV infections averted in the total population compared with the baseline scenario (table 1), where the number of infections averted was discounted at a rate of 5% per year. Additional details are provided in the web appendix.

RESULTS

Distribution of newly acquired HIV infections versus source of HIV transmission

Figure 2 depicts the distribution of newly acquired HIV infections in 2010 ($DI_{2010–2011}$), and estimates of the source of HIV transmission ($PAF_{1980–2010}$, $PAF_{2010–2011}$, and $PAF_{2010–2040}$) along subgroups. In all regions, the $DI_{2010–2011}$ underestimated the cumulative fraction of HIV infections that were due to high-risk sex (commercial sex or multiple partnerships) between 1980 and 2010 (figure 2A,D,G,H).

The $DI_{2010–2011}$ was similar to the $PAF_{2010–2011}$ of high-risk sex and sex within low-activity partnerships. Hence, over a short (1 year) time-frame, the sources of HIV transmission and the distribution of HIV infections are similar (when estimated by the same model). The estimates are similar because the time-frame is too short for a 'chain reaction' of secondary transmitted events to create a difference between where infections originate and where they manifest.

In 2010, most new HIV infections were acquired in the low-activity group ($DI_{2010–2011}$; figure 2C,F,I). The $DI_{2010–2011}$ and the $PAF_{2010–2011}$ both underestimated the fraction of HIV infections between 2010 and 2040 that would result from high-risk sex. The difference between the HIV distribution (or the

Table 1 Illustrative intervention strategies implemented in 2010

Strategy	Interventions	Subgroup targeted for the 'test and treat' programme	ART coverage of targeted subgroup in 2015*	
			Under a finite resource cap %	No resource cap %
Baseline scenario	cART initiated at 0.4 per capita per year when CD4 ≤350 cells/μL (all subgroups)	N/A	N/A	N/A
Directed by largest source of HIV transmission ($PAF_{2010–2040}$)	cART initiated at 0.4 per capita per year when CD4 ≤350 cells/μL (all subgroups), and targeted cART as a 'test and treat' programme	FSWs and clients (concentrated, mixed) individuals in multiple partnerships (generalised)	concentrated: 95 mixed: 98 generalised: 97	concentrated:90 mixed: 82 generalised: 88
Directed by largest distribution of newly acquired HIV infections ($DI_{2010–2011}$)	cART initiated at 0.4 per capita per year when CD4 ≤350 cells/μL (all subgroups), and targeted cART as a 'test and treat' programme	low-activity group (all scenarios)	concentrated: 78 generalised: 71 mixed: 74	concentrated: 90 generalised: 88 mixed: 89

*Coverage refers to all HIV-infected individuals, and includes those with CD4 ≤350 cells/μL who were initiated on cART as per the baseline scenario (separate from the 'test and treat' programme). Note that cART coverage varies over time in all scenarios.
FSW, female sex worker; PAF, population attributable fraction; cART, combination antiretroviral treatment; N/A, not applicable.

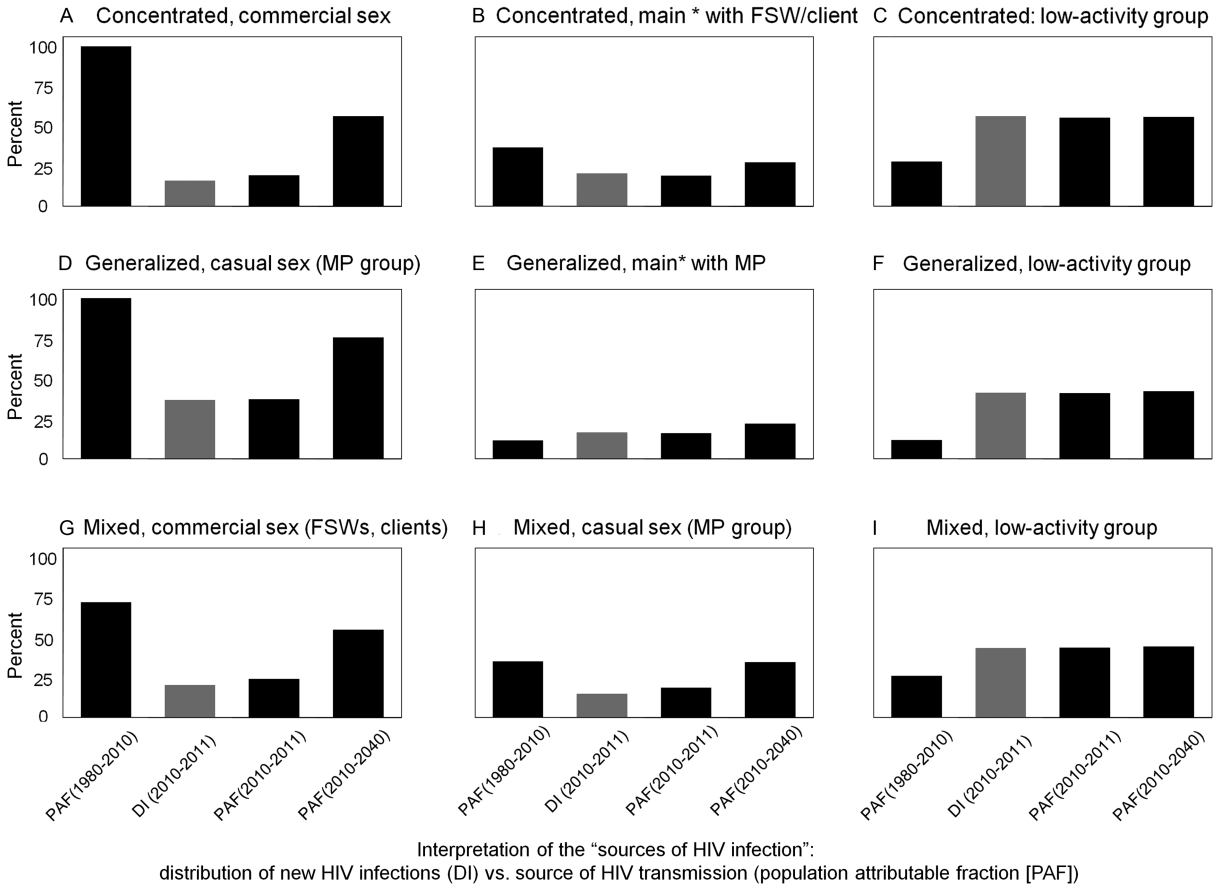

Figure 2 Single-year distribution of newly acquired HIV infections (DI), and cumulative population attributable fraction (PAF) over different time periods, in the concentrated (A–C), generalised (D–F), and mixed (G–I) epidemics. Most HIV transmission between 1980 and 2010 was due to commercial sex in the concentrated (A) and mixed scenarios (G). In the generalised scenario, HIV transmission between 1980 and 2010 was primarily due to casual sex (D). However, in 2010, the distribution of new HIV infections was greatest in the low-activity groups ($DI_{2010–2011}$) in all three regions (C,F,I). Over the subsequent 30 years, the cumulative $PAF_{2010–2040}$ was largest for commercial sex (concentrated, mixed) and casual sex (generalised). In the long term, HIV transmission from high-risk sex (commercial or casual sex) was underestimated by the distribution of HIV infection ($DI_{2010–2011}$) in the corresponding high-risk groups (FSWs and clients, or MP group). FSW (female sex worker); MP (multiple partnerships). *Low-activity individuals in a main partnership with high-risk individuals.

$PAF_{2010–2011}$) and cumulative $PAF_{2010–2040}$ of corresponding subgroups was primarily due to indirect (or secondary) transmitted events. As a result, the discrepancy was most pronounced for high-risk groups and increased over time. In all three scenarios, the contribution of high-risk sex increased over time, and high-risk sex was found to be the largest source of HIV transmission over the subsequent 30 years (figure 2A,D,G,H).

Intervention impact

Figure 3 depicts the potential impact of a targeted cART 'test and treat' intervention under equivalent resources. In the three illustrative scenarios, a 'test and treat' programme targeted to a high-risk group (based on the largest long-term source of HIV transmission, $PAF_{2010–2040}$) achieved a larger intervention impact, compared with the same intervention targeted to the low-activity group (based on the largest burden of newly acquired HIV infections). This was partly due to greater coverage of high-risk groups under an equivalent resource cap when the 'test and treat' programme was prioritised to the largest transmission source. Online supplementary figure A5 depicts the potential impact of targeting a cART 'test and treat' intervention without a resource cap. With 'infinite' resources, targeting the low-activity group achieves a larger impact in the short-term. However, even after discounting the value of future infections averted, the long-term impact is larger when this intervention is focused on the largest long-term transmission source.

DISCUSSION

During the strategic planning phase of Programme Science, decision makers use information on the source of regional HIV infections to design HIV prevention programmes.[5 17] This study illustrates the importance of distinguishing between the two interpretations of the 'source of HIV infections'. The distribution of newly acquired HIV infections will not always identify the source of HIV transmission, particularly in the long term. In practice, we commonly estimate 'sources of HIV infections' from a single-year distribution of new HIV infections using the static MOT model.[11 17] Interpreting the 'source of HIV infections' as the single-year distribution of new HIV infections, rather than the long-term transmission source, could potentially divert resources and attention away from prioritising high-risk groups.[11 26] Thus, the long-term impact of HIV prevention programmes is expected to vary depending on which interpretation informs prevention strategies. This work illustrates how an equivalent cART-based intervention could potentially achieve a larger impact when the transmission source, based on the $PAF_{2010–2040}$, directs the allocation of finite resources.

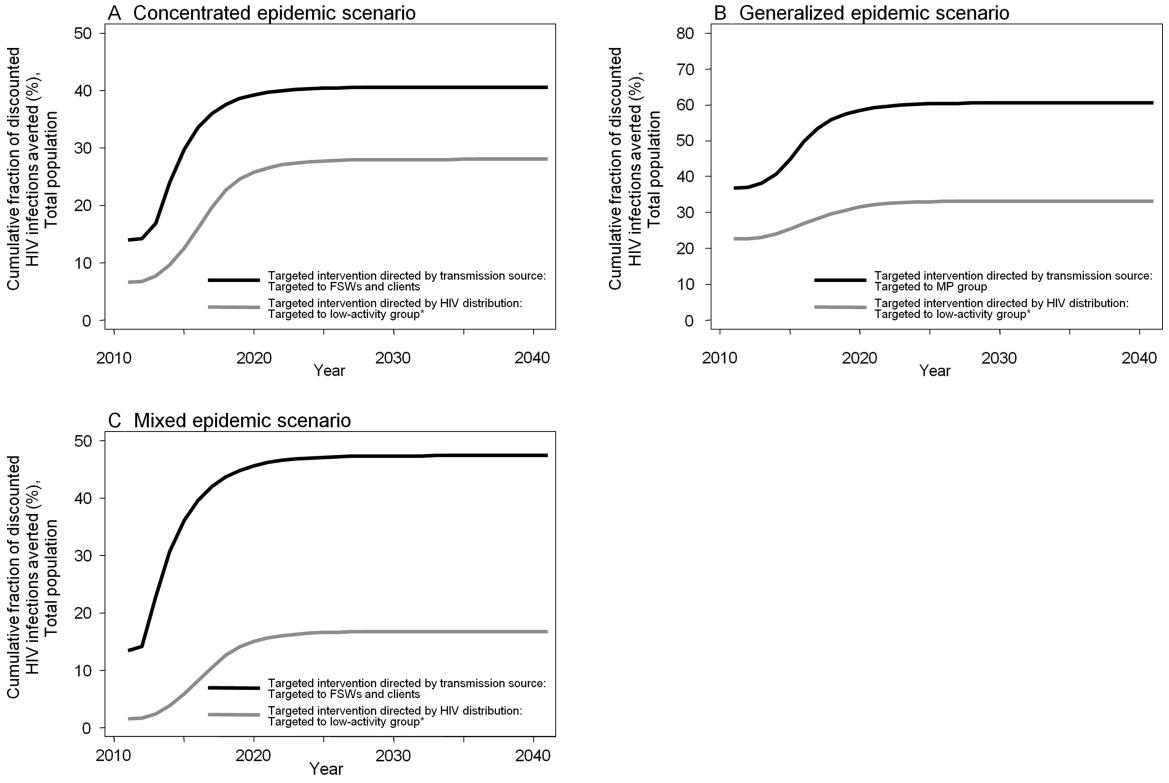

Figure 3 Fraction of discounted HIV infections averted in the total population under finite resources, following a combination antiretroviral treatment (cART) intervention guided by the largest long-term source of HIV transmission versus the largest distribution of HIV infections in 2010, in a concentrated (A), generalised (B), and mixed (C) epidemic. The source of HIV transmission was based on the cumulative population attributable fraction between 2010 and 2040. The intervention (cART initiated after acute-stage HIV, as a 'test and treat' programme), was scaled up over 5 years starting in 2010, under a fixed person-years of intervention (resource cap). Both strategies assumed that at baseline, antiretroviral treatment was also initiated at CD4 ≤350 cells/μL for all subgroups, scaled up to a yearly 0.4 per capita treatment initiation rate by 2015. FSW (female sex worker); MP (multiple partnership group). *Includes low-activity individuals in a main partnership with high-risk individuals. HIV infections averted in the total population were discounted at 5%/year.

The PAF of a given partnerships type is equivalent to the potential impact of ceasing all transmission within that partnership (ie, a 100% efficacious intervention). Therefore, not surprisingly, interventions targeted to the largest long-term transmission source resulted in the largest long-term impact in our illustrative scenarios—particularly when resources were capped, and despite a preference for short-term benefits (ie, discounting into the future). The translation of the PAF into intervention impact in HIV epidemics has been previously demonstrated in settings like Benin and India.[6–8] Similarly, the expected short-term benefits should be greater if interventions are targeted to the largest short-term source of transmission, and hence, the largest fraction of newly acquired HIV infections. In this study, the short-term benefit of a distribution-directed strategy was evident when resources were unlimited. However, the long-term impact of targeting high-risk groups remained larger even after discounting the future value of infections averted.

The findings have three main policy implications for HIV prevention, particularly for the interpretation and application of the widely used MOT model. First, we suggest that in order to avoid confusion and mistranslation, MOT results should be explicitly differentiated from the 'source of HIV transmission' in policy reports. In the context of HIV prevention, the source of HIV transmission should reflect the number or fraction of HIV infections that could be averted with a source-specific intervention. Precise labelling and reporting may avoid translation of MOT predictions into less effective HIV prevention policies.[16] While recommendations exist on how to perform the MOT for prevention planning (minimum data requirements, sensitivity analysis, more representative sexual structures),[13 16 27] there are no existing guidelines on reporting standards or how to translate MOT results into HIV prevention policies.[13] Second, appropriate (and validated) tools for estimating and identifying different sources of HIV transmission (in the short term and long term) are needed. Region-specific, calibrated, dynamical models are one such tool.[28] Alternate tools which do not depend on dynamical models have been suggested,[16] and are undergoing testing and validation. Third, further work is required to test and validate how we could best use estimates of the distribution of HIV infections for strategic decision making in the context of HIV prevention. Such work could help guide end-users of the MOT, so that estimates of HIV distribution are translated clearly, and used appropriately, in the design of HIV prevention programmes.

The aim of this study was to illustrate the difference between the distribution of newly acquired HIV infections and the sources of HIV transmission, and how this difference could translate into intervention impact. We used a dynamical model to generate synthetic epidemics and explore this difference. In practice, the MOT model uses the same data used here to estimate the distribution of newly acquired HIV infections, and one of its advantages is that the model is simple to use. Results from the MOT model, as with any epidemic model (dynamic or otherwise) depend on the same readily available input data. That is, model estimates of the distribution of newly acquired

HIV infections and the sources of transmission (short term and long term), depend on the same data that is currently available. Yet, an inherent limitation of long-term estimates is that they do not account for future changes that could alter long-term projections.

We restricted the intervention to cART under a 'test and treat' strategy to enable a fair comparison across targeted subgroups, and under highly optimistic coverage. In practice, cART-based interventions are allocated under an assumption that they will achieve equal coverage across the population, although targeted strategies are now being considered.[29] Intervention impact from the distribution-directed targeted strategy reflects scenarios where high-risk groups are not reached by universal 'test and treat' programmes (even if cART for CD4 ≤350 cells/μL is equal across subgroups). We assumed that the resources required to 'test and treat' across subgroups were equivalent, but reaching high-risk groups could be more difficult, costly and resource-intensive. Conversely, in countries where targeted condom-based and behavioural intervention programmes for high-risk groups (such as FSWs and clients) are already in place,[30] a targeted 'test and treat' strategy may require less effort, especially if FSWs and clients routinely (and frequently) receive HIV testing via the condom-based programme.[31] Our examination was restricted to heterosexual HIV transmission. However, the general insights are expected to be applicable for epidemics fuelled or sustained by high-risk sex among men who have sex with men, or people who inject drugs. This study only examined a 'test and treat' intervention which reaches individuals already infected with HIV. While we did not explore interventions aimed at reaching uninfected individuals, the findings are expected to be similar under a finite resource cap because there are fewer high-risk individuals to reach and high-risk sex contributes more to long-term transmission. The findings may be different with no resource restriction. An important next step will be an examination of whether, under 'infinite resources', a short-term distribution or long-term transmission approach varies by intervention type, different discounting rates, and whether this distinction will be important if comprehensive HIV prevention packages always reach high-risk groups. Finally, an important limitation of this work is that it is illustrative, and is not meant to be predictive for a given region. We therefore did not conduct an extensive uncertainty analysis. When making decisions based on predictive modelling, uncertainties surrounding input data and the cost effectiveness of different strategies remain important considerations.

CONCLUSIONS

The potential impact of HIV prevention strategies will vary depending on whether they are directed by the long-term transmission source or by the distribution of newly acquired HIV infections. Interpreting the distribution of new HIV infections as the source of HIV infections could potentially misdirect resources for HIV prevention. Syntheses of MOT studies and policy documents should explicitly report MOT estimates as the distribution of HIV infections, and use caution when applying the term 'source of HIV infections'. If this non-specific term is used, reports should explicitly differentiate the distribution of new HIV infections from the short-term and long-term sources of HIV transmission in the interpretation of MOT results. A validated approach for using the distribution of newly acquired HIV infections to guide HIV prevention is needed.

Key messages

- The 'source of HIV infections' has been referred to as the distribution of newly acquired HIV infections, and the source of HIV transmission.
- The distribution of newly acquired HIV infections does not necessarily reflect the long-term source of HIV transmission.
- The potential impact of HIV prevention may vary depending on which interpretation of the 'source of HIV infections' is used to prioritise intervention efforts.
- The Modes of Transmission model estimates the distribution of newly acquired HIV infections, which should not be misinterpreted as the source of HIV transmission.

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Contributors All authors conceived of the study, interpreted the findings, and critically reviewed the manuscript. SM designed and developed the model, performed the analysis, and wrote the manuscript. MP and M-CB contributed to model development and critical review of the methods.

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