The disconnect between individual-level and population-level HIV prevention benefits of antiretroviral treatment

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In 2019, the HIV pandemic is growing and soon over 40 million people will be living with HIV. Effective population-based approaches to decrease HIV incidence are as relevant as ever given modest reductions observed over the past decade. Treatment as prevention is often heralded as the path to improve HIV outcomes and to reduce HIV incidence. Although treatment of an individual does eliminate onward transmission to serodifferent partners (undetectable=untransmittable or U=U), population-level observational and experimental data have not shown a similar effect with scale-up of treatment on reducing HIV incidence. This disconnect might be the result of little attention given to heterogeneous HIV acquisition and transmission risks that exist in people at risk for and living with HIV, even in the most broadly generalised epidemics. Available data suggest that HIV treatment is treatment, HIV prevention is prevention, and specificity of HIV treatment approaches towards people at highest risk of onward transmission drives the intersection between the two. All people living with HIV deserve HIV treatment, but both more accurately estimating and optimising the potential HIV prevention effects of universal treatment approaches necessitates understanding who is being supported with treatment rather than a focus on treatment targets such as 90-90-90 or 95-95-95.

Given the consistent data supporting U=U, treatment as prevention at the population level was expected to reduce HIV incidence substantially through reductions in onward transmissions at the population level. Although the data on U=U at the individual level are clear, whether treatment has decreased HIV incidence at the population level in proportion to increases in coverage of effective ART remains less clear. However, a linear or dose-response effect between treatment and incidence reductions would require all people living with HIV to have similar risks of onward transmission if they were not virally suppressed. Data on the heterogeneities that exist in different setting in onward HIV transmission risks in the context of different sexual networks challenge the dose-response effects of treatment as prevention. These data are further contextualised by rich literature in disparities and inequities research showing that, often secondary to structural determinants, neither treatment nor viral suppression is equal among populations living with HIV. Three large-scale cluster randomised controlled trials did not show incidence declines attributable to universal access to ART. These experimental data complement observational data showing sustained HIV incidence despite increased HIV treatment across municipalities, regions, and nationally in countries across income levels.

Here, we synthesise data supporting U=U for serodifferent couples, treatment as prevention at the population level, and potential reasons for the disconnect in observed effect between these two intervention strategies.

Unequivocal data supporting benefits of U=U for individuals and serodifferent couples

A series of randomised controlled trials showed that early ART initiation can have immediate and clinically meaningful individual-level benefits, including reductions in morbidity and mortality among people living with HIV and reductions in the rate of linked partner transmissions.
cohort study, serodifferent gay male couples were recruited from Australia, Brazil, and Thailand. Between 2012 and 2016, 343 couples had at least one follow-up visit, with a total of 16,800 condomless anal intercourse acts and 258 (75%) HIV-positive partners having viral loads below 200 copies per mL. No linked transmissions were observed. In the prospective, observational PARTNER study, 1,166 serodifferent heterosexual and male homosexual couples who reported condomless sexual activity between 2010 and 2014 were enrolled. Inclusion criteria included that the partner living with HIV was to be virally suppressed for the couple to be eligible. Male homosexual couples reported approximately 22,000 condomless sex acts and heterosexual couples reported about 36,000. Similarly, no phylogenetically linked new infections were observed. Results of the second phase of the PARTNER study were recently published. No linked transmissions were found between homosexual couples for nearly 77,000 condomless anal intercourse acts, in which the partner living with HIV was virally suppressed. Importantly, these prevention benefits will only be sustained in the context of programmes that address long-term treatment needs for people living with HIV. Recent data from the USA suggest that achieving sustained viral suppression, especially among the most marginalised communities living with HIV, might be a challenge yet to be overcome. Taken together, the observational data combined with the efficacy data from the HPTN 052 trial do reinforce the veracity of U=U and the efficacy for treatment to prevent HIV transmission in the context of serodifferent HIV partnerships.

Figure 1: Experimental studies evaluating HIV treatment outcomes at the population level and individual level

Details of studies and comparisons are given in the main text. Blue lines represent studies with population-level outcomes and red lines are studies with individual-level outcomes. aHR=adjusted hazard ratio. aRR=risk ratio. IRR=incidence rate ratio. ART=antiretroviral therapy.
Treatment as prevention as a population-based approach

As of 2019, three fully powered cluster randomised trials have measured the effect of universal testing and treatment on population-level reductions in HIV incidence (figure 1). The ANRS 12249 TasP study16–18 was a cluster randomised trial designed to evaluate the effect of early ART, irrespective of CD4 count, on HIV incidence in specific clusters in northern KwaZulu-Natal, South Africa. Communities were randomly assigned either to immediate offer of ART or to standard of care in South Africa at the time (ART initiation at CD4 count ≤350 cells per µL or WHO stage 3 or 4 until December, 2014, then ≤500 cells per µL from January, 2015), and no differences were observed in population-level HIV incidence by group (adjusted HR 1·01, 95% CI 0·87–1·17).14,15 In the SEARCH study,16 32 communities in Kenya and Uganda were randomly assigned to receive universal ART with a multidisease model, which included patient-centred interventions related to hypertension, diabetes, tuberculosis, and HIV. The intervention reduced annual tuberculosis incidence and improved population HIV viral suppression.16 Although HIV incidence declined across all observed communities, no difference was observed in 3-year cumulative HIV incidence between groups (adjusted risk ratio 0·95, 95% CI 0·77–1·17).16 Conclusions for non-significance associated with treatment included that new infections were coming from outside the community, outbreaks of acute infection, and the small subset of the population living with HIV who were unsuppressed.16 Results from HPTN 071,17 also known as PopART, were presented at the Conference on Retroviruses and Opportunistic Infections 2019. The study17 was designed as a community-randomised trial among 21 urban communities across Zambia and South Africa. Communities were randomly assigned to three groups between 2013 and 2018: group A (full PopART intervention, which was a combination prevention and treatment intervention, and included immediate ART for all individuals with HIV irrespective of CD4 count), group B (PopART prevention intervention with ART per local guidelines), and group C (standard of care).17 Incidence reductions were observed between the prevention only (group B) and standard of care (adjusted incidence rate ratio 0·70, 95% CI 0·55–0·88).17 However, similar to the SEARCH study and ANRS 12249, HPTN 071 showed no reduction in incidence when comparing the intervention group that included universal treatment (group A) with standard of care (0·93, 0·74–1·18).17 Low rates of linkage to care were seen across the study groups, adding to the evidence that treatment interventions are challenging to implement perfectly in trial settings; challenges that would be amplified in real-world programme settings with more restricted per person intervention budgets than those in trials.

In 2016, the HIV Prevention Trials Network released a statement in response to null results released by the ANRS 12249 investigators at the International AIDS Conference in Durban in 2016.19 Specifically, HPTN 071 was to differ from ANRS 12249 in three important ways: first, HPTN 071 would take place in urban communities in which the hypothesis was that treatment as prevention would be more effective than in the rural setting of northern KwaZulu-Natal; second, HPTN 071 would be able to assess the full effect of the combination HIV-prevention package; and third, HPTN 071 would have a longer follow-up period in which to assess the intervention’s effect on incidence.17 That these differences did not change the outcome is now clear with the release of the HPTN 071 study results. The intervention did not have differential effect in urban communities compared with rural communities, and the longer follow-up period and larger sample size than in ANRS 12249 did not change HIV incidence outcomes. HPTN 071© and

![Figure 2: Numbers of new HIV infections and HIV treatment coverage in Botswana, Rwanda, and Ethiopia 2010-17. ART=antiretroviral therapy.](image-url)
SEARCH also provided insight into the potential for HIV prevention strategies to reduce HIV incidence. Group B of HPTN 071 was the most effective, and overall incidence was reduced in SEARCH but not more so with universal access to ART. These data complement the results of the Ya Tsie trial in Botswana released in 2018. Ya Tsie was a pair-matched community randomised trial of nearly 9000 individuals from communities covering about 10% of the population, and reported a significant reduction in HIV incidence of at least 30% (incidence ratio 0.65, 95% CI 0.46–0.90) associated with the delivery of a combination HIV prevention and treatment programme. The intervention included home-based and mobile testing and linkage-to-care support, with treatment guidelines changing in both groups of the trial over time, towards a treat all approach. Taken together, these studies reinforce the fundamental usefulness of HIV prevention in reducing population-level HIV incidence.

Observational data from a range of settings provide consistent conclusions across epidemic and income settings. Estimates by UNAIDS for Botswana, Ethiopia, and Rwanda show a marked increase in HIV treatment coverage since 2010, but a plateau in new infections (figure 2). Botswana, for example, has made substantial improvements in treatment coverage, going from 45% of those living with HIV on treatment in 2010 to just over 80% as of 2017. During the same period, however, Botswana has seen a plateau, or even a small increase in overall incidence was reduced in SEARCH but not more so with universal access to ART. These data complement the results of the Ya Tsie trial in Botswana released in 2018. Ya Tsie was a pair-matched community randomised trial of nearly 9000 individuals from communities covering about 10% of the population, and reported a significant reduction in HIV incidence of at least 30% (incidence ratio 0.65, 95% CI 0.46–0.90) associated with the delivery of a combination HIV prevention and treatment programme. The intervention included home-based and mobile testing and linkage-to-care support, with treatment guidelines changing in both groups of the trial over time, towards a treat all approach. Taken together, these studies reinforce the fundamental usefulness of HIV prevention in reducing population-level HIV incidence.

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**Importance of understanding heterogeneity of risks**

Early modelling results projected the comparative benefits of scaling up universal and early ART for all people living with HIV. However, relying on foundational work of epidemic theory might be informative for estimating the potential effect of large-scale HIV treatment programmes moving forward. Core-group theory posits that prevention gaps among the relatively few who are most at risk of acquisition and transmission can sustain an epidemic. Implications of this epidemic theory are two fold when considering treatment as prevention. First, viral suppression within a serodifferent partnership can avert an infection in a direct partner, but also leads to indirect benefits to the partners’ partners (and any onward serial partners). These indirect benefits stem from the way prevention among a relatively few can protect many along a potential transmission chain—especially if those few are at the highest risk of acquisition and transmission. Intersecting individual and structural determinants underlie heterogeneity in the risks of acquisition and transmission, including through biology (eg, greater mucosal tearing for anal vs vaginal intercourse or differing cervical surface area exposure for younger vs older women) or structural determinants driving disparities in intervention uptake. This heterogeneity can create pockets of residual transmission that might break a priori predictions of intervention effect. Acquisition risks (susceptibility) and onward transmission risks are intertwined but they are not synonymous, nor are they static: onward transmission risk, in particular, is dynamic over the sexual life course of individuals. Thus, for an onward prevention benefit associated with HIV treatment, the people living with HIV receiving treatment must still be at risk for onward HIV transmission but can no longer transmit because they are virally suppressed. The intervention-specific corollary to duration of time experiencing high onward transmission risks is the person time of viraemia before viral suppression, often stemming from structural barriers to engagement in HIV testing and ART initiation.

Historically, most HIV transmission models of universal test and treat in high-prevalence epidemics, such as that in South Africa, included some heterogeneity in risk between a few groups (usually high, medium, and low). However, these early models of high prevalence settings done before experimental treatment studies rarely included a focus on key populations because they are a smaller population and were assumed to be less relevant in generalised epidemic settings. Thus, heterogeneity has traditionally been collapsed within the number of risk strata incorporated into these models. Heterogeneity has been condensed further via assumptions about equal reach and access of interventions among populations with different transmission risks. For example, pre-trial modelling of the HPTN 071 study simulated heterogenous HIV transmission and anticipated over 60% reduction in HIV incidence in group A (home-based voluntary testing and counselling with universal ART) relative to group C (control group). The model included three levels of heterogeneity drawing on the available data at the time from demographic health surveys: low risk (on average one partner every 10 years), medium risk (on average one partner per year), and high risk (more than one partner per year). High-risk sexual practices were calibrated to overall HIV prevalence in the total population,
leading to 1.8–2.0 partners per year among a high-risk group that comprised 18–23% of males and females. Thus, the high-risk group subsumed the subset of women engaged in sex work (whose number of partners in South Africa range between four and 19 per day) and who comprised 0–5–2.0% of the adult female population in South Africa. Importantly, the intervention was also assumed to reach each risk group equally. Although the pre-trial modelling did not include key populations, the sensitivity analyses gave prescient insight hinting at the importance of transmissions via sex with a subset of a population that did not receive the intervention. In this case, the anticipated effect of group A and group B was reduced when the proportion of sex acts with individuals outside the community went from 0% to 10%, and especially when the number of partners increased in the community as a whole after the intervention started. Given the empirical data of sexual practices, engagement in HIV prevention and treatment, and incidences of HIV infections collected in the PopART study, modelling after the trial of the HIV epidemic in the PopART study sites and its interventions might provide crucial insights into the role that heterogeneity has in explaining the absence of population-level effectiveness attributable to universal testing and treatment alone.

Conclusion
The tools to end the HIV pandemic have existed for several years. But in 2019, the HIV pandemic is not over and, indeed, it is still growing and will likely do so for many years. The population-level treatment as prevention trials were well designed, well executed, and answered key questions regarding the population-level prevention benefits of universal HIV treatment. Their findings should not be discounted, but rather, they should be integrated into our understanding of the underlying HIV transmission dynamics powering the HIV pandemic. Successful application of tools to end the HIV pandemic necessitates a thorough understanding of HIV acquisition and onward transmission risks and effective implementation to support sustained viral suppression among people living with HIV and to prevent HIV acquisition among those people at risk of infection. The latter is crucial as treatment alone, as shown by both experimental and observational data, remains necessary but insufficient without primary prevention.

The expectation of one to one reduction in onward HIV transmission is only applicable (or restricted) to fixed serodifferent partnerships that are mutually monogamous over time. Thus, U=U is additive across such partnerships over time. If considerable heterogeneity exists in onward transmission risks (eg, 30% of onward transmissions stem from the unmet prevention needs of 2% of the population) then equal distribution of treatment might actually reinforce disparities and continue to underserve those people at highest risk of onward HIV transmission. The assumption challenges the usefulness of targets such as 90-90-90 and 95-95-95, which were designed with a focus on coverage of all reproductive-age results, regardless of risk, in specific geographical areas. However, results from the previously mentioned trials are consistent with core epidemic theory in that, from an HIV prevention perspective, knowledge of for whom we are providing treatment is more relevant than for how many people. A model leveraging data from southern Africa supported this perspective by showing that if those people most likely to be left behind are also the same people who are most at risk of onward transmission, projections could underestimate the potential effect of achieving and surpassing UNAIDS treatment goals. Implementation strategies of HIV treatment focused on addressing those most marginalised will have key differences compared with programmes and resources focused only on treatment numbers. The HIV community often considers the implementation strategies for HIV treatment as treatment and HIV treatment as prevention to be the same. However, the disconnect between population-level improvements in treatment coverage and viral suppression and HIV incidence suggests the need for a separate set of considerations for treatment as prevention. In this frame, we leverage the concept of patient-centred medicine to suggest that maximising the prevention effect of HIV treatment programmes to support HIV prevention outcomes necessitates understanding the individuals that we are trying to support in treatment in contrast to treating them as a general population.

The three cluster randomised controlled trials evaluating treatment as prevention that we described in this Viewpoint are unlikely to be surpassed in size or comprehensiveness. Integrating these experimental data into a large body of observational data from around the world suggest that HIV treatment is treatment, HIV prevention is prevention, and specificity of HIV prevention and treatment approaches towards those at highest risk of onward HIV transmission drives the intersection between the two. All people living with HIV deserve HIV treatment, but both accurately estimating and optimising the potential HIV prevention effects of universal treatment approaches necessitates understanding who is being supported with treatment rather than just how many.

Contributors
SB developed the concept for this Viewpoint and led the writing of the manuscript. SB and AR led the response to peer-review. AR managed the review process to inform the Viewpoint and drafting specific sections. SM led the modelling section with EG providing key inputs to the implementation components, with GM on the policy implications, and with PS, DD, NP-M, and HM providing overview and drafting of key sections.

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References


49 Knight J, Ma H, Baral S, et al. Who is left in 10-10-10? Importance of reaching key populations with the HIV cascade. CROI 2019; Seattle, WA, USA; March 4–7, 2019.