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Science magazine named TasP as its “Breakthrough of the Year 2011”.

TECHNICAL BRIEF

Antiretroviral Treatment as Prevention (TasP): Opportunities and challenges

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Introduction

Lowering HIV viral load is critical to interrupting transmission and preventing morbidity and mortality. Treatment as Prevention (TasP) is a term used to describe HIV prevention methods that use antiretroviral therapy (ART) in HIV-positive and HIV-negative persons to decrease the risk of HIV transmission.¹ Redoubling efforts to provide treatment for those with CD4 count ≤ 350 cells/mm³ and increasing access to treatment for those with CD4 count > 350 for their own health and to decrease transmission risk to HIV-negative partners is already making a significant impact on HIV incidence and should be a priority in resource-constrained settings.

The new scientific evidence increasingly supports the option of using ART earlier than the current recommended start at ≤ 350 cells/mm³ to maximize the health and prevention benefits of ART.²

Rationale for Treatment as Prevention: The HPTN 052 Study. New Thoughts about Using ART to Decrease Transmission from HIV-infected People

The HIV Prevention Trials Network 052 (HPTN 052) was a “game-changer” in our thinking around the use of ART as a prevention intervention.³ From 2005-2010, this randomized controlled trial hypothesized whether earlier treatment, with the concomitant decrease in viral load and presumed infectivity, would result in decreased risk of HIV transmission to the uninfected partner. Implemented in Africa, Asia, and America, couples were randomly assigned to one of two groups: immediate ART group in which the HIV-infected partner was placed on ART immediately, regardless of CD4 count, and the delayed ART group in which the HIV-infected partner was placed on ART when his/her CD4 count dropped below 250 cells per μL . This difference is important because trial participants were asymptomatic, did not yet require treatment for their own health, and certainly would not have been eligible for treatment according to most national guidelines. Each group received the same amount of care and prevention counseling.

1 World Health Organization, “Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update,” (Geneva: WHO Press, 2012), 5.

2 Ibid, 6.

3 Cohen MS et al. Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine*, 2011, 365(6):493–505.



Though long suspected that treatment reduces an individual's viral load resulting in decreased risk of HIV transmission, the HPTN 052 study is the first to conclusively prove this theory. Early initiation of ART (when cell counts are greater than 350) by HIV-infected individuals reduced the risk of HIV transmission to the uninfected sexual partners by 96 percent compared to initiation when CD4 counts were ≤ 250 . In addition, early initiation of ART significantly reduced the risk of extra pulmonary tuberculosis (TB) and other complications of HIV and AIDS.⁴

Pre-Exposure Prophylaxis: New Thoughts about Using ART in HIV-negative People to Protect against Infection

New developments in Pre-Exposure Prophylaxis (PrEP), which uses ART to provide prophylaxis to HIV-negative persons who may be exposed to HIV, are gaining wide acceptance. The use of PrEP has recently been approved by the United States Food and Drug Administration for use in that country. These results add to a growing body of evidence confirming the powerful potential of antiretroviral drugs for HIV prevention. The Partners PrEP study in Kenya and Uganda enrolled 4,758 heterosexual couples in which one partner was HIV-positive and the other HIV-negative.⁵ The trial showed that tenofovir or tenofovir plus emtricitabine taken daily reduced the risk of HIV transmission among heterosexual men and women by 62% to 73%, respectively. The TDF2 trial sponsored by the US Centers for Disease Control showed that tenofovir/emtricitabine taken daily reduced the risk of HIV infection in both men and women participants by an estimated 63 percent compared to those who received a placebo.⁶ Finally, the iPrEx trial, a study of daily oral tenofovir/emtricitabine in gay men, other men who have sex with men, and transgender women, showed a 44 percent reduction in HIV risk compared to placebo.⁷

4 World Health Organization, "Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update," (Geneva: WHO Press, 2012).

5 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* 2012 Aug 2;367(5):399-410. Epub 2012 Jul 11.

6 Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* 2012 Aug 2; 367(5):423-34. Epub 2012 Jul 11.

7 Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L et al.; for the iPrEx Study Team. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010 Dec 30;363(27):2587-99. Epub 2010 Nov 23.

In addition, data presented at the 2010 International AIDS Conference highlighted the positive results of the CAPRISA 004 trial of 1% tenofovir vaginal gel in heterosexual women, which showed that women who received the gel had an estimated 39 percent lower risk of infection compared to those who received an inactive placebo gel.⁸

While encouraging, these prevention approaches are not foolproof and do not offer 100% protection against acquisition of HIV. More work is required in formulation, adherence support, and user targeting before broad adoption throughout the world. While the current WHO guidance does not include the use of PrEP and ARV-based microbicides, these technologies will likely be important additions to the prevention arsenal within the next one to two years.



Global Policy Guidance

WHO's working definition of Treatment as Prevention for HIV and TB is:

- Providing ART to people living with HIV irrespective of CD4+ cell count for the prevention of HIV and TB
- Includes provision of ART to all people living with HIV who are:
 - severely immunocompromised with AIDS and/or have a CD4+ count ≤ 350 cells/mm³ and below those
 - with higher CD4+ cell counts > 350 cells/mm³

On the basis of recent scientific evidence, WHO recommends the more strategic use of antiretrovirals in the following ways:

1. Immediate enrollment of people living with HIV on ART, especially serodiscordant couples regardless of CD4 count, to reduce the risk of HIV transmission to the uninfected partner. As nearly 50% of HIV-positive people in committed relationships are estimated to have HIV-negative partners, Zambia already provides ART to the HIV-positive partner in serodiscordant couples irrespective of CD4+ count. More than a dozen other countries, including Rwanda and Mozambique, announced plans to revise their guidelines to boost national prevention and treatment efforts.

8 Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010; **329**: 1168–74.

2. Reviewing/revision of current practices to prevent mother-to-child transmission (MTCT). In July 2011, Malawi implemented Option B+ as its primary strategy for reducing vertical transmission of HIV. Under *Option B+*, **all HIV-positive pregnant women are enrolled on ARVs for life, regardless of their CD4 count.** This not only treats HIV infected women and prevents transmission to their infants; it can also reduce the risk of HIV transmission to their sexual partners.⁹ As a result of Malawi's experience, both Namibia and Uganda have received Ministry of Health (MOH) approval and are working on implementation plans to implement Option B+ in their National Plans for elimination of MTCT, while four other countries (Kenya, Mozambique, South Africa, and Zambia) are engaged in high level MOH discussions for transition to Option B+.

3. Provide ART for all TB patients irrespective of CD4+ count: HIV-associated TB is a major global public health threat, and HIV infection is the strongest risk factor for TB-related deaths. A recent WHO-led meta-analysis found that ART reduced the individual risk of TB by 65%, irrespective of CD4+ count, while Isoniazid preventative therapy combined with ART can reduce the risk of TB among people living with HIV (PLHIV) by up to 97%.¹⁰

4. ART for children: Recent research suggests that HIV-infected children should be placed on ARVs at or near the time of diagnosis.¹¹ Still, many pediatric treatment programs struggle to meet the needs of infected infants and children. Without treatment, 50% of HIV-infected infants will die before they reach two years of age and three quarters will die by their fifth birthday.

5. Review recent evidence on potential health benefits of enrollment on ARVs earlier to inform future policy guidance: Although the current WHO guidelines recommend that people diagnosed with HIV start taking ARVs when the CD4 cell count drops below 350 cells/mm³, evidence increasingly shows that HIV infection causes chronic inflammation, thus increasing the risk of other health problems, such as certain types of cancers, heart disease, and diabetes. WHO is therefore reviewing recent studies that point to the potential health benefits of giving ART earlier, before the immune system weakens. WHO plans to release revised and consolidated guidelines on the use of ARVs for both HIV treatment and prevention in 2013.¹²

Regional Practices

A recent WHO-led review of global TasP research concluded that there are more than 50 ongoing or planned field trials and analyses, including a number of large randomized controlled studies. Funding opportunities are increasing and more data on TasP will become available in the near future as the experience and evidence base of the outcomes of expanding access to ART increase.¹³

Although most national HIV guidelines focus on the clinical benefits of treatment, the concept of using ART earlier to prevent HIV and TB has been around for nearly a decade and a number of countries have already incorporated such recommendations into national guidelines. A 2011 WHO-led study reviewed the ART guidelines of 72 countries/regions on national ART initiation criteria for asymptomatic HIV-positive people, pregnant women living with HIV, people with HIV and TB, serodiscordant couples, injecting drug users, and sex workers. The review did not include ART eligibility for children living with HIV or use of ARVs to prevent MTCT (except when part of ART for pregnant women).¹⁴ The table below provides information for select SADC member countries whose ART guidelines were included in this WHO review.¹⁵

| CD4 initiation criteria (cells/mm ³) | Countries |
|--|--|
| ≤350 | Lesotho, Malawi, Namibia, South Africa Swaziland, Zambia, Zimbabwe |
| ≤250 | Botswana, Mozambique |
| ≤200 | Tanzania, Democratic Republic of Congo |

A number of countries have included TasP in their guidelines, and/or are implementing TasP as part of their national HIV response.¹⁶ However, none of the countries reviewed have specific recommendations for ART or TasP for sex workers, drug users, or men who have sex with men.¹⁷ At the end of August 2012, the Swaziland National AIDS Programme announced that the country will soon pilot the TasP program and that a National Implementation Framework has already been developed.¹⁸

13 World Health Organization, "Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update," (Geneva: WHO Press, 2012), 15.

14 Ibid.

15 Ibid, 9.

16 Ibid, 11.

17 Ibid.

18 Swazi Observer, "Swaziland to pilot HIV treatment as prevention," August, 29, 2012, <http://www.observer.sz/index.php?news=42455>

9 Schouten EJ, Jahn A, Midiani D, et.al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet*. 2011 Jul 16;378(9787):282-4.

10 World Health Organization, "Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update," (Geneva: WHO Press, 2012). 8.

11 Violari A, Cotton MF, Gibb DM, et.al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008 Nov 20;359(21):2233-44.

12 WHO, News release "'Strategic use' of HIV medicines could help end transmission of virus," July 18, 2012, http://www.who.int/mediacentre/news/releases/2012/hiv_medication_20120718/en/.



Recommendations

Given the increasing range of treatment and prevention options, and growing resource constraints, difficult decisions need to be made. Using ARVs most strategically requires careful decision-making at the clinical, operational, and programmatic levels. Strong evidence, good practice, and solid ethical and equity principles should guide those decisions.¹⁹

By the end of 2011, eight million people living with HIV in low- and middle-income countries were accessing ART for their own health although an estimated 15 million people are in need, for a treatment coverage rate of just 54%.²⁰ While efforts are underway across the region to increase the numbers of people on treatment in Sub-Saharan Africa, treatment expanded by only 20% between 2009 and 2010.²¹

Providing ARVs to people living with HIV who are in serodiscordant relationships, pregnant women, and high risk populations, regardless of CD4 count would increase the number of people eligible for treatment in low- and middle-income countries from the current figure of 15 million to 23 million.²² While this will increase the cost of providing treatment in the short term, studies predict that the economic benefits of early treatment will substantially offset, and likely exceed, program costs within 10 years of investment. Changing the ART threshold from 350 to 500 cells/mm³ (in addition to including the groups mentioned above regardless of CD4+ levels), would further increase the pool of people eligible for ART to 25 million. In the wake of recent research findings and modeling exercises, some have called for a “test-and-treat” approach. This would involve regularly screening entire populations for HIV and initiating immediate treatment for everyone found to be HIV-positive. Such a scenario would increase eligibility for ART to the total 32 million people living with HIV in low-and middle-income countries.²³

While the benefits of implementing some or all of these strategies are apparent, most low- and middle-income countries have yet to achieve “Universal Access” to ART, and indeed many are struggling to put those with the lowest CD4 counts on treatment. There are many reasons for this:

- The majority of people do not know their HIV status.
- Large proportions of people who initiate ART only do so once their health has seriously deteriorated, i.e., when their CD4 counts are less than 200.
- There is substantial attrition in the “test-treat-retain” continuum, even in countries with well-developed health systems and high testing rates.

Other issues need to be addressed as well. These include: the emergence of drug resistance; improving the reliability of supplies; continued integration of HIV services with other health services; task shifting to deal with growing workloads of health care providers; addressing social and structural barriers to treatment and care; and assuring community participation.²⁴ The economic benefits of starting ART at a CD4+ count of ≤ 250 cells/mm³ are well established. A recent costing study based on South African data suggests that starting ART at higher CD4+ cell count (>500 cells/mm³) could yield potential cost-savings, but would require considerable “front loading” of investments, i.e., it would be quite expensive to initiate, but cost savings would be realized down the road. Further economic and epidemiological modeling is needed to refine projections of the expected resource needs and public health impact of such recommendations in different settings. Further modeling is being done to examine the impact, costs, and cost-benefits of investing in different types (and combinations) of HIV prevention and treatment interventions.²⁵ In settings where resources are scarce, there are strong reasons to conclude that ART should first be provided for those who are the most immunocompromised (i.e., those with the lowest CD4 counts) and require immediate access to ART for their own health and to stay alive. Treatment as Prevention activities should then commence after those with the lowest CD4 counts are cared for. Targeting individuals at higher risk of transmitting the virus could also have a large impact on the epidemic, beyond the prevention benefit through provision of ART to those that are clinically eligible.²⁶

²⁴ Ibid, 10.

²⁵ Ibid, 18.

²⁶ World Health Organization, “Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update,” (Geneva: WHO Press, 2012), 11.

¹⁹ WHO, “The strategic use of antiretrovirals to help end the HIV epidemic,” (Geneva: WHO Press, 2012), 15.

²⁰ Ibid, 8.

²¹ United Nations, “The Millennium Development Goals Report 2012,” (New York, 2012), 42.

²² WHO, “The strategic use of antiretrovirals to help end the HIV epidemic,” (Geneva: WHO Press, 2012), 8.

²³ Ibid.

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