

Undetectable viral load and HIV transmission dynamics on an individual and population level: Where next in the global HIV response?

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Abstract

Purpose of review: To examine recent literature on the efficacy and effectiveness of HIV treatment in preventing HIV transmission through sexual exposure, at both an individual and at a population level.

Recent findings: Two recent studies on the individual-level efficacy of treatment as prevention (TasP) have added to the now conclusive evidence that HIV cannot be transmitted sexually when the virus is suppressed. However, four large cluster-randomised population-level trials on universal HIV testing and treatment in Africa have not delivered the expected impact in reducing HIV incidence at a population-level. Two of these trials showed no differences in HIV incidence between the intervention and control arms, one demonstrated a nonsignificant lower incidence in the intervention arm, and the fourth trial found a reduction between the communities receiving a combination prevention package and the control arm, but no difference between the immediate treatment plus the prevention package and the control arm. Factors contributing to the disconnect between individual high-level efficacy and population-level effectiveness of TasP include undiagnosed infection, delays in linkage to care, challenges in retention and adherence to ART, time between ART initiation and viral suppression, and stigma and discrimination.

Summary: Suppressive ART renders people living with HIV sexually non-infectious. However, epidemic control is unlikely to be achieved by TasP alone.

Key words: HIV treatment as prevention, universal test and treat, HIV prevention, viral suppression, undetectable viral load

Introduction

'Treatment as prevention' (TasP) refers to the HIV prevention strategy of treating HIV-positive individuals with suppressive antiretroviral therapy (ART) to prevent onward HIV transmission to HIV-negative sexual partners (1). At the population level, this approach is also known as 'test and treat' (2) or 'universal testing and treatment (UTT)' (3), referring to the scale-up of voluntary HIV testing and offering immediate ART to those diagnosed (4). This concept has more recently gained attention as 'Undetectable = Untransmittable' ('U=U'), after the launch of a global campaign in 2016 to galvanise educational efforts around TasP and fight HIV-related stigma (5). The U=U global consensus statement has to date been endorsed by over 900 organisations (6). TasP underpins the global 2014 UNAIDS 90-90-90 targets, which aim, by 2020, to have 90% of all people living with HIV (PLWH) diagnosed, 90% of all diagnosed PLWH on ART, and 90% of all PLWH on ART virally suppressed (7).

The purpose of this review is to examine recent literature on the efficacy and effectiveness of HIV treatment in preventing HIV transmission through sexual exposure, at both an individual and at a population level.

Individual-level efficacy of ART to prevent the sexual transmission of HIV

Evidence on the efficacy of ART to prevent sexual HIV transmission on an individual level has been building for many years. The evidence base has reached such levels over the past two years that it is now accepted that the risk of sexual transmission of HIV in the context of suppressive ART is effectively zero. This is all the more remarkable as science is generally

unable to prove a negative. It is helpful for context to briefly review the historical evidence and then the recent definitive studies in this area.

In the 2000s, observational studies among heterosexual serodifferent couples indicated there was a gradient of risk between viral load and HIV transmission (8, 9). In 2008, the 'Swiss Statement', issued in response to criminalisation of HIV in Switzerland, increased the profile of TasP, stating that PLWH on suppressive ART for six months or more, engaged in care, and without other STIs were sexually non-infectious (10). However, concerns remained due to lack of precise estimates for risk, with no data at all for anal sex in men who have sex with men (MSM) (14) and concerns around compartmentalisation of genital tract viral loads due to variable ART penetration (11).

The landmark study in the field was the *HPTN 052* randomised clinical trial in predominantly heterosexual serodifferent couples. Randomisation to early or deferred ART was stopped early by the Data Safety and Monitoring Board in 2011, as results indicated a 96% reduction in HIV transmission risk in couples where the HIV-positive partner began ART immediately, compared to delaying until CD4 counts fell below country-specific guidelines (12). In 2016, the final results showed an overall 93% reduction in HIV transmission risk in the early ART arm, with no transmissions in serodifferent couples with HIV viral load <200 copies per mL (13, 14). With only 37 MSM couples (2%) in *HPTN 052*, there remained no data for MSM. Thus, concerns remained that the benefits of TasP for MSM were highly plausible, but not certain (15). Self-reported condom use was also high in *HPTN 052* and so reduction in risk with ART alone was uncertain.

To address these gaps, two observational cohort studies were established: the European-based study, *Partners of people on ART – a New Evaluation of the Risks (PARTNER)*, and the

Opposites Attract Study conducted in Australia, Brazil and Thailand (16-18). In 2016, *PARTNER* reported the first phase results in heterosexual and MSM serodifferent couples, showing zero phylogenetically-linked infections in 1,238 couple-years of follow-up (CYFU) and 58,213 reported acts of condomless intercourse. The overall upper limit of the 95% confidence interval (CI) around zero transmissions was 0.30 per 100 CYFU. In MSM couples, the upper confidence limit was twice that of heterosexual couples due to the lower number of MSM couples, so the study continued recruiting and following MSM couples until 2018 (18). Further evidence for MSM emerged in July 2018, when *Opposites Attract* reported zero phylogenetically-linked infections in 232 CYFU with 12,447 acts of condomless anal intercourse (CLAI) where HIV-positive partners were virally suppressed with no pre-exposure prophylaxis (PrEP) use in HIV-negative partners (19). The study reported an upper confidence limit of 1.59 per 100 couple-years in those reporting any CLAI. More recently in May 2019, *PARTNER* reported on its second phase in MSM couples only. The study accrued 1,593 eligible CYFU in MSM and 76,088 acts of CLAI among 782 eligible couples. There were no phylogenetically-linked transmissions, with upper confidence limits around the zero transmission rates of: 0.23 per 100 CYFU overall, 0.43 per 100 CYFU for receptive CLAI without ejaculation, and 0.57 per 100 CYFU for receptive CLAI with ejaculation (20). Thus, when combining both phases of *PARTNER* and *Opposites Attract*, there have been over 125,000 acts of condomless sex reported within heterosexual and MSM serodifferent couples and no phylogenetically-linked HIV transmissions. This provides the definitive evidence that risk of HIV transmission from an HIV-positive individual on suppressive ART through condomless sex is effectively zero regardless of sexual orientation. This is now commonly accepted and the U=U concept underpins global responses to the HIV epidemic.

HIV can obviously also be transmitted through non-sexual routes, and the issue of whether U=U applies to other routes of transmission has been raised. However, although there is strong evidence of the dramatic impact of ART on reducing mother-to-child transmission (MTCT) (21), there have been cases of transmission in the context of fully suppressive ART in the mother including through breastfeeding (22, 23), indicating the risk in this context is not zero. There is much less evidence in people who inject drugs (PWID), and although it is likely that there is a highly significant reduction in transmission risk through intravenous drug use to HIV-negative injecting partners with suppressive ART (24), the evidence does not currently exist to give precise risk estimates.

Population-level effectiveness of TasP to prevent sexual HIV transmission

Despite the very strong evidence of zero risk on an individual basis, the population-level effectiveness of TasP to prevent sexual HIV transmission is less clear. Mathematical modelling from 2009 suggested that annual voluntary HIV testing and immediate ART could eliminate HIV transmission in a generalised epidemic setting by 2020 (25). However, despite immense increases in ART coverage and uptake worldwide (26), no setting has seen the kinds of prevention gains predicted by such modelling. A recent analysis published in 2018 from New South Wales, Australia, found that although the UNAIDS 90-90-90 targets were met state-wide in 2016 (27), there was not a corresponding reduction in new HIV diagnoses until after rapid, largescale PrEP rollout in 2016 and 2017 (28). Similarly, data from Rwanda, Botswana and Ethiopia reported in 2019 demonstrated a substantial increase in ART coverage between 2010 to 2017, but a stable number of new HIV infections remained (29).

Of course, key limitations of any ecological study include the inability to support causal association and possibility of major confounding factors.

To address these limitations, several large-scale, well-designed cluster-randomised trials to assess the effect of universal testing and treatment on HIV incidence at a population level have been implemented since 2012; four such trials have recently reported results (Table 1). In 2018, the *Treatment as Prevention (TasP)* cluster-randomised trial (ANRS 12249) reported data from 22 communities in rural districts of KwaZulu-Natal, South Africa (30). Between 2012 and 2016, communities were randomly assigned to immediate ART or to standard of care (which changed over time as national ART guidelines were updated). Though the trial increased rates of HIV testing, overall viral suppression was low due to poor linkage to care, with no differences observed in population-level HIV incidence.

In 2019, three further trials reported results demonstrating varying levels of effectiveness of population-level TasP interventions (3, 31, 32). Between 2013 and 2017, the *Sustainable East Africa Research in Community Health (SEARCH)* trial randomly assigned 32 communities in Kenya and Uganda to either universal ART, within the context of patient-centred interventions related to several diseases, or to current standard ART access within multi-disease testing (33). After three years, population-level HIV viral suppression was higher in the intervention communities (79%) than in the control communities (68%), but HIV incidence decreased in all study communities with no observed difference between the two arms, possibly because near-universal ART eligibility was implemented in control communities soon after the start of the trial. The *Ya Tsie* trial in Botswana was a pair-matched, community-randomised trial randomly allocating 30 rural or periurban villages to either a multifaceted intervention (intensive HIV testing at baseline; ART initiation;

voluntary medical male circumcision [VMMC]) or to standard of care, from 2013 to 2018 (32). During the trial, universal ART became available in all communities, leading to a rise in ART coverage in control communities. Viral suppression was higher in the intervention communities than control communities (88% versus 83%), and although HIV incidence was 31% lower in the intervention arm (0.59 vs 0.92 per 100 person years), the result remained nonsignificant. Finally, the *HPTN 071* trial, known as *PopART*, randomised 21 communities in Zambia and South Africa to one of three groups between 2013 and 2018: Group A (full *PopART* combination prevention package including community-based universal HIV testing, VMMC, condom distribution, and education *plus* immediate ART); Group B (*PopART* combination prevention package with ART initiated as per local guidelines), or Group C (standard of care) (3). Local guidelines changed midway through the trial to universal ART access for all communities, eliminating the difference between Group A and B interventions. The proportion of PLWH who were virally suppressed was highest in the prevention intervention package plus immediate ART group (Group A) and lowest in the standard of care group (Group C). No reduction in HIV incidence was observed between Group A and Group C but a 30% reduction was observed in the combination prevention package only group (Group B) compared to Group C. This result was unexpected and was considered inconsistent with the observed viral suppression data. The authors conducted a post-hoc analysis combining Groups A and B, which showed a 20% reduction in incidence.

Factors impacting on TasP at the population-level

There are several potential explanations for why the population-level impact of TasP is not as effective as that seen in individual-level efficacy studies.

HIV testing and undiagnosed infection

HIV testing is critical to the success of TasP at the population-level. Testing is the gateway to linkage to care and ART initiation, and is crucial to reducing the time between HIV infection and diagnosis. Globally, it was estimated that 25% of PLWH were living with undiagnosed HIV infection at the end of 2017 (34). Stigma and the fear of stigma are associated with late presentation generally (35), and the prevalence of undiagnosed infection is often higher in more marginalised groups, such as migrants (36, 37). In addition, key population groups that are particularly vulnerable to HIV such as sex workers, PWID and MSM frequently lack adequate access to services. One reason for this globally is that in many countries such populations are often subject to punitive laws and policies that block an effective HIV response (38-40).

In settings with concentrated epidemics and high levels of testing and ART uptake in key populations, HIV transmission is increasingly being driven by undiagnosed infection. For example, a recent analysis from Australia demonstrated that undiagnosed infection accounted for 33% of new infections in 2004, increasing to 59% in 2015 (41). However, undiagnosed infection may contribute more than has been previously acknowledged even in generalised epidemics and lower ART uptake settings. In the cluster-randomised trials described above and in Table 1, the source person for infection may have been from outside of the trial areas or from the control communities and be exposed to less intensive HIV testing efforts (42). For example, 35% of infections in the *TasP* trial were estimated to be from individuals living outside the intervention communities (43). As noted in a recent editorial, community trials are unable to eliminate this confounding effect by using couple-

level phylogenetic analysis as utilised in the individual-level efficacy studies (42).

Furthermore, the logistics of reaching and testing every at-risk individual for HIV is a major challenge, as shown in the community trials, which were not able to diagnose 20-30% of PLWH (42).

It is also being increasingly recognised that there is a great deal of heterogeneity in HIV epidemics, including in generalised epidemic settings. Even in the context of high uptake of ART and viral suppression, pockets of residual transmission risk among those not connected to care can diminish the effects of interventions (29, 42). The cluster-randomised trials indicated that certain groups were harder to reach and thus under-represented in the interventions, such as men and younger people (3, 42). Furthermore, stigmatised key populations such as MSM and sex workers have often been ignored in larger-scale trials focusing on the general population (29, 44). In 2018, more than half of new infections were in key populations (45).

Modelling studies have identified substantial within-country heterogeneity in HIV prevalence and incidence, particularly in countries in sub-Saharan Africa (46). This has important implications for targeting resources and interventions to areas of greatest need, with geographically targeted prevention strategies proving more efficient in preventing new HIV infections than non-targeted interventions (47). In addition, advances in bioinformatics methods such as phylogenetics and phylodynamics coupled with the rapidly decreasing cost of gene sequencing, can provide important information about linked individuals within transmission clusters to direct prevention efforts. One cross-sectional household survey of randomly selected individuals aged 15–49 years in KwaZulu-Natal, South Africa undertook phylogenetic analysis in those found to be HIV-positive and the results suggested that men aged 25–40 years were the primary source of high rates of HIV acquisition in adolescent girls

and young women (15–25 years) (48). This has important implications for targeted prevention initiatives with rapid scale up of test and treatment, scale up of VMMC and the use of PrEP targeted specifically to girls aged 15–25 years in this region.

It is clear therefore that epidemics can be sustained even with high levels of HIV testing and linkage to care if those most at risk of HIV acquisition and onward transmission are not targeted.

Linkage, retention and adherence to ART

Once tested and diagnosed, there can be challenges in linking PLWH to appropriate care, retention in ART programs, and sustaining high enough adherence to achieve and maintain viral suppression. Newly-diagnosed PLWH are often lost-to-follow-up immediately after diagnosis, and there are often delays in linkage to care (42). Increased linkage to care has been associated with: same-day or rapid ART initiation, home-based or peer-led services, incentives, and intensified follow-up (49-52), while identified barriers have included stigma and discrimination, transportation costs, poverty or financial pressures (49, 53-55). Similarly, retention in ART programs and adherence to ART are major issues in many settings (5). At the individual-level, four of the eight linked transmissions in *HPTN 052* where the HIV-positive partner was on ART occurred after treatment failure, often years after ART initiation (56). It is estimated that over one-third of PLWH receiving ART globally do not achieve durable viral suppression (57). A recently published analysis of 2,054 PLWH in four African countries demonstrated relatively high levels of viraemia (19%), persistent viraemia (8%) and virologic failure (9%) among patients on ART for more than six months (58). Much

research has identified factors associated with lower retention and adherence, including ART stock-outs, clinic locations and capacity, available drug regimens, individual psychosocial factors, and health and HIV literacy (59-64). However, even in settings with universal access to free or affordable ART, high levels of stigma – either related to HIV or to membership of specific key populations – can be associated with challenges in retaining PLWH in care. For example, in August 2018, results were reported from an observational cohort of PLWH among key populations in four cities in Indonesia, showing very poor rates of retention in treatment and viral suppression, as well as high rates of loss-to-follow-up in those initiating ART (65). Young people often face particular challenges linking to care and adhering to long-term ART (66, 67).

Once individual PLWH have been linked to care and successfully initiated on ART, it is important to note that achieving durable viral suppression can take several months or longer. In *HPTN 052*, four of the eight linked transmissions in couples where the HIV-positive partner was on ART occurred early and prior to viral suppression (56). The *Partners PrEP* study among 4,747 heterosexual serodifferent couples in Kenya and Uganda also demonstrated residual HIV transmission risk in the first six months after ART initiation. Although these transmissions occurred while the HIV-positive partners were on ART, all three occurred in the first six months after ART initiation and prior to viral suppression in blood (68). The real question is whether in early ART treatment, viral kinetics in blood and genital secretions are different, especially during the first months of ART when genital viral shedding is not uncommon. After starting ART, there are similar patterns of viral decay in both blood and semen, with an initial rapid exponential decline during the first days (first phase) followed by a slower second phase lasting weeks. One study of viral kinetics in seminal plasma and blood in the first 12 weeks of ART treatment found that rilpivirine (RPV)

and elvitegravir/cobicistat (EVGcobi) plus tenofovir and emtricitabine achieved an undetectable viral load in blood and semen at the same rate and much faster than darunavir/ritonavir (DRVrtv), likely due the better penetration of EVGcobi and RPV than DRVrtv in the male genital tract (69).

Finally, it is critical to acknowledge that U=U (and thus, its potential population-level impact) is only easy to apply in settings where PLWH have access to regular, affordable, and accessible viral load monitoring, as recommended by the World Health Organization (70). However, although global demand for viral load testing is projected to increase dramatically in the coming years, in many countries, access to affordable viral load monitoring is still limited (71-73).

Reducing HIV-related stigma and discrimination: a critical component of achieving the elimination of HIV transmission

The promise of TasP to greatly reduce HIV incidence on a community level and enable a truly effective global HIV response will not be realised without addressing stigma, discrimination and criminalisation of PLWH and key populations affected by HIV. Criminalising people for having HIV undermines efforts to control the epidemic, promotes stigma, discourages testing and treatment, and stigmatises vulnerable populations when engagement with services is vital. Such laws have not evolved to reflect scientific advancements; it is essential that legal frameworks be updated with the most recent evidence (74, 75). Stigma is repeatedly recognised as a major barrier at every step of the testing and treatment cascade (76). Further initiatives and more robust research are needed to improve HIV testing and diagnosis, linkage to care, time to ART initiation, retention and

adherence to ART, and access to diagnostics. Interventions are needed at all levels to address health system problems, structural and political problems, and psychosocial issues experienced by individuals. As noted in a recent editorial, it is critical that the message of U=U be promoted to all PLWH, and that providers should discuss the recent scientific findings with patients (77). However, this alone is not nearly enough: U=U must be actively promoted to HIV-negative and untested individuals in key populations. Even for PLWH, the clinical relationship between patient and doctor needs to be supplemented and supported by wider community education about U=U.

Conclusion

Suppressive ART renders PLWH sexually non-infectious. However, epidemic control is unlikely to be achieved by TasP or UTT alone. As was shown in the community-level trials and other observational analyses, achieving the UNAIDS 90-90-90 targets has typically not been sufficient to see concomitant declines in HIV incidence. UTT must be supplemented by intensified efforts in primary prevention, including the increased scale-up of PrEP, and increased efforts to address stigma and discrimination, along with other structural barriers, are critical.

Key points

- Recent studies have definitively proven that HIV cannot be sexually transmitted from an HIV-positive person on ART with suppressed virus.
- Population-level universal test and treat (UTT) studies have not demonstrated the expected reductions in HIV incidence, despite large increases in the proportion of virally suppressed PLWH.
- Challenging structural and social barriers exist in HIV testing and diagnosis, linkage to care, long-term retention on and adherence to ART, impacting viral suppression and the population-level impact of UTT.
- Achieving the UNAIDS 90-90-90 will not be enough to achieve epidemic control globally; universal testing and treatment must be supplemented with intensified interventions in primary HIV prevention and efforts to combat stigma, discrimination and structural barriers.

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This comment article outlines the published evidence on the individual-level efficacy of TasP, and argues that all patients living with HIV should be informed by their healthcare providers about U=U.

Table. Summary of recent cluster-randomised trial results of universal testing and treatment in sub-Saharan Africa.

Study	Timing	Study design	Sample size	Location	Proportion virally suppressed at end study	Eligible sample for HIV incidence analysis	HIV incidence (per 100 person-years)	Comparison statistics
<i>TasP</i> (30)	2012 to 2016	Phase 4, open-label, cluster randomised trial of 22 rural communities. Biannual RHT at home-based visits offered to both arms. Referral to ART clinics for immediate initiation (intervention) or according to national guidelines (control).	28,419	KwaZulu-Natal, South Africa	Intervention: 87% Control: 84%	Intervention : 6,756 Control: 7,467	Intervention: 2.11 Control: 2.27	Adjusted hazard ratio: 1.01 (95%CI=0.87-1.17), p=0.89
<i>SEARCH</i> (33)	2013 to 2017	Pair-matched cluster randomised trial of 32 rural communities. Multi-disease health campaigns involving multi-disease testing, and home-	150,395	Kenya and Uganda	Intervention: 79% Control: 68%	Intervention : 49,590 Control: 45,493	Intervention: 0.25 Control: 0.27	Relative risk: 0.95 (95%CI=0.77-1.17) #

		based testing. ART offered immediately and enhanced contact and follow-up (intervention) or ART offered according to national guidelines (control).						
<i>Ya Tsie</i> (31)	2013 to 2018	Pair-matched community randomised trial in 30 rural and peri-urban communities. Intensive HIV testing, immediate ART initiation, and VMMC (intervention) or standard of care (control).	12,610	Botswana	Intervention: 88% Control: 83%	Intervention : 4,487 Control: 4,487	Intervention: 0.59 Control: 0.92	HIV incidence ratio: 0.69 (95%CI=0.46-0.90), p=0.09
<i>PopART</i> (HPTN 071) (3)	2013 to 2018	Community randomised trial of 21 communities. Group A received the full combination prevention intervention (community-based universal HIV testing, VMMC, condom distribution, education) <i>plus</i>	48,301	South Africa and Zambia	Group A: 72% Group B: 68% Group C: 60%	Group A: 9,591 Group B: 8,794 Group C: 9,116	Group A: 1.45 Group B: 1.06 Group C: 1.55	Adjusted incidence rate ratio: Group A compared to C: 0.93

immediate ART initiation. Group B	(95%CI=0.74-
received the prevention intervention	1.18), p=0.51
with ART provided according to	Group B
guidelines. Group C received	compared to C:
standard of care.	0.70
	(95%CI=0.55-
	0.88), p=0.006

TasP: Treatment as Prevention; SEARCH: Sustainable East Africa Research in Community Health; RHT: rapid HIV testing; ART: antiretroviral therapy; VMMC:

voluntary male medical circumcision. # p-value was not provided in the original publication.