HIV/AIDS Programme

PROGRAMMATIC UPDATE

ANTIRETROVIRAL TREATMENT AS PREVENTION (TASP) OF HIV AND TB

JUNE 2012

World Health Organization

Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update
WHO/HIV/2012.12

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1. BACKGROUND

In 2010, an estimated 34 million people were living with the human immunodeficiency virus (HIV), around 70% of them in sub-Saharan Africa. By the end of 2010, 6.6 million people, or 47% of those in need (CD4+ cell count <350 cells/mm^3), were on antiretroviral therapy (ART), and an estimated 7.5 million people were still in need of treatment. While considerable progress has been made in extending ART coverage, there continue to be critical gaps. In the same year, coverage for children was reported to be less than 23%, there were 2.7 million new infections and more than 20 million people were not yet treatment-eligible (as most of them did not know their HIV status). There were an estimated 1.1 million new cases of HIV-associated tuberculosis (TB), which led to 24% of HIV-related deaths. HIV is the strongest risk factor for developing TB, and people living with HIV have a 20–37 times higher risk of developing TB than those who do not. ART has a significant secondary prevention benefit for both HIV and TB, and expanded access to ART has probably averted millions of HIV infections and cases of TB. The World Health Organization (WHO) has introduced the concept of HIV elimination through the use of combination prevention and prevention of mother-to-child transmission (PMTCT) of HIV. Additionally, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched Treatment 2.0 to look at ways to provide better services to a larger number of persons at lesser cost, and in a way that helps to retain them on lifelong ART. This would also greatly benefit HIV prevention efforts.

WHO WORKING DEFINITION OF TASP FOR HIV AND TB

- ART irrespective of CD4+ cell count for the prevention of HIV and TB
- Includes provision of ART to people living with HIV who are:
  - severely immunocompromised with AIDS and/or have a CD4+ count ≤350 cells/mm^3
  - those with higher CD4+ cell counts >350 cells/mm^3
- Does not include the use of antiretrovirals (ARVs) for post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) and ARV-based microbicides

Treatment as prevention (TasP) is a term used to describe HIV prevention methods that use ART in HIV-positive persons to decrease the chance of HIV transmission independent of CD4 cell count. While this update focuses on TasP of HIV and TB, there have been exciting developments in the use of other biomedical interventions such as antiretrovirals (ARVs) and microbicides for pre-exposure prophylaxis (PrEP), which are the topics of other WHO documents.

2. GUIDING PRINCIPLES

Combination prevention: contribution of biomedical prevention interventions

Combination HIV prevention includes evidence-based biomedical, behavioural and structural interventions, such as interventions to increase the use of condoms, sterile needles and syringes, and opioid substitution therapy. Although this paper focuses on a single biomedical intervention,

it is recognized that all biomedical interventions such as ART, PrEP with ARVs, post-exposure prophylaxis (PEP), and treatment of sexually transmitted infections have behavioural components. Another effective biomedical intervention is male circumcision, which reduces the risk of female-to-male sexual transmission of HIV by approximately 60%. Although still unavailable, in the future, microbicides and/or an HIV vaccine could become additional important interventions.

Progress in the prevention sciences has been promising; the randomized controlled trial HPTN 052 and observational studies have sparked strong interest in the potential of ART for preventing HIV and TB morbidity, mortality and transmission. Scaling up and providing access to treatment for individual benefits according to the WHO 2010 treatment guidelines (CD4 count ≤350 cells/mm^3) as part of combination HIV prevention is already making a significant impact and remains a top priority in resource-constrained settings. New scientific evidence increasingly supports the option of using ART earlier before severe immunocompromise at ≤350 cells/mm^3 to maximize the health and prevention benefits.

3. THE EVIDENCE BASE ("WHAT DO WE KNOW")

HIV prevention efforts focused on people living with HIV make sense from an individual and public health perspective, and there is high-quality evidence supporting the use of ART to prevent HIV transmission.

Clinical benefits and when to start

Both the clinical and prevention benefits of ART initiation at the WHO-recommended eligibility criterion of CD4+ count <350 cells/mm^3 are unequivocal. Recent studies suggest that even earlier initiation of ART is warranted, both for HIV prevention and clinical benefit. WHO will systematically review the evidence regarding when to start ART for the guidelines update in 2013.

ART and HIV transmission

Viral load is the greatest risk factor for HIV transmission, and lowering the viral load is critical to interrupting transmission and preventing morbidity and mortality. Studies suggest that the risk of transmission is near zero when the viral load is below 1500 copies/mm^3. In 2011, the HPTN 052 trial showed that, among HIV-serodiscordant couples, ART given to the HIV-positive partner with a CD4+ count <550 cells/mm^3 decreased HIV transmission by 96% when compared with those who started ART at CD4+ counts <350 cells/mm^3; this confirmed data from observational and ecological studies.

EVIDENCE SUPPORTS THE USE OF ART FOR PREVENTION OF HIV TRANSMISSION

- Transmission only occurs from persons with HIV.
- Viral load is the single greatest risk factor for HIV transmission.
- ART can lower the viral load to undetectable levels.
- PMTCT provides proof of the concept that ART reduces HIV transmission.
- Strong evidence from observational and randomized controlled trials in heterosexual couples support the efficacy of ART in preventing HIV transmission.
- Knowing one's HIV status is key to the use of ART for prevention.
- Starting ART below CD4+ 350 cells/mm^3 (according to current WHO guidelines) has clinical and prevention benefits.

ART and PMTCT

Further proof of the concept that ART interrupts HIV transmission is provided by the fact that the risk of mother-to-child transmission (MTCT) of HIV is directly linked to maternal viral load. ART use has led to the virtual elimination of perinatal HIV cases in the United States, and different regimens of ARVs, including ART, are being successfully used to decrease the risk of MTCT worldwide. The 2010 WHO guidelines on ARVs for PMTCT recommend ART for women eligible for treatment, and one of two prophylaxis regimens (Options A and B) for women with CD4+ counts >350 cells/mm^3. In the light of changing evidence and operational experience, many countries are moving towards the use of one ART regimen and some countries are proposing to start all HIV-infected pregnant women on lifelong ART, irrespective of whether they are eligible as per clinical guidelines (Option B+). This could also have a significant impact on the prevention of HIV transmission both to children and to sexual partners. Additionally, safer conception is possible when the HIV-infected partner is virally suppressed on ART.

ART and children

Children are the most vulnerable of all individuals with HIV. Without ART, mortality approaches 50% at two years and 80% by five years. Of the estimated 2.1 million children in need of ART today, only 23% are receiving it, compared with 48% of adults. Bottlenecks limiting paediatric treatment include poor access to diagnosis, weak systems for patient retention, few health facilities and providers equipped to deliver paediatric ART, and drug regimens that are more complex to administer than adult regimens. Global programmes to expand access to ART and eliminate new HIV infections among children provide an unprecedented opportunity to address the burden of untreated paediatric HIV. Elimination of MTCT will result in fewer infected children and, as more HIV-exposed infants are tested, a larger proportion of infected children will be identified. It is essential that national programmes continue to set aggressive targets for paediatric ART even as they strive to simplify ART, decentralize services and eliminate new infections in children.

ART and community transmission

Analyses of programme data combining HIV surveillance and cohort data with high ART coverage for those eligible for treatment in British Columbia, Canada, San Francisco, USA and Taiwan, Republic of China, demonstrate a decrease in community- and regional-level HIV transmission associated with expanded access to ART. More recently, the Africa Centre in KwaZulu Natal, South Africa reported a decrease in individual risk associated with increased ART coverage. Modelling programme interventions for optimal provision of ART and HIV testing and counselling (HTC) suggests that HIV can be eliminated in some geographical and epidemiological settings.

ART and tuberculosis

HIV-associated tuberculosis (TB) is a major threat to global public health and HIV infection is the strongest risk factor for TB. In 2010, there were an estimated 1.1 million cases of TB among 34 million people living with HIV worldwide; the 350 000 HIV-associated TB deaths accounted for 19% of all HIV-related deaths and 24% of all TB deaths. ART has been found to significantly reduce the risk of morbidity and mortality due to TB. A recent WHO-led meta-analysis (in press) found that ART reduces the individual risk of TB disease by 65%, irrespective of the CD4+ cell count. Isoniazid preventive treatment and ART given together can reduce the risk of TB among people living with HIV by up to 97%. Expanded access to ART has been shown to have a significant impact on community-level TB incidence, morbidity and mortality. Modelling data from nine African countries on the impact of starting to expand ART in 2010 with results determined for the years 2015 and 2050 suggest that initiating ART two years after HIV seroconversion would reduce the incidence of TB by 63%; delaying ART until five years after seroconversion would reduce the incidence of TB by 48% by 2015. WHO recommends ART for all TB patients irrespective of CD4+ count.

Status of TasP research

Robust scientific evaluations and discussions are available on how to best use ART for the prevention of HIV. A recent WHO-led review of global TasP research concluded that there are more than 50 ongoing or planned field trials and analyses, which include 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 regarding the outcomes of expanding access to ART increase.

4. CURRENT STATUS OF NATIONAL HIV TREATMENT GUIDELINES AND IMPLEMENTATION EXPERIENCE WITH TASP

National HIV treatment guidelines

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).

The United States recommends offering ART for all people living with HIV irrespective of CD4+ count; Algeria, Argentina, Bolivia, European AIDS Clinical Society Guidelines, France, Guinea, Italy and Uruguay recommend or consider ART for asymptomatic HIV-positive people with CD4+ counts between 350 cells/mm^3 and 500 cells/mm^3; Bolivia and Italy also consider ART at CD4+ counts of ≥500 cells/mm^3 if good adherence can be maintained (*see* Table 1).

Table 1: Guideline ART initiation criteria by CD4+ count and country or region

CD4 initiation criteria (cells/mm^3)	Number of countries	Countries/Region(s)
Irrespective of CD4 count	1	United States
≤500	3	Algeria, Argentina, Bolivia
≤350 (consider ≤500)	3	Uruguay, France, Italy
≤350	40	Bangladesh, Britain, Kenya, Cambodia, Haiti, Lesotho, Malawi, Namibia, Nigeria, Swaziland, Zambia, Zimbabwe, Sierra Leone, Ghana, Thailand, Guyana, Nepal, Brazil, Rwanda, Burundi, Chile, Ecuador, Guinea, Mexico, Nicaragua, Panama, Papua New Guinea, Canada, European AIDS Clinical Society, Paraguay, Venezuela, China, El Salvador, Djibouti, Guatemala, India, Niger, Spain, Indonesia, Viet Nam
≤200 (consider ≤350)	5	Cape Verde, Caribbean, Cuba, Russia, Ukraine, Afghanistan
≤250	5	Botswana, Uganda, Mozambique, Colombia
≤200	15	Ethiopia, South Africa, Tanzania, Philippines, Myanmar, Bhutan, Liberia, Democratic Republic of Congo, Ivory Coast, Comoros, Dominican Republic, Pakistan, Malaysia, Peru, Cameroon

Of the 72 countries, 49 mention ART initiation criteria for people with HIV and TB in their HIV treatment guidelines; 22 of these 49 countries recommend ART for all people coinfected with HIV and TB irrespective of CD4+ count; 25 countries recommend ART for people coinfected with HIV and TB with a CD4+ count ≤350 cells/mm^3. Zambia recommends ART at a CD4+ count >350 cells/mm^3 for HIV and TB coinfected people with other WHO clinical stage 3 or 4 illnesses; Myanmar and Ethiopia recommend ART irrespective of CD4+ count for people living with HIV with extrapulmonary and disseminated TB; South Africa recommends ART irrespective of CD4+ count for HIV-positive people with drug-resistant TB.

For serodiscordant couples, 13 countries and the regional guidelines for Europe have included recommendations on the use of ART to prevent HIV transmission (*see* Table 2). The United States, Algeria, Canada, Italy, Uruguay, Venezuela, Europe and Zambia recommend initiating ART irrespective of CD4+ count for serodiscordant couples as well as for other indications; Mexico recommends ART for serodiscordant couples if the CD4+ count is between 350 cells/mm^3 and 500 cells/mm^3. Argentina, Britain, France, Thailand and Nigeria recommend considering initiation

of ART for the HIV-positive partner in serodiscordant couples irrespective of the CD4+ count. Burundi recommends ART irrespective of CD4+ count if partners of HIV-negative pregnant women are HIV-positive. Malawi recommends initiating ART for life, irrespective of CD4+ count, in HIV-positive pregnant women, the rationale being that it will prevent HIV transmission in serodiscordant couples. Although China and Rwanda do not mention serodiscordant couples in their published national ART guidelines, they have announced plans to initiate ART in this population.

Table 2: Guideline ART eligibility criteria for asymptomatic people and serodiscordant couples

Country	Year	Asymptomatic people (CD4 initiation criteria cells/mm^3)	Serodiscordant couples (CD4 initiation criteria cells/mm^3)
USA	2012	Irrespective of CD4 count	Irrespective of CD4+ count
Algeria	2010	≤500	Irrespective of CD4+ count
Argentina	2010	≤500	Consider ART irrespective ofCD4+ count (>500)
Bolivia	2009	≤500	No mention
Uruguay	2011	≤350 (consider for ≤500)	Irrespective of CD4+ count
Europe	2011	≤350 (consider for ≤500)	Irrespective of CD4+ count
France	2010	≤350 (consider for ≤500)	Consider ART irrespective of CD4+ count (>500)
Italy	2011	≤350 (consider for ≤500)	Irrespective of CD4+ count
Nigeria	2010	≤350	Consider ART irrespective of CD4+ count (>350)
Rwanda	2007	≤350	Plan to treat irrespective of CD4+ count
Zambia	2010	≤350	Irrespective of CD4+ count
China	2008	≤350	Plan to treat irrespective of CD4+ count
Thailand	2010	≤350	Consider ART irrespective of CD4+ count (>350)
Venezuela	2010	≤350	Irrespective of CD4+ count
Canada	2009	≤350	Irrespective of CD4+ count
Mexico	2011	≤350	350– 500
Malawi	2011	≤350	Irrespective of CD4+ count for HIV-positive pregnant women
Burundi	2010	≤350	Irrespective of CD4+ count for HIV-positive serodiscordant pregnant women
Britain	2008	≤350	Consider ART irrespective of CD4+ count (>350)

Of the countries reviewed, none have specific recommendations for ART or TasP for sex workers. Most guidelines do not specifically mention TasP for drug users or men who have sex with men (MSM); however, Guyana, Myanmar and Viet Nam recommend ART for injecting drug users at the same CD4+ count eligibility criterion recommended for other people living with HIV.

Implementation experience with TasP

There are a number of examples of recent implementation of TasP beyond the eligibility criteria for asymptomatic people living with HIV. Zambia currently provides ART for the HIV-positive partner in serodiscordant couples irrespective of CD4+ count. In China, the Chinese Center for Disease Control and Prevention has started providing ART to the first of an estimated 30 000 serodiscordant couples irrespective of CD4+ count as part of its countrywide HIV Testing as Prevention Strategy and Treatment as Prevention Strategy. Rwanda and Mozambique recently announced plans to revise their guidelines to include ART irrespective of CD4+ count for HIV-positive individuals in serodiscordant relationships to boost national HIV prevention and treatment efforts. Malawi, while not making any specific recommendation for serodiscordant couples, has recently begun implementing a strategy of lifelong ART for all HIV-infected pregnant and breastfeeding women, regardless of CD4+ count and/or clinical stage (Option B+), and 16 other countries are actively considering this approach. A number of other countries have included TasP in their guidelines, and/or are implementing TasP as part of their national HIV response.

5. PROGRAMMATIC AND OPERATIONAL CONSIDERATIONS

Setting programme priorities based on local resources and epidemiological context

Programme managers face difficult decisions on how to best use their limited resources for interventions that have the greatest impact on reducing HIV-related morbidity and mortality and new HIV infections, while ensuring that equity and ethical issues are considered.

Although there has been considerable investment in the global HIV response, the epidemic requires increased and sustained efforts. In settings where resources are scarce, there are strong reasons to conclude that ART should first be provided for those who are immunocompromised and require immediate access to ART for their own health and to stay alive. 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 who are clinically eligible for it. Understanding the economic impact and benefit of expanding HIV prevention and treatment services is critical for policy-makers, donors, programme managers and the community. The favourable findings of economic analyses that include the prevention benefit of ART as part of combination prevention are largely due to the high inpatient costs averted, low overall ARV drug costs and new HIV infections averted—this effect is far greater when ART is part of a combined prevention approach. More recently, some studies have found a significant potentially favourable economic impact for individuals living with HIV, their families and the society.

Although the economic benefits of starting ART at a CD4+ count ≤350 cells/mm^3 are well established, a recent costing study based on South African data suggests that starting ART at a higher CD4+ count (>500 cells/mm^3) could have potential cost savings but would require considerable "front loading". Further economic and epidemiological modelling is needed to

refine projections of the expected resource needs and public health impact when these recommendations are planned and implemented in different settings.

Programme planners and national decision-makers will require guidance on how best to prioritize interventions to achieve the maximum impact, and how to make allocative decisions accordingly.

Deploying TasP in concentrated and generalized epidemic settings

While the principle of using ART to prevent HIV and TB transmission applies to most settings, the design, prioritization and impact of TasP-centred interventions will differ according to the type of epidemic. For example, interventions for testing and linkage to care including ART in a generalized epidemic setting would need to be designed quite differently from those for a concentrated epidemic setting, which would need to focus on services for key populations.

Knowledge of HIV status and early access to TasP

The prevention benefits of TasP interventions are likely to be most effective if made available early for populations at risk of transmitting HIV. This will require early identification and linkage to care through the availability of HTC in facilities (where there is increasing emphasis on provider-initiated HTC) and in the community (e.g. door to door, multi-disease prevention campaigns, peer outreach, new information technologies such as the internet, SMS).

Service delivery: effective linkage to HIV care following HTC, acceptance, long-term adherence and retention

Maximizing the potential benefits of TasP requires access to HTC with subsequent linkage to HIV care and the option for clients to access ART if and when eligible. TasP requires a shift in perspective for clinicians and patients, who now need to consider not only the clinical benefits but also the HIV and TB prevention benefits of accepting and adhering to treatment. Treatment acceptance, retention and long-term adherence are of serious concern for all ART programmes, and introducing TasP may improve or decrease performance in these areas. Retention in care after testing for HIV and then starting on ART is dependent on a number of critical interlinked factors, including accessibility of services, nature of ART regimens used, services provided, competing priorities and stigma.

TasP and the acute phase of HIV

Understanding the nature of the acute phase of HIV infection and its contribution to transmission has been challenging and often depends on the stage of the epidemic. Data on acute HIV infection and viral replication are surprisingly scarce. Some studies in generalized epidemics suggest that the acute phase with viral load peaking probably lasts around 21 days; approximately 30 days are required for the viral load to reach a steady state. Other studies have suggested that the duration of the acute phase is around four months. Given the potentially short duration and extent of transmission that occurs outside of the acute phase during an estimated 10-year lifespan (off ART), concerns about the duration or importance of the acute phase should not preclude the use of TasP as an effective prevention intervention at any stage of infection.

TasP, disinhibition and risk compensation

Concern that the availability of ART would result in behavioural disinhibition or HIV risk compensation was raised as a potential issue in the early 2000s when ART expansion was being

proposed for resource-constrained settings. Particular concerns were raised in the context of epidemics where MSM are the most affected population. Experience and research in Africa and other resource-constrained settings has not found that the availability of ART results in disinhibition or risk compensation. The prevention effect of ART among sex workers and their clients, MSM and injecting drug users is not known. In particular, structural issues should be addressed around these communities, in whom arguments about risk compensation may be used to justify refusal of access to TasP. The added benefits of TasP combined with earlier knowledge of HIV status as people seek earlier access to ART has actually served to reduce HIV risk behaviours and risk of HIV in some resource-constrained settings.

TasP and drug toxicity

Some experts have raised concerns regarding drug toxicity, which may subsequently affect retention and adherence. Selection of regimens that are less toxic and easier to administer will be even more important when starting treatment earlier for asymptomatic persons (both below and above CD4+ count 350 cells/mm^3) than in symptomatic patients. The regimens will include ARVs that can be used at higher CD4+ counts in both women and men. Current WHO recommended first-line recommendations will work above and below a CD4+ count 350 cells/mm^3 with TDF- and EFV-based regimens being preferred, given considerations such as durability, price and toxicity profile (*see* 2010 ART Guidelines for more details). There is growing experience with early ART in concentrated epidemics in Europe and the US, where MSM are mainly affected. While there will be some upfront risk of adverse events or drug toxicity with concomitant lack of adherence, these risks must be weighed by the patient and their clinician against the duration to eligibility (often an average of 1–4 years depending on the eligibility criteria), and the clinical (e.g. reduced TB and other pathogen burden, improved retention since ART and clinical support are being offered) and preventive benefits of an earlier start.

TasP and drug resistance

Expansion of ART translates into widespread availability, and the use and potential misuse of ARVs. Resistance is a serious concern given the expansion of ART. An increasing number of WHO-recommended surveys show moderate levels of HIV drug resistance (5%–15%), suggesting that despite resistance remaining low in most surveyed areas, a moderate degree of resistance is appearing as ART expansion continues. Unless carefully monitored and contained, resistance has the potential to reduce the efficacy of standard ART regimens in a large proportion of patients, and also because the limited availability of alternative regimens restricts treatment options based on drug resistance test results. However, the growing concerns of emergence and transmission of resistance should not prevent expanded access to ART including TasP, which can be safely delivered if accompanied by routine implementation of surveillance for resistance at the population level and robust programmatic assessment to identify factors associated with the emergence of resistance.

TasP and monitoring and evaluation

Monitoring and evaluation of expanded HTC and ART are part of TasP efforts and are essential for ensuring programme quality and monitoring progress towards global targets to reduce new HIV infections among young people aged 15–24 years, eliminate new HIV infections in children, and reduce HIV- and TB-related mortality by 2015. Successful monitoring of progress towards HIV

control and elimination will require a few additional indicators along the testing and treatment cascade, and special periodic surveillance studies to monitor viral load suppression and HIV incidence. To achieve this, estimated denominators at each step in the cascade of interventions, from the target population, to testing and treatment and retention in care need to be collected and analysed. Where possible, viral load should be measured as a surrogate for prevention benefits and adherence. Monitoring and evaluation systems will need to be built around decentralized services to community-based health centres, task shifting that includes ART initiation by nurses and other health workers, and less frequent follow up after initiation of ART (e.g. every three months) as people become more comfortable being on ART. Triangulation of programmatic data and modelling will continue to play an important role in estimating the impact of expanded access to HTC and ART as part of TasP in programme settings.

TasP, human rights and ethics

The HIV epidemic highlights important equity and human rights concerns. The perspectives of those posing questions on ethics will vary. There are a number of important stakeholder perspectives (e.g. people living with HIV, their partners and family; the affected community; international and local policy-makers; and donors). A primary ethics question concerns the lack of access to treatment for millions of people. Some stakeholders have also raised concerns about the potential for coercion to treatment. Others have called for more data supporting the individual benefit of earlier treatment. On the other hand, the issue of denying access to TasP for people living in resource-poor settings while providing it in resource-rich settings must also be carefully considered. Arguably, in settings where ART is scarce, there are good reasons to conclude that ART should first be provided to those who are immunocompromised and in urgent clinical need but the ethics of resource-driven policy decisions regarding rationing of ART are questionable, as in the early days of rapid ART scale up witnessed with the WHO "3 by 5" Initiative.

TasP and community engagement

Engaging and supporting the community as a meaningful partner in the design, implementation and evaluation of HIV programmes is critical for using TasP successfully, particularly where there is potential for stigma and human rights violations. Although many programmes recognize this principle in theory, its practice is challenging and further efforts are needed to implement this essential aspect of a successful HIV response.

6. WHO'S FOCUS: THREE PRIORITY AREAS OF WORK

WHO PRIORITY AREAS OF WORK

WHO will work in three priority areas, in close collaboration with Member States, implementing partners, UNAIDS and other UN cosponsors, civil society and researchers:

Priority area of work 1. Develop norms and standards for the strategic use of ARVs (including TasP).

Priority area of work 2. Inform programmatic and operational decisions.

Priority area of work 3. Define metrics for monitoring/evaluating TasP impact.

Current WHO guidelines and policy on ART for treatment and prevention

The WHO public health paradigm conceptualizes ART as critical to keep people alive and healthy, and as part of the solution towards the UNAIDS and WHO goals of ZERO new infections and ZERO deaths, and the vision of eliminating HIV. Scaling up ART to current WHO-recommended eligibility criteria and targeting utilization of TasP above WHO criteria (i.e. CD4+ count <350 cells/mm^3) for certain populations (serodiscordant couples, pregnant women, key populations such as MSM, sex workers and injecting drug users, and people at risk for TB) underpins WHO's current approach to expanding its normative guidance ("incremental approach to TasP").

The 2010 WHO ART guidelines address the prevention of HIV- and TB-related morbidity and mortality by increasing the threshold for eligibility to ART from people with a CD4+ count ≤200 cells/mm^3 to include the much larger group of those with a CD4+ count ≤350 cells/mm^3. It is clear that the shift in eligibility threshold to ≤350 cells/mm^3, if fully implemented, will also have significant prevention gains (*see* Table 3).

Table 3: ART eligibility criteria in the WHO 2010 and 2012 guidelines

Population (people living with HIV)	Criteria
Asymptomatic patients, ARV-naive individuals	CD4 ≤350 cells/mm^3
TB disease, ARV-naive individuals	Irrespective of CD4 count for confirmed TB
Pregnant women	CD4 ≤350 cells/mm^3
Seropositive partner in discordant relationship	Irrespective of CD4 count (≤350 and >350 cells/mm^3)
Key populations*	CD4 ≤350 cells/mm^3, no specific recommendations.

* People who inject drugs, sex workers and men who have sex with men.

With the important changes that have taken place since the publication of the 2010 guidelines, including global ART scale up, decreased ART cost, improved first-line regimens and the strong evidence for ART as prevention, WHO is moving to address TasP in a number of key guidelines and updates.

a. WHO refers to ART for prevention of TB among HIV-infected individuals in the 2012 WHO HIV/TB collaborative policy document.

b. The 2012 guidelines on HIV testing and counselling and ART for serodiscordant couples is the first WHO guidance with a formal TasP recommendation. It recommends ART for the HIV-positive partner irrespective of CD4+ count.

c. The WHO 2012 technical update on the recommended PMTCT options discusses the advantages and implications of "Option B", which provides triple ARVs to HIV-infected pregnant women throughout the pregnancy and postpartum breastfeeding risk period for PMTCT of HIV. The technical update also recognizes the potential advantages of Option B+ (lifetime treatment for all HV-infected pregnant women), which is in the very early stages of implementation in some countries (*see* recent 2012 WHO programmatic update at http://www.who.int/hiv/pub/mtct/programmatic_update2012/en/index.html). Option B would provide the additional benefit of TasP for children and partners during the prophylaxis period,

while Option B+ would provide lifelong treatment as a prevention benefit to reduce transmission to infants, sexual partners and in future pregnancies.

d. WHO is also currently reviewing evidence on the use of ARVs in HIV-negative individuals (PrEP) in two populations towards issuing a "rapid advice" document by mid-2012.

WHO will be publishing consolidated ART guidelines in 2013, which will include all WHO guidance related to the use of ARVs for HIV prevention and treatment. The guidelines will include TasP and use the standard WHO Grading of Recommendations Assessment, Development and Evaluation (GRADE) review process to answer key questions and consolidate previously standalone recommendations, including those currently found in guidance related to PMTCT, HIV/TB, HIV care, ART for adolescents and adults, paediatric ART and service delivery. The consolidated guidelines will incorporate technical, programmatic and operational guidance.

WHO'S STRATEGIC APPROACH TO TASP

1. Continue to support the implementation of current ART guidelines and recommendations, which will have significant preventive and clinical benefits for the individual and community:
   - Accelerate the intensity and scale up implementation of the WHO 2010 ART guidelines for adults and adolescents and children, notably by increasing access to ART for all HIV-infected individuals with CD4+ cell counts ≤350 cells/mm^3 irrespective of WHO disease stage, and those with WHO stages 3 and 4 illness, and offering immediate ART (irrespective of CD4+ cell count) to all patients with HIV-related TB, HIV/hepatitis B coinfection and all infants below 24 months of age.
2. Support countries in identifying additional opportunities for TasP ("incremental approach"): this will include support to:
   - Implement WHO guidelines on couples HIV testing and counselling and ART as prevention for serodiscordant couples.
   - Identify opportunities to move towards harmonizing ART and PMTCT programmes to optimize the clinical and preventive benefits of ART.
   - Progressively review the evidence and explore the feasibility and acceptability of expanded HIV testing and ART as prevention in other populations including sex workers, MSM, transgender people, and people who inject drugs and their sexual/injecting partners.
   - Provide technical assistance to regions, countries and other geographical settings regarding the impact of the new guidelines (e.g. number of additional cases that will need ART, health outcomes, economic outcomes, etc.).
3. During 2012, conduct systematic evidence reviews towards revised and consolidated ART guidelines in 2013 (which will include TasP and PreP).

Priority area of work 1: Develop norms and standards for treatment as prevention

WHO's first priority is to continue to support the implementation of its current guidelines and recommendations, which are likely to provide considerable preventive and clinical benefits for HIV and TB for the individual and community. Over the past few years, WHO has been conceptualizing the use of ART to explicitly consider ways by which both the individual and public health preventive benefits of ART can be maximized. WHO recognizes the need to provide timely, state-of-the-art guidance on the use of ARVs for both HIV treatment and prevention, including TasP. It also recognizes that programmes are in various stages of expanding access to ART to achieve universal access goals, and will need to prioritize their interventions. WHO will expand the public health approach to include programmatic and operational guidance, specifically on the service delivery aspects of linking HIV testing approaches to care and treatment as well as prevention. The first guidance that explicitly addresses TasP is the 2012 couples HIV testing and counselling guidelines.

WHO has embarked on formulating critical questions for TasP, which will be answered partly by systematic reviews and the standard WHO GRADE review of the evidence, including data from modelling as well as ongoing demonstration projects and implementation research. WHO will address both individual- and community/population-level benefits of earlier initiation of treatment.

At present, the key questions being addressed for the development of WHO TasP recommendations for the 2013 guidelines are as follows:

- What is the impact of earlier initiation of ART on morbidity and mortality? What is the impact of earlier initiation of ART on TB incidence and mortality?
- What is the impact of earlier initiation of ART on behavioural outcomes?
- What is the prevention benefit of starting ART earlier for people living with HIV within key populations?
- What is the impact of earlier initiation of ART on ARV toxicity?
- What is the impact of earlier initiation of ART on transmitted drug resistance to HIV?

Priority area of work 2: Inform programmatic and operational decisions

WHO is working on a number of programmatic and operational areas, including programmatic guidance and ethics consultations focused on the strategic use of ARVs, and operational guidance as part of Treatment 2.0, which will inform scale-up models. WHO is also supporting implementation research efforts in Asia and Africa.

Key questions for decision-makers include the following:

1. What is the magnitude of the prevention benefit of ART in the local epidemiological context? What will the impact of ART be on TB morbidity, mortality and transmission? (Annual national TB programme case notification rates can provide good proxy for ART impact.)

2. How can the results of research and programme data be translated into effective programmes implemented at scale and at what additional cost?

3. In which settings and populations should ART be initiated early to have the greatest overall impact on the HIV and TB epidemic curve?

4. What is the appropriate mix of prevention interventions to optimize this impact?
5. What are the best (most effective and efficient) ways to deliver ART and how can optimal retention in treatment be achieved?

This highlights the principles of knowing your epidemic and response, and the potential role of mathematical modelling to inform programme implementation. Strengthening existing systems for surveillance and response monitoring remains critical, and implementation research is increasingly being recognized as an important tool for decision-makers. Key components of implementation sciences are related to measurement, operational research and impact evaluation, and can include estimation of cost and cost–benefit. The experience from early programme implementation, demonstration projects and observational/cohort studies will provide valuable information for formulating critical programmatic questions and help arrive at policy decisions based on the modelled impact and cost–benefit of ART for prevention interventions, including HIV drug resistance.

Priority area of work 3: Define metrics for monitoring and evaluating the impact of TasP

WHO will continue to lead a process to promote retention in care, defining the challenges and identifying solutions towards providing decentralized and integrated services. This includes addressing the current lack of consistency in definitions of terms relating to retention and loss to follow up, time period definitions and, in general, poor programme reporting on retention and adherence. The metrics for ART as prevention will be based on monitoring the existing indicators for retention in and adherence to treatment. In addition, the role of individual- and community-level viral load, HIV biological and behavioural surveillance, and triangulation of data will be determined.

In this context, WHO is addressing a number of key questions:

- Which indicators are currently being measured in national HIV and TB control programmes, and how are the data being collected and interpreted? Which set of indicators should be used along the cascade of interventions from HIV testing, re-testing, and starting and continuing ART for both prevention and treatment of HIV and TB?
- What are the strengths and weaknesses of measurements made at the individual and population levels for evaluating the effectiveness and impact of TasP?
- What approaches and methods can be used to measure the epidemiological impact of TasP? Which of the methods of measurement used under routine programme conditions can also be implemented as part of research studies in resource-limited settings?
- How can modelling studies contribute to the choice of measurement indicators and the evaluation of data in different epidemic contexts?
- How is resistance to ARV drugs measured? How and when should resistance be measured in the context of TasP?

7. CONCLUSION

HIV causes an infectious disease that, with the right prevention interventions delivered within a human rights framework, can be controlled and possibly even eliminated. WHO, UNAIDS and

the United Nations General Assembly have called for 15 million people to be on ART by 2015. ART has considerable benefit, both as treatment and in preventing HIV and TB. It is certain that TasP needs to be considered as a key element of combination HIV prevention and as a major part of the solution to ending the HIV epidemic. In the short and medium term, while countries are concentrating their efforts on scaling up treatment according to the eligibility criteria recommended by WHO, it is expected that they will concurrently identify opportunities to maximize the use of ART for prevention purposes (TasP). The focus will be on specific populations in whom the prevention impact is expected to be greatest (e.g. serodiscordant couples, pregnant women, key populations). During 2012, WHO is issuing updates and guidance for these populations, and is working with countries to address programmatic and operational challenges to inform the consolidated guidelines to be released in mid-2013.

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