The economics, financing and implementation of HIV Treatment as Prevention: what will it take to get there

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ABSTRACT:

The 2013 Lancet Commission Report, Global Health 2035, rightly pointed out that we are at a unique place in history where a “grand convergence” of health initiatives to reduce both infectious diseases, and child and maternal mortality – diseases that still plague low income countries –would yield good returns in terms of development and health outcomes and be a good economic investment. Such investments would support achieving health goals of reducing U5 mortality to 16 per 1 000 live births, reducing deaths due to HIV/AIDS to 8 per 100 000 population, and reducing annual TB deaths to 4 per 100 000 population.

Treatment as Prevention (TasP) holds enormous potential in reducing HIV transmission and morbidity and mortality associated with HIV/AIDS – and therefore contributing to global health 2035 goals. However, TasP requires large financial investments, and poses significant implementation challenges.

In this review, we discuss the potential effectiveness, financing and implementation of TasP. Overall, we conclude that TasP shows great promise as a cost-effective intervention to address the dual aims of reducing new HIV infections and reducing the global burden of HIV-related disease. Successful implementation will be no easy feat, though. The dramatic increases in the numbers of persons who need ART under a TasP approach will pose enormous challenges at all stages of the HIV treatment cascade: HIV diagnosis, ARV initiation, ARV adherence and retention, and increased drug resistance with long-term enrolment on ART. Overcoming these implementation challenges will require targeted implementation, not focusing exclusively on TasP, MARP-friendly services for key populations, integrating services, task shifting, more efficient program management, balancing supply and demand, integration into
UHC efforts, demand creation, improved ART retention and adherence strategies, the use of incentives to improve HIV treatment outcomes and reduce unit costs, continued operational research and tapping into technological innovations.

Key words
Investment; ART, TaSP; implementation; cost-effectiveness; impact
Introduction

Current and future investments in proven HIV interventions will help address global health goals

Although having tapered, globally, the HIV epidemic has been the fastest growing cause of disease burden of the past 20 years and is second only to malaria in its amount of disease burden in sub-Saharan Africa (Institute for Health Metrics and Evaluation, 2013). In the last decade, evidence has emerged of interventions that reduces HIV disease burden: HIV treatment (through antiretroviral therapy) once a person living with HIV (PLHIV) reaches a threshold CD4 count, male circumcision, comprehensive prevention programmes for key populations and condom promotion during casual sex. Of these, HIV treatment has received the most funding: in 2012, over half (55%) of the global total of USD 18.9 billion went towards AIDS financing in low and middle income countries (LMIC), was spent on HIV treatment (UNAIDS 2013). In both generalized and concentrated HIV epidemics, HIV treatment dominates budgets for HIV programs and services (Amico, Gobet, Avila-Figueroa, Aran & De Lay, 2012). Although some care needs to be exerted in terms of assuming an impact in all populations, these current investments in proven HIV interventions, and future ones, can help to address global health goals, including those from the recent Lancet Commission report (Global Health 2035) to reduce deaths due to HIV/AIDS to 8 per 100 000 population (Jamison et al., 2013).

The concept of expanding antiretroviral therapy (ART) coverage and access as a preventative HIV intervention at the population has gained much support within the global community. Here, we will discuss important aspects of HIV Treatment as Prevention (TasP), including its potential effectiveness, financing and implementation. Specifically, we will address the varying evidence of TasP effectiveness across different settings, with regard to its population-level impact on the HIV epidemic and more largely on health and social welfare. We will also
discuss its cost-effectiveness and required financing for its implementation. Finally, the many challenges associated with TasP implementation will be highlighted, along with strategies to address them. We maintain that TasP could be a great tool in our strategy to combat global HIV/AIDS, provided that careful consideration is given to how this intervention is implemented.

**Earlier initiation of PLHIV on ARVs has the potential to amplify the contribution of HIV treatment on reducing HIV disease burden to less than 8 per 100 000 population**

While the purpose of HIV treatment has been to reduce HIV-related morbidity and mortality, recent evidence has shown that ART can also have an effect on reducing new HIV infections. The landmark HIV Prevention Trials Network (HPTN) 052 study demonstrated the ability of ART (initiated at CD4 counts of less than 550 copies/ml) to reduce by 96%, through viral suppression, the risk of HIV transmission from an HIV positive person to his/her sexual partner (Cohen, Chen, McCauley, Gamble, Hosseinipour, Kumarasamy *et al.*, 2011).

Simultaneously, the study also showed that clinical outcomes (HIV-related morbidity and mortality) decreased with earlier ART initiation (Grinsztejn *et al.*, 2014). This study therefore proved definitely that ART not only reduced morbidity and mortality, but also new HIV infections: thus proving itself as essential in achieving the global health goal of reducing AIDS deaths to fewer than 8 per 100 000 population by 2035.

The results of this study gave rise to the concept of HIV Treatment as Prevention (TasP) – this refers to the notion of initiating people living with HIV (PLHIV) earlier on ART (either at CD4 count of 500, or even initiating them on HIV treatment at the point of HIV diagnosis) with the intention of reducing the risk of HIV transmission to their sexual partners and with anticipated wider effects of reducing HIV incidence in the population. There is evidence that ART use can reduce HIV risk within a population (Tanser, Barnighausen, Grapsa, Zaidi &
Newell, 2013); as such, earlier ART initiation shows promise as an effective HIV prevention tool at population level. It is therefore important to examine the economics, logistics and feasibility of implementing TasP.

The effectiveness of TasP at the population level varies in different regions and populations

One important consideration with regard to the effect of TasP, is the contrast between efficacy of ARVs on preventing onward transmission at the individual level (96%, as per (Cohen et al., 2011) and the effectiveness of TasP (implemented in real life settings instead of in a clinical trial) at the population level. In real life implementation situations, where HIV diagnosis is harder, ART coverage is likely to be less than ideal, ART adherence and retention is likely to be lower, fewer persons are likely to be virally suppressed, resulting in lower population-level impact than individual-level efficacy of ART.

So far, data from real life implementation has shown that the contrast between individual level efficacy and population-level effectiveness can be quite dramatic: In KwaZulu Natal, there was only a 34% reduction in HIV incidence rates between areas which recently reached 30-40% ART coverage versus areas with below 10% ART coverage (CD4 count <350)(Tanser et al., 2013). Data from Swaziland suggest that high HIV incidence can be maintained even under high population-level ART coverage. An estimated 74% of adults (persons older than 15) needing ART (CD4 count <350) were enrolled in ART in 2011 in Swaziland (WHO, UNICEF & UNAIDS, 2013). In the same year, the Swaziland HIV Incidence Measurement Survey (SHIMS) found that among those on ARVs, 85% had viral loads under 1 000 copies/milliliter (Justman, Ellman, Donnell, Duong, Reed, Bicego et al., 2013) and yet, that measured HIV incidence was 2.4% (Kingdom of Swaziland Ministry of Health, 2012) (Figure 1).
One interpretation was that HIV transmission in Swaziland (and in other countries) is more likely driven by high viral loads in undiagnosed or untreated individuals, who are likely to be at higher CD4 counts.

Other studies confirm that the population-level impact of ART on averting new infections may be much lower in real life. An observation study in discordant couples in China showed only 26% lower HIV incidence, and this protection was only maintained in transfusion or sexually infected groups, not those acquiring HIV through injecting drug use (Jia, Mao, Zhang, Ruan, Ma, Li et al., 2013). A cohort study in Uganda did not show any differences in HIV incidence in discordant couples in a rural ART program (Birungi, Wang, Ngolobe, Muldoon, Khanakwa, King et al., 2013). A key difference that may explain the discrepancy of results between these more recent studies and HPTN052 is CD4 count; CD4 count at initiation was at or below 250 in the Jia et al and Birungi et al studies,
whereas the HPTN052 study treated patients with counts lower than 550 copies/ml.

Inversely, TasP, even if implemented well, may not work in all populations. It is suspected that TasP is less effective in HIV epidemics amongst men who have sex with men (MSM), and although MSM communities in developed countries are highly treated, HIV infections are alarmingly rising within these communities (Wilson, 2012). In a large MSM study in England and Wales over a decade, the proportion of HIV-positive men with CD4 counts <350 taking ART rose from 69% to 80% and rates of HIV testing increased by 3.7 times. However, despite these improvements, the population-level incidence of HIV infection did not decrease in MSM (Birrell, Gill, Delpech, Brown, Desai, Chadborn et al., 2013).

Clearly, the available data on TasP effectiveness at the population level are inconclusive, and a better understanding of the levels of ART coverage required to significantly impact an HIV epidemic is imperative for HIV programmatic efforts, especially as one considers the financial investment to implement TasP effectively. As such, a number of prospective randomized clinical trials are being carried out in sub-Saharan African countries with generalized epidemics, with the statistical power to determine population level effectiveness of TasP and evaluate treatment regimens for immediate ARV initiation upon HIV diagnosis (studies in planning stages in Zambia, Botswana and South Africa).

**TasP can have a widespread positive impact on health, economy, and social welfare**

Successfully and effectively implementing TasP will be no menial feat, but doing so could have tremendous positive effects on the health, economies, and social welfare of countries. In South Africa, ART program rollout was associated with both a reduction by 20% in all adult mortality and an 11-year increase in life expectancy (Bor, Herbst, Newell & Barnighausen, 2013; Herbst, Cooke,
Barnighausen, KanyKany, Tanser & Newell, 2009). TasP could also have beneficial effects on other disease epidemics and co-infected individuals within the HIV-positive population. Modelling analyses show that early ART (CD4 count <500) provides greater health benefits per year on treatment (DALYs averted per 100 person-years on ART) for HIV/hepatitis B virus (HBV) co-infected individuals than those only infected with HIV. Furthermore, it could reduce sexual transmission of HIV by 47%, and vertical transmission of HIV and HBV by 25 and 32% in (Martin, Devine, Eaton, Miners, Hallett, Foster et al., 2014). The TB epidemic could similarly benefit from expanding ART eligibility and coverage. Mathematical models predict a 6-30% decline in cumulative TB incidence over the period 2014 – 2033 if ART eligibility was expanded to all HIV-positive individuals, and 28 – 37% if expanded eligibility was combined with 80% ART coverage. Universal eligibility combined with 80% coverage could also reduce cumulative TB mortality by 13 – 35% for that same period (Pretorius, Menzies, Chindelevitch, Cohen, Cori, Eaton et al., 2014). This is an excellent example of how focusing on HIV treatment and prevention beneficially spills over into helping achieve other Global Health 2035 targets (reducing TB deaths).

TasP potential goes beyond its impact on health. Labor and education benefited from HIV treatment programs in both Botswana and Kenya. Absenteeism from work returned to pre-infection levels in Botswana (Habyarimana, Mbakile & Pop-Eleches, 2010), and Kenya experienced an increase in adult working hours and reductions in child labor, with higher attendance at school and better nutrition (Thirumurthy & Zivin, 2012)).

**TasP as a cost-effective HIV prevention tool in different settings**

Aside from its social benefits, TasP implementation could be cost-effective and falls in line with the Grand Convergence scheme and investing in health. The recent Lawrence Summers chaired Commission on Investing in Health concluded that eliminating AIDS in Africa would yield the continent an economic
benefit comparable to a full year of continental GDP, and modelling studies have also supported expanding ART eligibility for TasP. A study that looked at the cost-effectiveness of a number of HIV interventions in South Africa found that TasP would cost USD 8 400 per HIV infection averted (Barnighausen, Bloom & Humair, 2012), and based on the WHO criteria of three times a country’s per capita GDP, TasP implementation is considered a cost-effective strategy for HIV prevention in this country (WHO). Another modeling study by Eaton et al (Eaton, Menzies, Stover, Cambiano, Chindelevitch, Cori et al., 2014) demonstrated that in both generalized and concentrated HIV epidemics, expanding ART eligibility to CD4 counts <500 or to all HIV-positive individuals was very cost effective over a 20 year period, based on the incremental cost per disability-life year (DALY) averted. Using 6-7 models on South African data, costs of changing ART eligibility from CD4 counts <350 to 500 ranged from USD 273 to 1 691 per DALY averted over 20 years or USD 438 to 3 790, if scaling-up to treat all HIV-positive adults. Similar analyses showed that expanding ART eligibility in Zambia to CD4 counts <500 would cost USD 738 per DALY averted and USD 790 if all HIV-positive adults were treated. In countries with concentrated HIV epidemics driven primarily by female sex workers, MSM, or IDU, the incremental costs associated with expanding ART eligibility from CD4 counts <350 to all HIV-positive adults were even lower. Doing so in Vietnam would cost USD 289 and ranged from USD 131 to 198 in three districts in India.

Costs associated with increasing ART eligibility and coverage for TasP will vary by epidemic context. A number of studies have estimated the cost-effectiveness of ART, including TasP, based on different counterfactuals (early vs delayed treatment, expanded eligibility or access over current levels, etc.), and settings (generalized vs. concentrated epidemics, high-income vs. low-income). A number of these comparative analyses are summarized in Table 1. Note that analyses used different models, time frames to estimate cost-effectiveness, and metrics (cost per HIV infection or DALY averted or quality-adjusted life years – QALY – gained. According to available data, VMMC is very cost-effective, but
this intervention is only relevant in a priority group of 14 African countries with generalized HIV epidemics that is primarily sexually transmitted and low levels of male circumcision. Evidence does suggest TasP to be cost-effective in the long-run, based on costs per health returns. Considering how TasP should be rolled out, expanding eligibility or coverage levels or combining with other interventions, will be very important to investing in and implementing TasP as a cost-effective HIV prevention tool.

Table 1. Example results of costs associated with different HIV interventions to avert one HIV infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Countries/Regions</th>
<th>Cost per HIV infection averted (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoogstede et al. 2005</td>
<td>Voluntary counseling and testing</td>
<td>sub-Saharan Africa</td>
<td>1 516</td>
</tr>
<tr>
<td>Sweat et al. 2010</td>
<td>Voluntary counseling and testing</td>
<td>Kenya, Tanzania</td>
<td>249 346</td>
</tr>
<tr>
<td>Walensky et al. 2013</td>
<td>Antiretroviral therapy (early vs delayed initiation)</td>
<td>South Africa, India</td>
<td>590 530*</td>
</tr>
<tr>
<td>Masseale et al. 2012</td>
<td>Antiretroviral therapy (adding ART to standard national program of cotrimoxazole prophylaxis, with ART eligibility of CD4 count &lt;350 and WHO clinical stage 3 disease, WHO clinical stage 4 disease: CD4 count &lt;200)</td>
<td>Zambia</td>
<td>6 118 **</td>
</tr>
<tr>
<td>Cleary et al. 2008</td>
<td>Antiretroviral therapy (ART or no ART)</td>
<td>South Africa</td>
<td>13 754*</td>
</tr>
<tr>
<td>Freedberg et al. 2001</td>
<td>Antiretroviral therapy (ART or no ART, varying CD4 count eligibility)</td>
<td>United States</td>
<td>13 000 - 23 000***</td>
</tr>
<tr>
<td>Barnighausen et al. 2012</td>
<td>Antiretroviral therapy (increasing access and eligibility over base case of 50% ART coverage with eligibility CD4 count &lt;350 and VMMC coverage 45%)</td>
<td>South Africa</td>
<td>6 800 - 8 400</td>
</tr>
<tr>
<td>Eaton et al. 2014</td>
<td>Antiretroviral therapy (expanding eligibility or access)</td>
<td>India</td>
<td>35 - 5 648****</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral therapy (expanding eligibility or access)</td>
<td>Vietnam</td>
<td>161 - 21 656****</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral therapy (expanding eligibility or access)</td>
<td>South Africa</td>
<td>273 - 3 790****</td>
</tr>
<tr>
<td></td>
<td>Antiretroviral therapy (expanding eligibility or access)</td>
<td>Zambia</td>
<td>749 - 790****</td>
</tr>
<tr>
<td>Vickerman et al. 2006</td>
<td>Harm reduction</td>
<td>Ukraine</td>
<td>97</td>
</tr>
<tr>
<td>Vickerman et al. 2006</td>
<td>STI treatment and prevention</td>
<td>South Africa</td>
<td>1 384 - 3 635</td>
</tr>
<tr>
<td>Price et al. 2006</td>
<td>STI treatment and prevention</td>
<td>Malawi</td>
<td>15.42</td>
</tr>
<tr>
<td>White et al. 2003</td>
<td>STI treatment and prevention</td>
<td>East and West Africa</td>
<td>321 - 1 065</td>
</tr>
<tr>
<td>Kahn et al. 2006</td>
<td>Voluntary medical male circumcision</td>
<td>South Africa</td>
<td>181</td>
</tr>
<tr>
<td>Gray et al. 2007</td>
<td>Voluntary medical male circumcision</td>
<td>Uganda</td>
<td>1 269 - 3 911</td>
</tr>
<tr>
<td>Martin et al. 2007</td>
<td>Voluntary medical male circumcision</td>
<td>Lesotho</td>
<td>202</td>
</tr>
<tr>
<td>Martin et al. 2007</td>
<td>Voluntary medical male circumcision</td>
<td>Swaziland</td>
<td>175</td>
</tr>
<tr>
<td>Neuhart et al. 2011</td>
<td>Voluntary medical male circumcision</td>
<td>sub-Saharan Africa</td>
<td>369 - 4 096</td>
</tr>
<tr>
<td>Barnighausen et al. 2014</td>
<td>Voluntary medical male circumcision</td>
<td>South Africa</td>
<td>1 100</td>
</tr>
</tbody>
</table>

* per life-year saved over lifetime
** per death averted (program costs over life-time)
*** per QALY gained
**** per DALY averted
^South African Rand

Note: A wide range of models, population data, comparison strategies, time period evaluated, and output metric were used in these analyses. Each study is unique to itself, but this summary provides range of costs associated with HIV prevention strategies across many different contexts.

Realising TasP poses significant financial challenges which will need to be partially financed from domestic resources
History has proven that treatment scale-up is possible, despite it being a financially daunting task. Between 2011 and 2012, several countries had made monumental efforts to increase coverage, for instance, as Tanzania reported an additional 155,000 people on ART (coverage gain of 21%) and South Africa reported an additional 448,000 on ART (coverage gain of 12%). In contrast, several countries with weak health systems had low ART coverage despite relatively small numbers of eligible cases, such as the Democratic Republic of the Congo (29% coverage and 64,000 people on ART), Angola (36% coverage and under 42,000 people on ART) and Chad (40% coverage and just over 40,000 on ART), giving a poignant reminder of the scale-up challenges in conflict and post-conflict situations (WHO et al., 2013).

The magnitude of the scale-up, with regard to numbers, was mentioned earlier, but this must be coupled with the costs associated with it. Only 9.7 million people estimated are on ART in LMIC, which is less than 60% of the 17 million HIV-positive individuals eligible for treatment, based on 2010 WHO guidelines of CD4 count <350, and less than half of the 21 million, if all serodiscordant couples and HIV-positive pregnant women are included. The most current recommendation of treatment initiation at CD4 count <500 makes 26 million eligible for ART (Apollo, 2013) and is estimated to cost USD 16 billion annually. Treating all 32 million people living with HIV could cost up to USD 20 billion annually. These ART cost estimates are considerably greater from the USD 5 billion that was spent on HIV/AIDS care and treatment in 2011. ART costs for TasP implementation will also vary greatly from country to country. Costs for treatment at CD4 count <350 in South Africa could equal this country’s entire health budget, while TasP in Nigeria could cost approximately 10% of its health budget.

The suggested global health goals 2035 place a great focus on the convergence of health in LMIC closer to standards enjoyed in upper-middle income countries

The report shows that the burden of global child mortality, AIDS and TB deaths rests overwhelmingly within LMICs including having the majority of prevalent and incident HIV cases (Jamison et al., 2013).

At present, 43 LMICs finance over 75% of HIV treatment costs from international sources. In Malawi, HIV treatment is almost completely financed from external sources, and its costs are nearly equal to the country’s total health budget. However, the rapidly growing economies of the BRICS (Brazil, Russia, India, China, and South Africa) countries have enabled these countries to increase their own investment in HIV financing. South Africa currently has the second largest HIV budget globally (USD 1.9 billion) which grew by 500% in a decade. Brazil and Russia now fund almost all of their HIV programs, and China will completely do so after Global Fund resources end. India funds 93% of its HIV programs.

The concept of a grand convergence will require that LMICs converge towards UMIC health standards, and it will also require that they close the current gap in external versus domestic funding for HIV programs in these countries. This is especially important as overall development assistance funding saw a 2 and 4% decline in 2011 and 2012 (Organisation for Economic Co-operation and Development Health Status, 2013), and there may be many competing investment priorities in the post-2015 development assistance. However, LMIC economies have been growing and are projected to continue to do so. Between 1990 and 2011, GDP growth averaged between 3.9% and 4.6% among LMICs (World Bank, 2012b), and Africa’s real GDP from 2001 - 2010 has been on an overall rise, with a compound annual growth rate of 1.9% – 4.8%. Projecting ahead, it’s estimated LMIC will experience a 4.3% – 4.5% real GDP growth per year from 2011 – 2035, resulting in 180% – 195% higher GDP in 2035 than 2011. By that same time, the GDP would have grown enough that the annual incremental cost of convergence would only be 1% – 3% of annual GDP (Jamison et al., 2013).
It is believed by experts that the grand convergence is financially feasible, and if resources are allocated optimally to health budgets, including HIV programs, expanded ART coverage and TasP could be part of this strategy. Convergence would cost LMIC between USD 23 – 38 billion annually during the period 2016 – 2025 and USD 27 – 53 billion per year from 2026 – 2035. Programmatic investment in the scale-up of existing HIV interventions, including ART, would be 6 – 10% of those overall convergence estimates for that first period and 11 – 16% for the second period. Our broad estimate of global costs of universal TasP of USD 20 billion is much higher but notably applies to all HIV-infected people in LMICs and all other countries, including those already on ARVs. The Lancet Commission’s report does prioritize HIV prevention and early treatment, as this approach will work synergistically to reduce child mortality and deaths from TB (Jamison et al., 2013).

**All about implementation: need to get it right**

Modelling suggests that earlier ART initiation is cost effective, and the potential of TasP as a component of our HIV prevention armory seems great: it is efficacious in reducing the risk of HIV transmission at the individual level, has the potential of amplifying its effect at the population level, and improves clinical outcomes if initiated earlier. TasP will significantly contribute to achieving the 2035 goal of reducing HIV disease burden to less than 8 per 100 000 population, provided that financing is available and that we get implementation right.

**Realising TasP poses enormous implementation challenges**

TasP implementation will result in a dramatic increase in the number of people who need ART. Based on current WHO recommendations (HIV-positive individuals with CD4 count <350 or concurrent TB or hepatitis B virus co-infection, HIV serodiscordant couples, and HIV-positive pregnant women), 21
million people are eligible for ART, yet only 9.7 million are being treated (Apollo, 2013). Expanding coverage to HIV-positive individuals with CD4 counts <500 and children aged <5 year increases eligibility to 26 million people, and universal “test and treat” of all HIV-positive individuals would see 32 million people eligible for treatment. On a global scale, the effort to expand ART coverage for such eligibility criteria is massive. But even at country-level the task may be very challenging, considering the financial and logistical resources available.

Recently there have been reports of limited or waning resources for the national ART program in some countries: Uganda was suffering from a lack of ARVs (IRIN, 2013), Zambia had started rationing them (Mbulo, 2013), and insufficient resources in Malawi prevented making a complete switch to a new ART regimen with less side effects (IRIN, 2012). By end 2012, most African countries have not yet met their nationally agreed ART coverage targets, and there was a wide range of coverage levels across countries. While Somalia and South Sudan’s very low ART coverage levels in adults (15 and 9% by end 2012) are uncommon, several countries had not yet achieved coverage greater than 50% (CD4 counts <350). On the other hand, many African countries reported ART coverage above 50%, and Namibia, Rwanda, Cape Verde, and Botswana reached universal ART coverage at >90% at CD4 counts <350 (UNAIDS, 2013).

These dramatic increases in the numbers of persons who need ART, will pose enormous implementation and scale-up challenges at all stages of the HIV treatment cascade: HIV diagnosis, ARV initiation, ARV adherence and retention, and increased drug resistance with long-term enrolment on ART.

1) Challenges with HIV diagnosis

Currently, less than 40% of persons in Africa infected with HIV are aware of their infection status, despite massive HIV testing campaigns and efforts. But, this discrepancy in HIV status knowledge exists within specific demographics and populations globally, which be imperative to address for successful TasP
implementation. With this comes the additional cost and feasibility challenges of diagnosing and treating PLHIV in four discrete groups: (i) the HIV-positive healthy; (ii) HIV positive persons in urban areas and at higher wealth quintiles who have full time employment and is less likely to access HIV testing; (iii) the geographically remote or socially fragmented populations; (iv) stigmatized and marginalized populations like drug users, sex workers and men-having-sex-with-men. Reaching geographically remote or socially fragmented populations can be improved through better national infrastructure, while focusing on improving HIV testing within most at risk populations can help identify the HIV-positive healthy. Identifying and enrolling this latter group, PLHIV who do not know their HIV-positive status due to being otherwise healthy (individuals with higher CD4 counts and at earlier stages of the disease), to ART will be a significant challenge to TasP. New effective targeted strategies for populations in geographic areas with the highest HIV prevalence, so as to increase the percentage of PLHIV that know their HIV status, are key to addressing this challenge. Equally, the challenges associated with reaching the stigmatized or marginalized populations should not be overlooked either; in concentrated HIV epidemics, these groups are responsible for driving transmission, yet, appropriately addressing the epidemic within these populations is complicated by lack of evidence on TasP effectiveness in them and highly politicized issues surrounding them (legality of homosexuality and prostitution in many countries and severity of punishment for drug users). Extending treatment – and indeed providing equitable access to health services – to these populations has not yet reached acceptable levels.

2) Challenges with ART initiation

Once a person is diagnosed with HIV, he/she is not immediately enrolled into ART or into a 'pre-ART' care program, and often he/she presents late for AIDS care at health facilities, even after an earlier HIV diagnosis. In Zambia, 43% of pre-ART patients were loss to follow up (LTFU), compared to 7% of patients enrolled in ART (Van Dijk et al, 2010); 25% of pre-ART patients where LTFU in
Ethiopia (Mulissa et al, 2010vi). Focusing on pre-ART made a significant difference in Swaziland, where the percentage of ART-eligible patients starting treatment increased from 53% to 81%, and the number of days from being ART eligible to being enrolled in treatment decreased from 61 days to 14 days after introducing a comprehensive care package which followed each person diagnosed with HIV until ART enrollment and beyond (Burtle et al, 2011vii).

3) Challenges with ART adherence and retention in care
Key challenges in long-term TasP implementation are adherence to ART regimens (non- or partial adherence leads to lower viral suppression) and retention on HIV treatment and care, which form part of the leaky treatment cascade. There is evidence that a proportion of individuals on ART are infectious despite ARV use. In South Africa, 30% of ART patients maintain viral loads above 1 500 viral copies/ml, and 10% have over 50 000 copies (Kranzer, Lawn, Johnson, Bekker & Wood, 2013). Similarly, in Kenya, 22% of HIV-positive individuals reporting ART use have over 1 000 copies/ml (National AIDS and STI Control Programme, 2013). In West Africa, only 10% of all HIV-positive people are virally suppressed through AIDS treatment. Even in the United States, only 28% of people living with HIV are virally suppressed (<200 viral copies/ml) (Althoff, Buchacz, Hall, Zhang, Hanna, Rebeiro et al., 2012). Challenges with viral suppression could be overcome by strengthening and carefully monitoring the treatment cascade, such as has been done in the previously mentioned British Columbia ART program. In this situation, only 22% of ART adherent patients have viral loads greater than 50 copies/milliliter (Nosyk, Montaner, Colley, Lima, Chan, Heath et al., 2014).

Data on retention on ART over time suggest that losses can be very significant. UNAIDS reports indicate that fewer than 60% of Malawians and less than 50% of Indonesians are retained on treatment after 5 years. Young adults (15 – 24) living with HIV are also at greater risk for attrition after ART initiation than younger adolescents and older adults, but this risk can be reduced if adolescent
support groups and sexual and reproductive health services are offered at the clinics they attend (Lamb, Fayorsey, Nuwagaba-Biribonwoha, Viola, Mutabazi, Alwar et al., 2014). Even before ART initiation, it will be equally important to retain HIV-positive individuals within a system of monitoring and care, so that they may be enrolled in the treatment cohort at the appropriate time. Therefore, significant logistical and programmatic efforts will need to be made towards linking diagnosed HIV cases to ongoing medical provision and strengthening the retention of these individuals in a pre-treatment cohort to improve morbidity and mortality. One approach could be to use home-based care, including adherence support. A cluster-randomized trial in Uganda found that patients initiating ART and receiving home-based care had similar survival rates as those that received clinic-based care, even among those with very low CD4 counts (Woodd, Grosskurth, Levin, Amuron, Namara, Birunghi et al., 2014).

4) Challenges with ART-related drug resistance if enrolled for long periods of time

Drug resistance to ARVs is another potential problem associated with implementation of TasP. Resistance to ARVs may occur due to poor adherence to ART or use of ARV regimens more susceptible to drug resistance. Expanding ART coverage to HIV-positive individuals with higher CD4 counts and otherwise feeling healthy may be associated with poor adherence in this population. This could be averted if first-line, once-daily ARVs with minimal side effects and less susceptibility to drug resistance are used. Additionally, if access to and availability of ARVs continues to be a problem during, or is the result of, ART scale-up, there is a greater risk for drug resistance to occur. One study suggests that acquired HIV drug resistance in low resource settings rises from over 5% in patients on less than one year of treatment to greater than 20% after 3 years (Stadeli & Richman, 2013). Moreover, patients from countries with older ART programs (>5 years) were more likely to have transmitted drug resistance than those from younger programs (<5 years) (Stadeli & Richman, 2013). The
Development of drug resistance in patients over their treatment duration has also been described in high-income countries (Phillips, Dunn, Sabin, Pozniak, Matthias, Geretti et al., 2005). Furthermore, mathematical models expect transmitted drug resistance to increase throughout the course of an HIV epidemic, with respect to the baseline prevalence of drug resistance, and significantly impact mortality at the population level (Cambiano, Bertagnolio, Jordan, Lundgren & Phillips, 2013). Thus, increasing drug resistance as treatment is scaled-up and as ART programs and HIV epidemics mature seems likely. To minimize this, significant financial, technical, and logistical resources will need to be put into ensuring access and adherence to first-line ARVs and careful monitoring of patients to detect and address ART failure as soon as it occurs.

**Addressing implementation challenges and facilitating TasP**

TasP can be facilitated through a variety of mechanisms in order to maximize cost-effectiveness and address its implementation challenges:

1) *Prioritized ART access and scale-up can contribute to the economic feasibility of TasP and its cost-effectiveness.*

Achieving high ART coverage under previous guidelines in some settings is a challenge associated with TasP. One approach to this is focusing first on increasing access (HIV testing and linkage to care) to those most in need (CD4 counts <350) before extending ART eligibility to higher CD4 counts. In some settings, increasing access among HIV-positive adults with CD4 counts <350 may result in greater HIV incidence reductions over 20 years than expanding ART eligibility to higher CD4 counts. However, the latter may cost less per DALY averted (Eaton, Johnson, Salomon, Barnighausen, Bendavid, Bershteyn et al., 2012; Eaton et al., 2014). Of note, these modeled analyses were carried out in countries with moderate to high ART coverage (South Africa and Zambia), and in
settings with low coverage, expanding access within lower CD4 count groups may be more cost-effective. For concentrated epidemics such as in Vietnam and India, expanding ART eligibility within the general population is cost-effective, but increasing HIV testing and linkage to care should be focused on specific populations driving the epidemic (Eaton et al., 2014).

2) Combining TasP with other high impact interventions

In a cost-effectiveness model of HIV prevention tools, it was found that high male circumcision and ART coverage (among HIV-positive individuals with CD4 counts <350) implemented together could reduce HIV incidence in South Africa to a similar degree as TasP, and this approach was estimated to be USD 5 billion less expensive than TasP implementation from 2009 to 2020 (Barnighausen et al., 2012). The most cost-effective intervention, however, was increased male circumcision, costing USD 1 100 per infection averted, followed by high ART coverage (USD 6 800) and TasP (USD 8 400). As such, while TasP is cost-effective, as per WHO guidelines, the authors here suggest that increased male circumcision and ART coverage is more so, and should be rolled out first.

3) Prioritized TasP scale-up in key populations at high risk of transmitting HIV

The best implementation strategies for specialized HIV-positive communities and their larger population in which they reside should also be investigated and employed to ensure the success of TasP. For instance, it was found that prioritizing access to care to female sex workers and their clients was the most efficient way to expand ART and avert remaining HIV infections within the general population in a ten year period in South India, rather than expanding ART eligibility (Mishra, Mountain, Pickles, Vickerman, Shastri, Gilks et al., 2014).

4) Integrating HIV and health services
A strong focus on the strengthening and integration of health systems and interventions delivered across key delivery platforms, including community outreach, clinics, and hospitals will be needed. This is particularly important for LMICs, as they have limited resources (logistical, financial, and human) to expand health services, and many HIV-positive patients from LMICs are unable to access or remain in care, due to time and cost required to travel to health facilities. One way to address this for TasP is to “decentralize” HIV treatment from hospitals to health facilities or communities to facilitate patients’ access to care and treatment. A review of studies in which patients were initiated or maintained on ART in a decentralized setting in LMICs found that ART initiated in a hospital and maintained in a health center appeared to have less attrition and loss to care than hospital alone (Kredo, Ford, Adeniyi & Garner, 2013). Moreover, decentralization did not result in worse health outcomes (Kredo et al., 2013). Indeed, the Lancet Commission’s report supports decentralization, as it maintains that clinics play an important role in healthcare service delivery and that many diseases can be treated at a primary care level, including HIV (Jamison et al., 2013).

5) Task shifting

Task shifting of healthcare services is another way in which use of limited (human) resources can be maximized in biomedical HIV interventions, including TasP. In Uganda, personnel costs were reduced by moving from a physician-intensive model for ART services to models that relied more heavily on nurses or pharmacy workers. In the latter scenario, costs were reduced by two-thirds (Babigumira, Sethi, Smyth & Singer, 2009). Additionally, the best use of available resources should be considered. For instance, expanding ART eligibility will require more clinical monitoring of patients, including routine viral load testing, which might impair the process of expanding ART coverage and eligibility in limited resource settings. In these cases, it may be preferable to use resources towards earlier ART initiation rather than routine virological testing, as
a modeling study using HIV data from East African countries showed the former to be a more cost-effective mechanism (Scott Braithwaite, Nucifora, Toohey, Kessler, Uhler, Mentor et al., 2014).

6) More efficient program management: Smarter implementation for HIV services, including TasP, should also include more efficient program management

There is great variation in the costs of HIV program management globally, providing an opportunity to explore the most appropriate, efficient, and cost-effective allocation of HIV resources for program management. The Middle East/North Africa and Caribbean regions spend 29-32% of their HIV resources on program management, and in sub-Saharan Africa, 19%. Eastern Europe, Asia and the Pacific spend less than 10%, but not as low as the minimal amount of 4% of HIV resources going into program management in Central and South America. More efficient HIV program management could lead to a freeing up of overall resources that could be allocated towards TasP implementation programs. Costs per ART patient are also quite variable among HIV/AIDS programs sites, decreasing as sites mature and acquire more patients (Menzies, Berruti & Blandford, 2012). Along the same lines, treatment costs across national facilities can vary, and driving costs from less efficient, higher cost facilities to those more efficient, with lower costs is a strategy to increased overall HIV program efficiency in Kenya.

7) Integration into UHC schemes

There is a global acknowledgement of the importance of include Universal Health Coverage (UHC), under which, by definition, essential health services must be available to all, free of financial hardship required to pay for them. UHC can support TasP scale-up where HIV testing, treatment and care are part of the essential package. Also, UHC calls for strong, efficient health systems to be in place, well-run by a cadre of skilled health workers, all required for TasP
implementation and meeting Global Health 2035 goals. But, most importantly, UHC mandates access to affordable health services. Not only will this promote increased ART coverage, as more people are able to access it, but it will also support the cost-effectiveness of TasP. If TasP is to be included within the UHC framework, it will be required to remain financially feasible within national health budgets. To do so, additional financial allocation will need to be made to ARV-based interventions, which are, however, expected to be cost-saving in the long run (decreased HIV incidence, lower morbidity and mortality).

8) The use of incentives to improve HIV treatment outcomes and reduce unit costs

In regard to external funding of HIV/AIDS programs, a Results-Based Financing (RBF) approach could help address the leaky treatment cascade. This approach has been supported by the Global Fund to fight AIDS, Tuberculosis, and Malaria and the World Bank, the latter having recently financially invigorated their Health Results Innovation Trust Fund. A new partnership between these two global funding entities will center around using RBF for projects related to Millennium Development Goals (MDGs) 4 and 5, reducing child mortality and improving maternal health. HIV programs and services are included among the projects, specifically focusing on service integration and effective supply chain management of essential health commodities, all relevant to effective TasP implementation. Additionally, Rwanda and the Global Fund just announced a pilot HIV grant using RBF, in which indicators important for TasP, such as percent of adults and children receiving and retained in ART, will be used to assess performance.

The RBF strategy has been applied and successful in previous situations financing national healthcare. In Burundi, an RBF program was introduced in 2010 in which health facilities were rewarded up to 25% of their monthly earnings for meeting health indicator goals that included reproductive, maternal, and child
health and HIV services. By 2012 the number of children immunized rose by 20%, and HIV-positive pregnant women given ART to prevent mother-to-child-transmission of HIV by almost 60 percent (World Bank, 2012a).

9) Continued investment in biomedical, sociobehavioral, and operational research must be sustained

Investment in health research and development (R&D) is another area that is highly emphasized in the Lancet Commission report. The report argues that it has “extraordinary value” and recent R&D for the infections and disorders under the Grand Convergence scheme is under-funded. Global Health 2035 calls for at least a doubling of R&D funding from 2011 levels by 2020, with half of this investment coming from LMIC themselves (Jamison et al., 2013). This target, USD 6 billion per year, is only 2 – 4% of global spending on R&D and has also been recommended by WHO Consultative Expert Working Group on R&D: Financing and Coordination (Rottingen & Chamas, 2012).

HIV R&D investment will also be important to logistically and financially facilitate TasP implementation. Heavy financial investment in basic and clinical HIV research is to thank for current ARVs, including longer-acting combination drug regimens with fewer side effects and less susceptible to drug resistance. Continued investment in HIV R&D is necessary to continue this trajectory of ARV innovation, especially as ARV use becomes more widespread and with it the risk for drug resistance. Furthermore, investment in R&D for HIV treatment could lead to lower costs of ARVs, as has already been observed over the past 5 years (WHO, 2012), especially when development and production of HIV drugs happens in LMICs. Over 80% of donor-funded ARVs have been supplied by Indian manufacturers since 2006, due to their success in reverse engineering of HIV drugs developed by European and North American countries and their out-licensing agreements with these companies (Waning, Diedrichsen & Moon, 2010). The more LMIC manufacturers that are able to produce generic ARVs,
the more competitive the market will become, driving costs down. This is especially needed for the more expensive first-line ART regimens.

It is equally important to continue socio-behavioral and operational research to evaluate HIV programs and determine which strategies work best. With regard to TasP, better ART adherence and retention strategies (based on evidence of what works) will be essential to securing long-term economic, health and social benefits of TasP.

10) Technological innovations

Technological innovation can lead to improved ART service delivery, better patient satisfaction, and better adherence and retention. A good example of this is how the Themba Lethu Clinic in South Africa, the world’s largest ART center with 30,000 patients enrolled and 1,000 seen daily, cut back individual patient waiting time for ARV dispensing from upwards of 4.5 hours to 30 min with the use of an automated pharmacy robot. The robot connects to an integrated information and communications technology (ICT) system that is able to verify and validate a patient’s electronic prescription, and within minutes, dispense the appropriate medication. Not only has this technology cut back patient waiting time, but it has also reduced the number of pharmacists needed, freeing them to attend patients in the wards (Mkize, 2013). This successful integrated automated pharmacy machine and ICT system will be rolled out to three pilot sites in Tshwane and it will be first trialed for HIV drug dispensing. Additionally, the use of mHealth and eHealth approaches, such as those used for patient tracking or to remind patients to take medication, to improve ART adherence and retention, and decrease loss to follow up rates, have been tried and works, but has not yet been rolled out at a national level in all ART programmes.

Conclusion
TasP implementation will require significant financial investment and massive, painstaking implementation efforts at local, national and global levels. In its early stages, there will be many challenges to address, with regard to ART scale-up and coverage levels required for TasP effectiveness in various populations and demographics. However, the positive externalities of ART go beyond the individual; the public health, economies, and society of the communities and states can also benefit from increased ART coverage. Moreover, while costly, analyses suggest that TasP is cost-effective in both generalized and concentrated HIV epidemics. As such, it can be considered a good health investment and fits well within Global Health 2035 goals.

Given cost and implementation challenges, implementing TasP effectively will require meticulous, incremental, patient-by-patient planning and action, while also upholding quality and expanding access through unremitting daily exertion and care. This is especially true for low-income countries with large epidemics, for which it must be emphasized that TasP is no magic short-cut. In these cases, TasP implementation should be rolled out by first increasing ART coverage within the population of HIV-positive individuals with the most advanced infections and then progressively expanding ART eligibility. More targeted and diversified strategies for HIV testing within populations most at risk for HIV should also be included in TasP implementation to increase the percentage of PLHIV that actually know their HIV status. Finally, the use of other HIV prevention interventions such as medical circumcision (shown to be more cost-effective than TasP), along with behavioural interventions (condom usage, partner reduction, demand creation, etc.) should not be overlooked or decreased in favour of TasP, and could work synergistically with it.

TasP as part of a high-impact HIV strategy will be a major undertaking. It challenges the global health and development community to excel in strategic planning, supply chain logistics and local program implementation, as well as
devising sustainable financing mechanisms. TasP holds promise in driving the epidemic trajectory downwards while saving lives. And by making HIV-infected people live longer, more productive lives, we can hope to see invaluable socio-economic gains.
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ii Authors’ estimate based on global estimates of PLHIV and average global ART unit cost of USD 633 per case (derived from 2011 global ART expenditure of USD 5.07 billion and global ART data of 8 million cases treated.


v South Africa Ministry of Finance data, 2013


viii Data from NACC Kenya and World Bank 2012

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