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Antiretroviral Therapy for Prevention Is a Combination Strategy

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Abstract In the past several years, the debate of "treatment vs prevention" has shifted with the introduction of the concept of "treatment as prevention," (TasP), stemming from a series of compelling observational, ecological, and modeling studies as well as HPTN 052, a randomized clinical trial, demonstrating that use of ART is associated with a decrease in HIV transmission. In addition to TasP being viewed as 1 intervention in a combination strategy for HIV Prevention, TasP is, in and of itself, a combination of multiple interventions that need to be implemented with high coverage in order to achieve its potential impact.

Keywords HIV · Antiretroviral therapy · HIV prevention · Treatment as prevention (TasP) · Global epidemic · Combination intervention

Introduction

Until recently, HIV treatment and HIV prevention have been pitched too often as rival efforts in the debate on the optimal response to the HIV epidemic [1]. The origins of this debate stem from perceived competition over financial resources and initial concern about feasibility and sustainability of large-scale treatment programs in resource-limited settings [2]. Efforts at prevention of HIV transmission dominated the first decade of the epidemic given the limited number of, and access to treatment options, high-cost of drugs, and concern for resistance in settings of suboptimal medication adherence [3]. The global response then shifted to focus on scale-up of HIV treatment with an overwhelming amount of evidence establishing that combination antiretroviral therapy (ART) significantly reduces HIV and AIDS-related morbidity and mortality [4, 5]. In addition, intensive advocacy efforts from HIV activists on the imperative to offer treatment, a decrease in HIV drug prices, and an increase in drug access with emergence of generic drugs led to an international response for unprecedented funding for ART in both resource-limited and resource-rich settings. Thus, during the second decade of the HIV epidemic, and since 2004, more than 60 billion USD have been invested in HIV programs in low- and middle-income countries which has led to an impressive 8 million persons initiating ART [6, 7].

In the past several years, the debate of "treatment vs prevention" has shifted with the introduction of the concept of "treatment as prevention," (TasP), stemming from a series of compelling observational, ecological, and modeling studies as well as HPTN 052, a randomized clinical trial, demonstrating that the use of ART is associated with a decrease in HIV transmission [8•, 9•, 10, 11•, 12, 13]. TasP includes universal testing of HIV combined with immediate initiation of ART for persons found to be HIV positive, with the ultimate goal of viral load suppression [14, 15].

With enthusiasm for the potential of TasP for control of the HIV epidemic fueled particularly with demonstration of its efficacy in stable discordant heterosexual couples, there has been interest in demonstrating the effectiveness of such an approach at a population level, in which TasP is 1 of a combination of HIV prevention strategies [1]. Other interventions in a combination strategy include voluntary medical male circumcision, expansion of HIV testing, prevention of mother to child transmission, condom availability, and in

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some settings the possibility of pre-exposure prophylaxis for high-risk HIV-negative persons [16–22]. In addition to being viewed as 1 intervention in the combination strategy for HIV Prevention, TasP is, in and of itself, a combination of multiple interventions that need to be implemented with reliability at a health systems level in order to achieve its potential impact. TasP is most intuitively conceptualized by some as a biological intervention, referring to the ART component of TasP, but this perception misses the fundamental elements that are implicit in the success of TasP, ie, the need for increased demand for HIV testing, expansion of HIV testing, effective linkage from a positive test to HIV care, retention in care, initiation of ART, and adherence with ART with durable viral suppression. The latter element is fundamental to optimal outcomes for the individual initiating ART and prevention potential at the population level. The theme of "Seek, Test, Treat, and Retain" has been used to describe these elements required for TasP [23•]. In this paper, we attempt to conceptualize TasP in its rightful framework as a combination intervention (Fig. 1).

Modeling Assumptions vs Real-Life Implementation

Modeling studies suggest that with optimal HIV testing and re-testing, linkage to care, retention in care, and medication adherence, TasP has the potential to lead to the elimination of HIV, defined as incidence less than 0.1 % in 50 years, in high-burden HIV settings [9•]. A recent meta-analysis of 12 TasP modeling studies in South Africa report TasP could substantially reduce new infections under similarly optimistic assumptions of annual voluntary testing, followed by greater than 90 % linkage to care with immediate ART initiation, and 85 % of patients remaining on treatment over 3 years [24]. However in the real world, testing

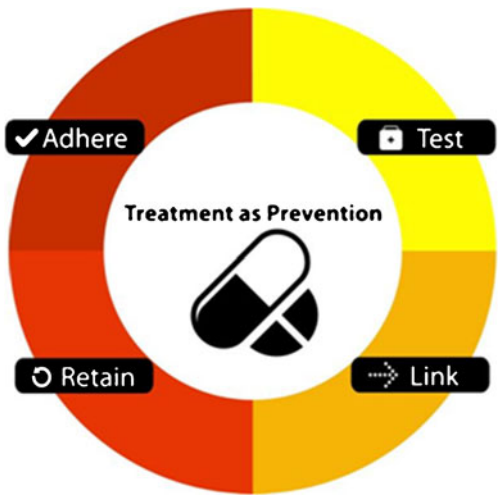

Fig. 1 TasP is a combination intervention

coverage, rates of linkage to, and retention in care, and ART adherence are significantly lower than the assumptions used in the modeling studies. For example, Granich et al used an assumption of 92 % of newly diagnosed patients would link to care, in contrast to findings that indicate that 59 % of persons who are diagnosed with HIV in sub-Saharan Africa are reported to ever link to care [25•]. Similarly, assumptions with regards to retention rates in many modeling studies of 85 % at 3 years contrast to 70 % and 64.6 % at 24 and 36 months, respectively, in public HIV treatment programs in sub-Saharan Africa [26]. In addition, 2 meta-analyses report that less than a third of persons testing HIV positive remain in care until ART initiation in sub-Saharan Africa [25•, 27•]. Similarly sobering statistics are reported in the United States where 19 %–29 % of persons with HIV are estimated to have achieved viral load suppression [28•, 29•, 30].

It is important to note that when Andrews et al [31] modeled the impact of TasP with a lower linkage rate of 53 %, based on data from the Masiphumelele township in South Africa, and took into account issues such as immigration and emigration, the outcome of elimination of HIV transmission was not achieved by 30 years, suggesting improved linkage to care is essential for TasP. Another modeling study suggested that ART initiation at entry into care would improve long-term survival of patients with high CD4+ cell counts only if associated with no increased withdrawal from care or lower ART adherence [32].

Interest in TasP Offers an Opportunity to Strengthen Each of its Required Elements

The discrepancies between TasP modeling assumptions and real-life implementation of HIV services highlight the need to conceptualize TasP as a combination intervention in which each element needs to be strengthened.

HIV Testing

HIV testing is the starting point for TasP for both HIV care and prevention services. In high-burden HIV settings, universal HIV testing is recommended [33]. In 2006, CDC recommended routine opt-out HIV testing in all medical settings including primary and urgent care clinics and emergency departments [34]. However, less than 40 % of PLWH have been diagnosed in resource-limited settings, with proportionally less men than women (17 % vs 34 %) [35], and only 80 % of PLWH in the US know their status [28•]. Higher testing rates are critical to identify PLWH and to identify high-risk HIV-uninfected individuals who are eligible for behavioral and biomedical prevention interventions. Novel approaches to testing such as home-based counseling

and testing (HBCT) and self-testing show promising results [36–39]. In a study of HIV self-testing using oral kits in Malawi, 92 % of persons reported the rapid HIV self-test was acceptable with 99 % of the results being accurate [39]. Provider-initiated counseling and testing (PICT) has not been implemented at scale per initial reports [40, 41] but could potentially be another strategy to increase testing coverage. Family-testing tools to identify other family members needing testing could identify other positive individuals needing HIV care and treatment services and also identify HIV-negative individuals who would benefit from HIV prevention services. It is important to note that the absence of a simple test for detection of acute HIV infection limits the potential for identifying all HIV infected individuals in a community [11•]. Also, approaches to HIV testing must address gender-influenced power disparities, stigma, and discrimination to optimize discordant partner testing.

Linkage to Care

Linkage to care typically refers to enrollment in HIV care at a clinic after testing HIV-positive in order to receive ongoing care and treatment services. For TasP, linkage to care is essential in order to determine eligibility for ART, initiate ART, if eligible, and establish life-long monitoring for treatment failure and drug side effects. Linkage to care appears to be the "weakest link" in the HIV care continuum and most variable step for TasP as rates of linkage are reported to be between 33 %–88 % (median 59 %) in resource-limited settings and far less than the target of 85 % by 3 months after testing in the United States [25•, 27•, 28•, 42, 43•]. Common barriers for successful linkage to care are transport costs, long distances to the clinic, stigma, and disclosure, and clinic factors such as wait times [44•]. Interventions such as case-managers could improve linkage to care and prevention services. One program that used case-managers after HIV testing in San Francisco led to 47 of 48 HIV positive patients successfully linking to care [45].

Linkage is equally important for HIV prevention as HIV-uninfected individuals need to enroll in care services to receive ongoing counseling and support on behavioral risk reduction, condom use, repeat HIV testing, recognition of acute HIV infection as well as in order to receive interventions such as voluntary medical male circumcision, if eligible.

Retention in Care

TasP requires retention in care to assess long-term adherence and durability of the effect as well as to provide long-term disease management including adherence support, monitoring for adverse events, and for ART resistant, if feasible. TasP, unlike other biomedical HIV preventions such as male circumcision or PrEP, requires life-long engagement in care. Viral load suppression is contingent on adherence to ART and is necessary for attaining benefits from treatment [46]. Viral load suppression is also critical for reducing HIV transmission. In the HPTN 052 study, 89 % of participant in the early therapy group had viral load suppression as compared with 9 % in the delayed therapy group by 3 months after study randomization [8•], clearly an important intermediate outcome that enabled demonstration of the efficacy of TasP. Concern over increased risk behavior in the setting of prevention interventions has been raised and retention in care is essential for ongoing counseling and monitoring of these behaviors [47–49].

While attention has been largely focused on those eligible for ART and those initiated on ART, a largely ignored issue has been retention of individuals who have yet to be eligible for ART. The latter group is at high risk for loss to follow-up [50–52]. HIV-negative individuals must also remain connected with care in order to provide ongoing risk behavior counseling, regular HIV and sexually-transmitted diseases screening, education about acute HIV infection, and adherence counseling for biomedical prevention interventions such as PrEP. Retention of such individuals is critical in order to provide them with evidence-based interventions to maintain their own health and to enable repeat CD4+ testing and clinical assessments to promptly determine ART eligibility.

The Elements of TasP Differ by Population and Epidemic Context

The elements of TasP as a combination intervention will need to be tailored to different country contexts and specific patient populations. In 1 modeling study, the effectiveness of TasP in discordant couples varied among countries due to differences in HIV prevalence, the proportion of couples in stable partnership, and the percentage of couples that are discordant [53]. Countries with high HIV prevalence may need more emphasis on annual testing which requires community-based models, while countries of low-prevalence may need to focus efforts on identifying at-risk populations. In addition, the elements of TasP may need to be tailored for specific patient populations such as pregnant women, men who have sex with men (MSM), commercial sex workers, intravenous drug-users, adolescents, particularly girl adolescents, and other at-risk groups and across the lifespan of persons within groups as knowledge and risk behaviors change [54, 55]. One vulnerable group is MSM who are the largest high-risk group in the US comprising 48.1 % of infections [56], and in 2006, 52 % of new HIV diagnoses [57]. The recognition that

the HIV epidemic among MSM is increasing in many low and middle-income countries despite increasing availability of ART and biomedical prevention interventions [58] highlights the need for increasing demand for services, overcoming individual, societal and structural impediments, improved delivery of HIV services, and engagement in those services across an integrated continuum of care. Another vulnerable group is sub-Saharan African adolescent girls who may lack negotiating skills for male partners' condom use and not know their partners' adherence to ART for TasP. Specific interventions tailored to the importance of ongoing HIV testing and access to treatment and prevention services is needed [59, 60]. Furthermore, the use of pre-exposure prophylaxis in high-risk adolescent women may be of high benefit.

The Spillover Effect

When TasP is viewed as a combination of interventions and each component is strengthened, there may be benefits on the larger health care delivery system . These may be realized in terms of improved testing and management of other infectious and non-communicable chronic diseases such as diabetes and hypertension [61]. Wood and Lawn [62] describe the "TB dividend" of TasP. TasP may result in a decrease in TB burden through the following 3 ways in high HIV/TB settings: (1) reduce the proportion of early patients who have low CD4+ cell count who are at the highest risk of development of TB; (2) provide an ongoing opportunity for increased TB screening through intensified TB case findings among HIV-infection population and decrease prevalence of untreated disease; and (3) decrease HIV transmission and thus the size of the HIV-infected population who are at risk for TB with consequent decrease in risk of transmission to others in the community. Tempering the "TB dividend" in resource-limited settings is the ongoing challenge of diagnosing TB in HIV-TB co-infected patients due to limited diagnostics and sensitivity of the diagnostics [63]. In a meta-analysis of 11 studies in developing countries, ART was significantly associated with reduced TB incidence across all CD4+ cell count strata examined (HR 0.35 95 % CI 0.28–0.44 all strata and greater than 350 cells/mm3 HR 0.42 vs 0.16 < 200 cells/mm3) [64]. However, only 3 of the 11 studies included in the meta-analysis had any patients on ART with CD4+cell count >350 cells/mm3. TasP, through early use of ART at higher CD4 cell count, may be of benefit in the prevention of non-AIDS events in PLWH, although definitive data with regards to this issue are awaited from the START study which is evaluating the risk/benefit of early ART for individuals with CD4+ count >500 cells/mm [65–68]. Ultimately, these effects are dependent upon linkage and retention in the continuum of HIV services.

The CDC recently released revised guidelines for integrated prevention services for HIV, viral hepatitis, sexually-transmitted diseases, and TB, urging provision of multiple prevention services at a single venue, coordination of referrals, and provision of linkages to services delivered at multiple venues to improve access to high-quality prevention services [69]. A study which recruited 658 at risk commercial sex workers in Burkina Faso provided integrated HIV prevention and care and treatment services, including STI counseling and testing every 6 months, risk behavior reduction counseling, and ART if eligible as per national guidelines. Nearly 80 % of women who started ART achieved viral load suppression within 6 months after initiation and 81.8 % at 36 months. Self-reported condom use at last sexual intercourse with clients increased from 81.7 % at enrollment and 98.2 % at 12 months ($P < 0.001$) and from 67.2 % to 95.9 % ($P < 0.001$) with regular clients [70]. Although there was no control group in this study, these results suggest providing integrated prevention and care services to an at risk group achieved positive results in terms of reduced risk behavior and sustained virologic control among women.

Conclusion

TasP as a combination intervention has a potential to transform the HIV epidemic. It offers a unique opportunity to strengthen the interrelated elements of increasing demand for testing, expanding testing services, improving linkage to, and retention in care as well as adherence with treatment. The challenge of TasP, however, will be in the implementation of its critical elements. Improving 1 element involved in TasP, in absence of improving all, will only increase health outcomes marginally. Substantive improvement will require improvements across all elements. This is evidenced by Gardner et al [29•] demonstrating that only small improvements in the magnitude of viral load suppression were noted when improving only 1 step in the HIV care continuum; however, when all steps improved to greater than 90 % fidelity, viral load suppression increased from 19 % to 66 %. Similar, in the context of prevention of mother-to-child transmission programs, programs need to perform with 90 %–95 % effectiveness across the various steps in the continuum to achieve less than 5 % mother-to-child transmission [71]. The concept of "no partial credit" for improvement in 1 element, in the absence of all steps, has been advocated for services in the HIV care continuum, and likewise can be applied to TasP [72].

Should we be able to strengthen these elements, TasP will be more than the sum of its parts and achieve the impact the modeling studies suggest—a future AIDS-free generation.

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