ART in Prevention of HIV and TB

Frequently Asked Questions

1. What is the global burden of HIV and TB?

At the end of 2009 there were 2.6 million new infections and 33.3 million people living with HIV infection [1]. The total number of people living with the virus in 2008 was more than 20% higher than the number in 2000, and the prevalence was roughly threefold higher than in 1990. More than 95% of all HIV-positive people are in low- and middle-income countries. The epidemic continues to exact an especially heavy toll on sub-Saharan Africa, home to two thirds of people living with HIV; more than 14 million children in this region under the age of 15 have lost one or both parents to AIDS.

In addition, HIV infection and AIDS killed approximately 1.8 million persons in 2009, including more than a quarter million children [1].

WHO estimates that HIV infection increases the risk of tuberculosis by 20-37 fold [2]. There were 1.2 million HIV positive incident TB cases in 2009, of which 910,000 (76%) were from Africa [3]. In some African countries, over 80% of incident TB cases were HIV positive [2]. There were 400,000 deaths among all HIV positive incident TB cases. These 400,000 deaths represent 24% of all TB deaths [3] and 22% of all HIV-related deaths [1].

2. What is the status of universal access

At the end of 2009, 5.25 million people were receiving ART in low and middle income countries, an increase of over 1.2 million from December 2008, with the greatest increase taking place in sub-Saharan Africa (3.91 million versus 2.95 million) [4]. Eight low and middle income countries have achieved universal access, treatment coverage of at least 80% of patients in need, to ART by WHO 2010 Guidelines eligibility criteria of treating all asymptomatic people with CD4 $\leq$ 350. Globally, 36% of adults and children in need have access to ART [4]. The figure for children under 15 years of age is 28% [4]. While there was a 19% reduction in mortality among children from 2004 to 2009, 370,000 children were infected with HIV through mother-to-child transmission in 2009 [1].

Despite these successes, over 9 million people in need worldwide are without access, and over the coming decade an additional 15 million will require ART. Furthermore, it is clear that ART access is not equitable. In particular, most-at-risk populations (MARPs), especially people who inject drugs, men who have sex with me and sex workers, are under-served in HIV treatment programmes. As the

epidemic evolves, a new population, those over 50 year of age, with specific treatment and care needs, is emerging.

HIV-associated opportunistic infections (OIs), cancers and other co-morbidities (hepatitis B & C) continue to cause considerable morbidity and mortality, particularly in resource limited settings. Even in high income settings, OIs represent a problem due to late presentation with severe immunosuppression, and ART treatment failure. Global guidance on the diagnosis, prevention and treatment of major OIs, cancers and other co-morbidities in adults and children are lacking, and has been requested by many countries.

3. What is the HIV prevention gap?

Despite the remarkable increase in access to ART between 2003 and 2009, the epidemic continues to outpace the HIV response. Globally, as of December 2009, an estimated 33.3 million people were living with HIV. By end-2009, while approximately 5.25 million people were accessing antiretroviral therapy in low- and middle income countries, an estimated 9.4 million in immediate need of treatment could not access it [4]. An additional 1.2 million people were added on treatment in 2009. With 2.6 million new infections in the same year, the treatment gap, which estimates the number of people with HIV eligible for HAART against those with access to HAART decreased from 72% in 2008 to 64% in 2009. Current efforts to treat HIV are not keeping pace with all those who need therapy and without a dramatic reduction in new HIV infections this trend will continue.

A major barrier to effective HIV prevention and treatment is that less than 40% of all people living with HIV in low and middle income countries are aware of their HIV status [4]. Without significant improvements in prevention, the likelihood of achieving the targets of the Millennium Development Goals for 2015 and universal ART access by 2010 appear increasingly remote.

There is no one intervention—no "magic bullet"—capable of eliminating HIV. No single prevention intervention is fully protective and each has its own strengths and limitations. HIV epidemics occur simultaneously within different populations and among people in diverse social networks, requiring a range of prevention interventions. *Combination prevention* combines mutually reinforcing biomedical, behavioral, and structural interventions to meet the needs of different groups. Drawing on epidemiologic and demographic data to determine the optimal mix of prevention services for a given population,

programmes should seek to achieve and sustain an effective and comprehensive response.

4. Why the increased focus on ART as a tool to prevent HIV and TB?

More than 30 years after the discovery of the HIV, control of the HIV epidemic remains elusive, and there have been calls to re-examine the current approach to controlling HIV [5]. There have been an increasing number of new HIV infections despite years of prevention effort. It is estimated that globally there were 2.6 million incident HIV infections in 2009, and 9.3 million who needed antiretroviral therapy in low- and middle-income countries, while only 5.25 million people or 36% were receiving ART [4]Universal access to HIV treatment and care will be greatly expedited as we invest in means to interrupt HIV transmission.

The concept of using ARVs to prevent HIV and TB is not new. ARVs have been used to prevent HIV transmission for over 10 years—the best examples include the use of ARVs to prevent transmission of HIV as part of prevention of mother to child transmission (PMTCT), the use of ARVs for post exposure prophylaxis (PEP) after needle stick and/or sexual exposure and more recent studies that suggest that ARVs could be used as part of a microbicide. A 2010 systematic review of late phase randomised control trials for prevention of sexual transmission of HIV categorised trials by type of prevention interventions [i.e., behavioural, microfinance, diaphragm, microbicides, preexposure prophylaxis (PrEP), male circumcision, sexually transmitted infection (STI) treatment, and vaccines] and their effect on HIV incidence [6]. Of 37 randomized controlled prevention trials reporting on 39 interventions to prevent sexual transmission of HIV, only 5 reported a positive effect (defined as intervention that significantly reduced the risk of HIV in the intervention arm compared to the control arm). These included three male circumcision trials, one trial of sexually transmitted infection treatment and care, and one vaccine trial [6]. Results released in 2010 from the CAPRISA 004 vaginal microbicide trial, using a tenofovir-based vaginal gel, were promising with an ARV-based microbicide thought to be a few years away from widespread use [7]. Pre-exposure prophylaxis (PrEP) is being assessed in at least 5 ongoing or planned international trials [8 - 10].The first results, published in November 2010 from the I-PREX study in men who have sex with men, showed a 44% decrease in transmission in those who received a daily drug regimen of tenofovir and emtracitibine [11]. While data showed that adherence to the

medications was a major challenge for participants, for those participants who did adhere and had detectible drug levels, no infections were observed.

Clinicians, public health experts and people living with HIV have also recognized the growing evidence base that earlier ART has immune restorative, survival, and prevention benefits. Community-based studies in San Francisco [12], Taiwan [13], and Vancouver [14] suggest that increasing ART coverage translates into a decrease in HIV incidence. ART also has a substantial effect on prevention of HIV-associated tuberculosis. Studies have shown that ART reduces the risk of tuberculosis by 80-92% [15-17]. Moreover, recent data indicates that ART reduces the risk of TB by 50% in people with a CD4 > 350 [18]. When coupled with the *Three I's* for prevention of HIV-associated TB; isoniazid preventive therapy, tuberculosis infection control, and intensified case finding; ART provides programmes with an excellent opportunity at limiting morbidity and mortality associated with HIV-associated with tuberculosis.

In summary, ART has been shown to be useful to prevent acquisition of HIV infection when provided prophylactically before or after exposure to HIV, to prevent transmission from HIV infected persons when provided as treatment that renders them less infectious, and to dramatically decrease the risk of HIV-associated TB, regardless of starting CD4. For prophylactic approaches to be effective, large numbers of people will have to be provided ART to prevent a single infection. On the other hand, ART for preventing transmission from HIV infected persons has the potential to have strong impact, and hence the increased focus on the role of ART in combination prevention strategies [19].

5. What are the current approaches to use of ARVs for prevention?

ARVs can be used for HIV prevention in three main ways:

1) ART: Treating people living with HIV to lower their viral load and hence decrease their infectiousness

2) PEP: Providing post-exposure prophylaxis after HIV exposure (sexual or needle sharing), or

3) PMTCT: using ARVs to prevent maternal to child transmission

6. What is the scientific evidence for effectiveness of ART as a prevention tool?

Plasma viral load is the single greatest risk factor for all modes of HIV transmission. A study from Uganda showed that patients with less than 400 copies of HIV RNA per millilitre have the lowest rate of HIV transmission, and demonstrated a stepwise increase in transmission rates for higher RNA levels [20]. In another study from Northern Thailand, the relation between viral load and HIV transmission showed a dose-response effect with each log increment of viral load increasing the risk of transmission by 81% [21].

The use of combination ART has been shown to reduce HIV-1 RNA plasma concentrations predictably to undetectable concentrations in most treated patients. International guidelines have uniformly recognized that sustained complete suppression of HIV-1-RNA is needed to achieve a steady increase in CD4-positive T-lymphocyte (CD4) cell count as well as a beneficial clinical response, and to avoid the emergence of drug resistant HIV mutants. Furthermore, the use of ART leads to a marked reduction in HIV-1 RNA concentrations in both the female genital tract and in semen [22].

Epidemic control requires that the basic reproductive rate (R_o), the number of secondary infections generated by one primary case, be reduced below 1 [23, 24]. By lowering viral load, ART reduces transmissibility as well as duration of infectiousness, the key determinants (along with rate of partner change) of R_o.

Evidence of the effect of ART on the prevention of HIV transmission is substantiated by the virtual elimination of paediatric HIV disease in high income countries by universal voluntary HIV testing of pregnant women and appropriate provision of ART. In addition, a recent study from Botswana showed that all regimens of HAART from pregnancy through 6 months post-partum resulted in high rates of virologic suppression, with an overall rate of mother-to-child transmission of 1.1% [25]. The study findings already have influenced WHO guidelines on the use of HAART to prevent mother-to-child HIV transmission [26]. In addition, for the first time, the new WHO guidelines recommend that all HIV-infected mothers or their infants take antiretroviral drugs while breastfeeding to prevent HIV transmission [26].

Observational data have shown reduced HIV transmission in serodiscordant heterosexual couples after the introduction of combination ART, and programmatic data support reduction in HIV transmission at the population level

[27]. Couples counseling and HAART in Uganda reduced HIV transmission by 98% [28]. A 2009 meta-analysis including 11 cohorts (5021 heterosexual couples) found zero risk of sexual transmission in patients treated with ART and with viral load below 400 copies per ml (upper confidence limit of 1.27 per 100 years) [29]. A recent randomized controlled study of genital herpes simplex virus (HSV) treatment among long-term, HIV-serodiscordant heterosexual couples in Africa found that transmission reduced by at least 90% if the HIV-positive partner is on antiretroviral therapy. The proportion of couples who had unprotected sex actually decreased when the HIV-positive partner started treatment, allaying fears about behaviour change [30].

There is also growing evidence of the impact of ART on community-level HIV transmission. In British Columbia a decrease in community plasma HIV RNA concentrations and HIV incidence among injecting drug users was associated with HAART use [31]. Between 2004 and 2008, the number of HIV diagnoses in San Francisco fell by 45%, the average viral load amongst the HIV-positive population by 40%, and the actual HIV incidence fell by one-third between 2006 and 2008 [12]. In Taiwan a 53% reduction in new HIV cases was associated with free access to HAART [13].

Modeling studies have also supported this concept. A modeling exercise undertaken for a 10-block area of Vancouver, Canada, suggested that declines in community viral load stemming from widespread ART were helping drive reductions in HIV incidence among injecting drug users [31, 32]. A WHO modeling team examined the potential prevention impact of ART on generalized epidemics and showed that annual universal voluntary HIV testing with immediate ART could transition the HIV response towards the elimination phase. Within 10 years of launching this approach, annual HIV incidence and mortality could fall below one case per 1000 people [23]. Modeling expanded HIV testing and access to ART for Washington, D.C. concluded that the strategy could potentially decrease the number of new HIV infections there by as much as 26% over 10 years and work in San Francisco suggests that incident infections could be reduced by 91% [33, 34]. Scientists in Vancouver have reviewed scientific evidence and modelled data derived from their programme and reached the conclusion that expanding access to ART could markedly reduce HIV incidence, decrease drug resistance, save lives, and be cost effective [35, 36]. Other mathematical modeling studies have reviewed assumptions and examined expanding HIV testing and counseling along with ART in other contexts and have arrived at contrasting conclusions [37-39].

7. What is the preventive efficacy of ART based on current WHO guidelines?

People living with HIV will eventually need treatment at some point in their life. Recent WHO guidelines recommend waiting until CD4 is ≤ 350 cells per cubic mm or until persons develop WHO clinical stage 3 or 4 events to start treatment. Expanding access to HIV testing and counseling and starting at CD4 count of 350 likely confers considerable HIV and TB prevention benefit both for the individual and the population relative to starting at CD4 counts less than 200.

Although knowing one's HIV status is key for prevention, the majority of people living with HIV do not know that they have the virus and many access ART only when severely immune-compromised. Despite the expansion of HIV counseling and testing services, knowledge of HIV status remains low. In population-based surveys conducted between 2003 and 2009, the median percentage of respondents aged 15–49 years living with HIV who reported having ever received an HIV test and test results prior to the survey increased from about 16.7% (2003–2006, 16 countries) to 38.6% (2007–2009, 10 countries) [4]. In addition, most patients in resource-limited and many patients in industrialized countries start ART late or very late. Review of data from 2003-2005 from 42 countries, 176 sites, (n=33,008 treatment-naïve patients) showed that since 2000, while CD4 at initiation in developed countries has remained stable at about 175 cells per cubic mm, in Sub-Saharan Africa, the median CD4 count at initiation of ART is around 100 cells per cubic mm [40].

A study from Africa that studied HIV discordant couples showed that across all study sites and, among all couples with one HIV-1 infected partner, almost half (49%) of couples were HIV-1 discordant [41]. Observational data have shown a reduction of approximately 92% in heterosexual transmission of HIV after the introduction of combination ART, irrespective of changes in other factors that affect transmission [30]. Clinical trials and additional data suggest that treating pregnant women reduces the risk of transmission to 1.1%, while also providing the best available treatment for the mother's health. In addition, ART will also provide protection during the breastfeeding period [25].

In settings with a large burden of HIV and TB, studies show that ART may contribute to TB control in both HIV-infected and HIV-uninfected individuals suggesting that the community wide benefit of ART extends even to those

without infection. Other studies show declining malaria incidence after ART initiation [42].

Therefore, there is a need to reach maximal coverage to get optimal benefits. Greater coverage of anti-HIV treatment would result in substantial reductions in the number of new HIV infections. A mathematical model developed by Canadian researchers showed that if 75% of patients started treatment when their CD4 cell count was 350 cells per cubic mm, then 40% of the projected new infections by 2030 would be averted, and this increased to 67% of anticipated infections if all patients started treatment when their CD4 cell count was around 350 cells per cubic mm. Increasing patient adherence would further modestly increase the number of averted infections [36].

8. How can the timing of initiation of ART potentially impact the HIV epidemic?

Epidemic control requires that the basic reproductive rate (R_o), i.e. the number of secondary infections generated by one primary case, be reduced below 1. Modelling analysis has shown that starting ART at CD4 count of 200 cells per cubic mm could reduce R_o to 4, starting at 350 cells per cubic mm could reduce it to 3, and starting at 500 cells per cubic mm could reduce it to 2.5. In addition, the study showed that testing all adolescents and adults at least 15 years old once a year, on average, and starting individuals on ART as soon as they test positive for HIV could reduce R_o below 1, and eventually eliminate HIV [23].

9. What recent strategies have been proposed for HIV testing and counseling and ART expansion?

WHO has revised its guidelines in November 2009 to recommend ART for all people living with HIV with CD4 $\leq$350 cells per cubic mm. In addition, ART is recommended for all people living with HIV with TB and those with HBV who require treatment for their HBV infection, irrespective of their CD4 count [43]. However, early access to HIV counseling and testing is essential for countries to reach WHO-recommended targets for ART, TB screening and initiation of isoniazid preventive treatment.

In light of the need for individuals to have earlier access to treatment, care, support and prevention, UNAIDS and WHO are supporting a major expansion of access to HIV testing and counselling through the scaling up of client and provider-initiated testing and counseling services through the emphasis has

been on facility-based approaches, recent interest has increased for community, household, and integrated campaign-based testing.Studies have shown that door-to-door HIV counseling and testing has the potential to significantly increase uptake and offers the opportunity for couples to learn their status together [44, 45]. While this approach shows considerable promise in many settings, it can be logistically challenging, time-consuming, and may miss key members of the household who are away at work and school. Project Accept HPTN 043 is the first international multi-site community-based randomized controlled study designed to determine the efficacy of a prevention intervention by measuring HIV incidence and stigma reduction as study endpoints [46]. Preliminary data indicate that the uptake of HIV testing increased four-fold in the communities receiving the intervention, suggesting that it is possible to break barriers, reduce stigma, promote discussion and encourage people to be tested [47].

Community-based integrated prevention campaigns can reach people living with HIV earlier with significant prevention and care benefits. A study from Kenya projected that using such an integrated campaign to provide earlier HIV testing and counselling and starting ART for all those with CD4 ≤ 350 cells per cubic mm could avert 27,000 HIV transmissions, 3,600 cases of TB and 76,000 deaths in this community of people [48].

In addition, the cornerstones of HIV counseling and testing scale up must include improved protection from stigma and discrimination, as well as improved access to integrated prevention, treatment and care services. A human rights approach, based on the "3 Cs" of HIV testing (confidentiality, counselling and informed consent) is a prerequisite for success [49].

Access to testing and counseling is a critical HIV service and there is considerable interest in determining the number of people that would need to know their HIV status to reach universal access goals including WHO recommendations regarding starting ART. Although exact figures are not available it is likely that the current efforts will need to be markedly expanded to reach international targets.

Modeling can shed some light on this problem. In November 2008, WHO scientists released the results of a modeling exercise conducted to assess the impact of expanded HIV testing and early initiation of ART as part of combination prevention on transmission of HIV. This approach predicts that the implementation of an annual voluntary universal HIV testing programme for

persons older than 15 years and with immediate initiation of ART for those individuals who test positive, regardless of their CD4 T-cell count or viral load, the HIV pandemic could be reduced within 10 years to just 1 incident case of HIV infection per 1000 people, and the overall prevalence of HIV infection reduced to below 1% before the middle of the century, thus theoretically bringing the pandemic to an end [23]. However, challenges to such an approach include conducting the necessary research; operational and financial feasibility; ethical and human rights challenges, acceptability; and the potential for drug resistance and toxicity [50].

10. When should ART be started to gain maximal individual and community benefits?

Although we now have over 5 million people on ART [4], we do not know with certainty when to start people living with HIV on ART. The WHO recommends ART in all individuals with CD4 $\leq$ 350. ART given below this threshold usually prevents opportunistic infections, and therefore improves survival. However, it is necessary to look beyond opportunistic infections and also consider the effect of HIV replication on deaths due to other causes (e.g. non-AIDS cancers, liver, cardiovascular, and renal-related deaths). Indeed, in the era of three drug antiretroviral therapy deaths due to these other causes now represent the majority of HIV-related deaths [51].

A publication from the SMART group compared the effect of uncontrolled viral replication when CD4 counts were > 350 on non-AIDS related deaths [52]. There were nine deaths which were not related to opportunistic infections during 2555 person-years in patients with a viral load ≤ 400 cp/mL, and there were 10 deaths which were not related to opportunistic infections during 865 person-years in patients with a viral load > 400 cp/mL. This means that patients with CD4 ≥ 350 who had uncontrolled viral replication were 3.28 times (95% CI 1.33 – 8.08) more likely to die of causes not related to opportunistic infections than patients with a viral load ≤ 400 cp/mL.

This interesting finding is supported by data which shows that HIV replication increases the risk of renal failure [53], endothelial dysfunction [54], liver-related deaths [55], and of non-AIDS cancers [56, 57]. As such, results from North America indicate that deferring therapy to a CD4 351-500 was associated with a 94% increase in the risk of death compared to starting ART at a CD4 greater than 500 cells per cubic millimeter [58]. Another recent study compared

mortality according to CD4 cell count at HAART initiation among adult patients in 18 cohorts in the United States and Europe. In this analysis, deferring HAART until CD4 cell count reached 251–350 cells per cubic mm was associated with a 28% higher rate of AIDS and death compared with starting when CD4 cell count was 351–450 cells per cubic mm [59].

In sub-Saharan Africa people start ART very late at a median CD4 count of around 100 cells per cubic mm and despite progress with improving earlier access, mortality remains markedly higher when compared with resource rich settings [59, 60]. Mortality risk is associated with starting late even for patients on HAART and is associated with the time spent below 200 CD4 cells per cubic mm [61, 62]. Although mortality rates at higher CD4 levels are lower, they are not zero, and people living with HIV may suffer an increased risk of morbidity and mortality relative to people living without HIV. In Zimbabwe, HIV mortality within 24 months postpartum in the absence of HAART was 54 times higher for those with CD4 cell counts less than 200 cells per cubic mm, 5.4 times higher for counts 400–600, and the hazard remained elevated at 6.2 for counts greater than 600 [63].Other cohort studies also suggest that starting earlier is warranted and the evidence increasingly points to the damaging effects of HIV even at higher CD4 count levels and the negative effects of letting CD4 counts drop too low [64-66].

Another argument for an earlier start is that ART has a significant role to play in preventing TB morbidity, transmission and mortality. ART has been reported to reduce TB rates by up to 90% at an individual level, by 60% at a population level and to reduce TB recurrence rates by 50% [67]. In a randomized clinical trial of 642 HIV positive patients with TB in South Africa, starting HAART earlier during TB therapy reduced mortality rates by 56% [68]. Given the devastating impact of TB, we may have to intervene with ART earlier before people living with HIV spend too long in the "TB death zone" which has been defined by some researchers as CD4 $\underline{\leq}$500 cells per cubic mm [61]. Recognising this, WHO has recently revised its guidelines to recommend ART for all people living with HIV with CD4 ≤ 350 cells per cubic mm and for all HIV positive patients with TB irrespective of their CD4 count [43].

Trial data confirms earlier observational studies and also points in the direction of an earlier start. The CIPRA HT 001 randomized clinical trial in Haiti was stopped by the Data Safety Monitoring Board as a result of the significantly fewer deaths and cases of TB in patients who started HAART earlier i.e. when their CD4 counts were between 200 and 350 cells per cubic mm compared with deferring

treatment until the CD4 count dropped below 200 cells per cubic mm [69]. In ACTG A 5164 trial, survival curves demonstrated a 47% reduced progression or death in patients receiving immediate as opposed to deferred HAART [70]. The SMART trial has also suggested that starting ART earlier was superior [52].

In addition, modeling analysis has shown that starting ART at different levels of CD4 cell count could substantially impact the number of lives saved. The number of HIV deaths between 2008-2050 could be about 11 million without ART, about 8.7 million with the strategy of starting ART when CD4 count is less than 350 cells per cubic mm, and 3.9 million with the theoretical strategy of universal voluntary HIV testing and immediate ART combined with the CD4 count less than 350 cells per cubic mm strategy [23].

According to the 2010 recommendations of the International AIDS Society-USA Panel, patient readiness for treatment is a key consideration when deciding when to initiate ART and there is no CD4 cell count threshold at which initiating therapy is contraindicated. While initiation of therapy is recommended for asymptomatic individuals with CD4 ≤ 500 cells per cubic mm, the guidelines recommend that treatment should be considered for asymptomatic individuals with higher CD4 cell counts [71].

WHO, after a rigorous review of the above and other data and in collaboration with a wide variety of stakeholders, has shifted its previous recommendations to recommend starting ART earlier for everyone with CD4 $\underline{\leq}$ 350 cells per cubic mm. In addition, ART is recommended for all people living with HIV with TB or those with HBV and chronic active hepatitis, irrespective of the CD4 count [43]. Pregnant women are also included in these recommendations with an eye to preventing morbidity, mortality and HIV transmission to their children [26].

11. What is Treatment 2.0?

The current response to HIV is often complicated and fragmented. Prevention, treatment, care and social support programmes are often complex and not integrated which translates into a lack of continuum of care and increased costs for programmes and patients. Treatment 2.0 is a new treatment paradigm in the global response to AIDS that through treatment optimization has the potential to improve access to treatment. It aims to simplify the way HIV treatment is currently provided and to scale up access to treatment. Using a combination of efforts it could bring down treatment costs, make treatment regimens simpler and smarter, reduce the burden on health systems and

improve the quality of life for people living with HIV and their families. In addition, it could maximize the collateral benefits of HIV treatment i.e. preventing new HIV infections, as well as reducing maternal, child and TB mortality.

Modelling suggests that compared with current treatment approaches, Treatment 2.0 could avert an additional 10 million deaths by 2025 [72]. In addition, the new approach could also reduce new HIV infections by up to 1 million annually if countries provide ART to all people in need, following the revised WHO treatment guidelines.

The approach calls for a combination of efforts in the following priority areas:

a. optimising drug regimens
b. advancing point-of-care and other simplified platforms for diagnosis and monitoring
c. reducing costs
d. adapting delivery systems
e. mobilising communities

12. What could be the operational challenges in expanding access to ART at CD4 ≤ 350?

Expanding access to ART at CD4 ≤ 350 cells per cubic mm or beyond would be hindered by weak health systems, lack of trained health personnel, choice of appropriate drug regimens, and difficulties could arise from drug resistance and adverse events related to medication. Significant ART expansion is likely to be costly initially, and it would be necessary to provide consistent and secure access to HIV rapid test kits, first-line and second-line ART, ensure high levels of adherence, and monitor the programme carefully. Scale up of HIV testing would require attention to sensitivity and specificity of the HIV tests used, the testing algorithm, and quality assurance as even a small false-positivity rate could lead to many people being falsely diagnosed as HIV positive. In addition, the behavioural implications of such a large cohort of people receiving ART on the community is not known [23].

However, recent studies have shown that increasing the provision of ART to CD4 ≤ 350 CD4 cells per cubic mm has the potential to reduce costs substantially in the long term, through significant reductions in morbidity, mortality, and HIV transmission. In addition, over time, the decreasing HIV incidence would free scarce health care resources that are currently overwhelmed by the immediate demands of the HIV epidemic.

13. What are the challenges that health systems would face in expanding access to ART at CD4 ≤ 350?

Significant additional work would be required to strengthen health systems to facilitate expanded access to ART to people living with HIV with CD4 counts ≤ 350 cells per cubic mm. According to a desk review of data commissioned by WHO, an additional US$ 251 billion would be required between 2009 and 2015 to deliver the health interventions in 49 countries required to ensure achievement of the health-related Millennium Development Goals [73]. However, more recent analyses have begun focusing on the costs and benefits of expanding access to ART with one recent study concluding that expansion to ≤350 for around 90% of those eligible could save 149,000 (11%) and 0.9 million (12%) new HIV infections over 5 and 40 years, respectively [74].

Health systems strengthening would need to be a prior priority before such a strategy could be implemented in resource constrained settings. Experiences from Kenya emphasized the health systems challenges associated with successful scale-up of testing, which included [75]:

- Burden on the health care system
    - Increasing demand of services, strain on human resources
    - Limited infrastructure (space, laboratory)
    - Inadequate drug procurement and supply management systems
    - Weak monitoring and evaluation system at all levels: particularly quality of care, treatment outcomes, retention and follow up
- System unprepared for chronic care
- Mismatch in testing vs. treatment sites
- Increasing number of patients with toxicities and 1st line treatment failure, high cost for viral load monitoring, HIV drug resistance monitoring, non-availability of salvage therapy in public health system
- Challenges posed by decentralization of care to lower cadres and lower levels vs. quality of care

Countries with higher HIV prevalence tend to have lower health staff-to-patient ratios compared with more developed countries. On average, there are 15 times the numbers of doctors and 8 times the number of nurses in Europe compared to Africa [76]. The World Health Organization estimates that the global shortage of trained health care staff exceeds four million [77]. Much could be done to increase capacity by increasing efficiency and various

national and international guidelines recommend ways of doing this. One such measure is the task-shifting of clinical responsibilities from doctors to nurses and the deployment of community health workers to overcome severe human resource shortages [78]. There are also emerging decentralised models of how to manage "stable" patients out-of-facility [79]. Such approaches provide alternative ways of improving cost savings and increasing access despite bottlenecks due to doctor shortages, and are consistent with health-systems approaches supporting the right to the highest attainable standard of health [80]. Experience from Malawi shows that a variety of measures including task shifting, decentralization of care to health centres and community involvement can help countries meet universal access targets while controlling the cost of the ART programme due to economies of scale [81, 82].

Current work is ongoing to examine the potential positive effects of starting ART earlier on the health system burden. Although it is too early to determine with certainty, hospitalizations and clinic visits do decrease as healthier people are started on ART earlier before major morbidity and mortality occurs.

14. What are the programmatic advantages with early initiation of ART?

Early initiation of ART has a number of important advantages.

Modelling estimates predict that the initiation of ART for individuals with a CD4 cell count of ≤350 cells per cubic mm or with WHO clinical stage 3 or 4 will result in the numbers of people on ART increasing by 49% and a reduction in HIV-related mortality of 20% by 2010−2015. Further modelling data suggest additional transmission benefit from earlier initiation of ART for both sexual transmission and mother to child transmission of HIV providing that there is high treatment coverage and high adherence. Earlier initiation and more time spent on ART may provide impetus to shift to less toxic first-line regimens and reduced prices for newer fixed-dose combinations (FDCs) [72].

Observational and RCT data confirm that there is an increased risk of TB and invasive bacterial diseases as CD4 cell counts decline. Conversely, there is a 80 to 92% reduction in TB in individuals receiving ART [15-17]. In settings with a large burden of HIV and TB, studies show that ART may contribute to TB control in both HIV-infected and HIV-uninfected individuals. By reducing mortality rates, ongoing scale up of ART may accelerate progress toward the MDG TB control target of halving the 1990 mortality rate by 2015 [83].

Additionally, although theoretical, advantages of immediate treatment at diagnosis irrespective of CD4 count could include simplified clinical management as initiation of ART would be based solely on a positive HIV test, when most infected people are well with fairly well preserved immune systems and before many clients are lost to follow-up. In addition, the supply chain for drugs could benefit from the predictable scale-up that relies on standard first-line and second-line therapy with newer regimens that are simpler to use. The approach could be cost saving over the longer term, because over time fewer individuals would be living with HIV and efforts would increasingly focus on treatment adherence and localized HIV transmission [19, 23].

Offering earlier ART $\leq$350 may also help people to remain alive and in care—current approaches that ask people to come back with severe immunocompromised often result in considerable loss to follow-up—much of which is likely due to premature deaths.

15. What about long-term toxicity and drug resistance with expanded access to ART?

Earlier treatment initiation at CD4 ≤ 350 cells per cubic mm will mean longer exposure to ART (estimated to be 1 to 2 years more) and the possibility of more ART-related side-effects and ARV resistance [43]. However, concerns about long-term drug toxicity have been lessened in the developed world as more potent and less toxic medicines became available [84, 85]. These concerns are still justified in developing countries, where older drugs with less favourable side-effect profiles still form the backbone of therapy, but would be largely overcome with the wider availability of less-toxic drugs.

It has been suggested that expanded treatment might cause a rise in population-level viral drug resistance, due both to earlier initiation as well as to the challenges associated with retaining all patients on treatment. This would have consequences both for individual health and at the population level. Yet, population-based mathematical modeling suggests that expanded access would only be associated with a small increase in population-level drug resistance and would therefore have a limited adverse impact on HIV transmission. Although modelling is important, there is a need for population based research studies and field trials to substantiate these findings.

Results from a longitudinal study in British Columbia using programmatic data showed an exponential decrease in the incidence of new cases of HIV-1 drug

resistance in patients on ART followed during 1996-2008, suggesting increasing effectiveness of highly active antiretroviral therapy at the population level [35]. A recent French nationwide study showed that in 2009, in treated patients with viral load >50 copies per ml, only 9.3% could contribute to the transmission of resistant viruses and among them, only 0.3% of patients had viruses with complete resistance to at least 2 families of drugs [86]. Adding to this finding, studies suggest that transmission of HIV from people with drug-resistant viral strains to sero-discordant contacts is reduced compared with people with wild-type HIV strains [87].

Implementing programme elements that minimize the emergence of HIV drug resistance, including optimizing access to ART, supporting appropriate ART prescribing and adherence, and ensuring adequate and continuous drug supplies, is essential for preserving the efficacy of the limited number of ARV drugs available in many countries. Transmission of resistant virus can be minimized through support for prevention programmes for HIV positive individuals [43].

WHO is working with stakeholders to monitor the situation through the WHO/HIVResNet HIVDR Laboratory Network which currently includes over 30 laboratories covering the WHO's African, South-East Asia, Western Pacific, and the Caribbean Regions [88, 89].

16. What about concerns regarding ensuring adherence to medications with early initiation of ART?

With earlier initiation of ART at CD4 ≤ 350 cells per cubic mm, facilitating adherence to therapy will be a key challenge. According to research studies, a 95 percent adherence rate is associated with controlling HIV replication, which allows an optimal therapeutic response to the medications. Suboptimal adherence to ART regimens results in incomplete suppression of HIV replication and emergence of resistance to ARVs. ARV resistance may increase the potential for regimen failure, compromise future treatment options and lead to increased risk of mortality.

Adequate patient support mechanisms and treatment literacy programmes must be in place to encourage and facilitate ART adherence. As well as the urgent need to increase treatment access, there is a growing awareness of the critical need for communities to be involved in education, preparation and support for ARV treatment. Having supportive family and community

environments, as well as significant involvement of networks of people living with HIV and other stakeholders in the community are key to promoting adherence to ARV treatment [90].

In resource-limited settings, major factors contributing to good adherence are free ARVS, ease of use, and preparedness for use [43]. People need to learn about ART so that they understand the full range of issues involved and can accurately pass on information to those who need it in their communities. This includes not only people who are taking, or will need to take, ART but also all those within the community who have a role in informing, supporting and advocating for treatment. The success of ARV treatment depends on achieving high levels of adherence, sustaining protective behaviours and reducing stigma at the personal and community levels.

17. How would patient retention be ensured?

With earlier initiation of ART, ensuring long-term retention of patients in the programme will be a challenge. High levels of retention on ART are vital for individual patients, for credibility of programmes and for on-going resource and financial support. In addition, the challenges of retaining patients might be higher in those who have not yet experienced AIDS symptoms. Retention varies widely across programmes, and programmes that have achieved higher retention rates can serve as models for future improvements.

In a population-based cohort presenting for HIV testing at two South African HIV outpatient sites, nearly half of newly diagnosed HIV-infected persons had pre-treatment loss to care as defined by not following up with a CD4 count [91]. Understanding reasons for pre-treatment loss to care is critical for the development of focused interventions to increase the number of people who access and remain in HIV care. A systematic review of patient retention in ART programmes in sub-Saharan Africa has shown that since the inception of large-scale ART access early in this decade, ART programmes in Africa have retained barely 70% of their patients at the end of 2 years and 65% by 3 years. Loss to follow-up was the major cause of attrition, followed by death [92]. The following interventions have been proposed to improve patient retention in ART programmes [93]:

a. Simple and standardized monitoring systems,
b. Reliable ascertainment of true outcomes of patients lost to follow-up,

c. Implementation of measures to reduce early mortality in patients both before and during ART,
d. Ensuring uninterrupted drug supplies,
e. Use of simple, non-toxic ART regimens,
f. Decentralization of ART care to health centres and the community,
g. Reduction in indirect patient costs particularly in relation to transport to and from clinics,
h. Strengthening links within and between health services and the community,
i. Leveraging ART clinics to deliver other beneficial patient or family-orientated packages of care, and
j. Innovative interventions in ensuring drug adherence and compliance with follow up.

18. What would be the potential cost of expanding access to ART?

Maximising the prevention potential of ART has important financial implications. In November 2009, the World Health Organization revised its ART guidelines to include a CD4 threshold of 350 cells per cubic mm [43]. This translates to an estimated 50% increase in the number of people needing ART, compared to need under the pre-2009 guideline of 200 CD4 cells per cubic mm. It is estimated that increasing the threshold for ART initiation can increase ART cost up to 57% by 2010−2015 [74]. The guidelines have raised questions regarding the short-term economic feasibility of delivering life-saving ART, and the long-term sustainability of treatment, especially if treatment is started earlier in the course of infection with less toxic but more expensive regimens.

However, recent studies have shown that increasing the provision of ART to ≤350 CD4 cells per cubic mm and beyond has the potential to reduce costs substantially through significant reductions in morbidity, mortality, and HIV transmission. In addition, over time, the decreasing HIV incidence would free scarce health care resources that are currently overwhelmed by the immediate demands of the HIV epidemic. Canadian investigators constructed a mathematical model to predict the cost savings which would be achieved if the proportion of HIV-positive patients with a CD4 cell count below 350 cells per cubic mm treated with antiretroviral drugs increased from 50% to 75%. The study showed that increasing the proportion of HIV-positive patients treated with antiretroviral therapy could save the Canadian province of British Columbia US$900 million over 30 years - and prevent 26% of projected new HIV transmissions. After only four years, increasing the number of treated patients

became cost-effective, and after ten years much of the cost benefit could be attributed to the number of new infections averted [94].

A cost and cost-effectiveness analysis of the projected treatment and prevention benefits of voluntary HIV testing and counseling and expanded ART in South Africa was recently completed [74]. It estimated that versus current practice, expanding ART to CD4 ≤350 cells per cubic mm would prevent 149,000 (11%) and 0.9 million (12%) new HIV infections over 5 and 40 years, respectively. Cumulative deaths and DALYs declined by an estimated 11%, from 11.7 to 10.3 million and from 104 to 93 million over 40 years. Costs dropped by about $477 million over 5 years, and $1.8 billion over 40 years, reaching breakeven by 2014. In addition, expanding to all CD4 levels further decreases HIV infections by about 3.8 million (59%) and costs by $11.1 billion over 40 years, with breakeven by 2023 [74].

19. Why is community engagement critical to the success of expanded access to ART?

Much of the success to date in the AIDS response is due to the unprecedented engagement of affected communities as advocates, educators and service providers. Ensuring expanded access to ART requires considerable community engagement within a strong human rights framework. Communities can play critical roles in both creating the context for treatment and the actual implementation of treatment programmes. A WHO evaluation of 186 community based mobilization and service delivery projects in Eastern Europe, South-East Asia, and Latin America found that local level community based organizations led by people living with HIV are often best able to reach populations at higher risk of HIV and get people to utilize health services effectively [95]. Without the engagement of affected communities, it will be impossible to get the people who are most at risk into care, and get them to utilize care effectively. This is especially true for the vulnerable and marginalized populations who experience severe discrimination when they seek out health services. Strengthening community mobilization efforts can increase demand for HIV prevention and treatment services, ensure protection of human rights, advocate for equitable care, and provide community based prevention and care support services.

Engaging the community as a meaningful partner in the design, implementation and evaluation of HIV programmes is critical for programme success, particularly

when the potential for stigma and human rights violations exist [96]. Coordinated action between health care workers and people living with HIV, community leaders and other support providers, will provide a much better possibility of reaching the goals of universal access to prevention, treatment, care and support for all who need it.

20. What are the ethical implications of ART for HIV prevention as a public health intervention for the individual and community?

Ethical considerations include principles of respect for the individual, beneficence and justice. Considerations regarding the individuals obligation to community health are more complex and more difficult to clarify.

Observational data from various studies have shown that deferral of therapy to lower CD4 cell thresholds is associated with a significant increased risk of death among people living with HIV. In a recent analysis deferring HAART until CD4 cell count reached 251–350 cells per cubic mm was associated with a 28% higher rate of AIDS and death compared with starting when CD4 count was 351–450 cells per cubic mm [59]. In addition, recent studies have raised concern about the risk of death from liver, renal, and heart diseases, as well as from "non-AIDS" cancers; incidence of these diseases is increased at lower CD4 counts, with significant differences seen between those with CD4 $\leq$350 cells per cubic mm and those with CD4 >350 cells per cubic mm [97]. Clinical trials and additional data suggest that treating pregnant women with a CD4 ≤ 350 cells per cubic mm could prevent at least 75% of all mother-to-child transmission while also providing the best available treatment for the mother's health. ART will also provide protection during the breastfeeding period [26]. With respect to sexual transmission of HIV, the epidemiologic evidence suggests a very low risk, although never absent, when HIV load is optimally suppressed with HAART. ART also provides hope for sero-discordant couples wishing to have children.

Considering the significant benefit to the individual, it is an ethical imperative to provide access to ART within the current treatment guidelines, which recommend initiating therapy for adults and adolescents and all pregnant women at CD4 ≤ 350 cells per cubic mm.

Beyond individual benefits, by rendering an individual less infectious, expanding access to ART could also have a larger public health impact of curbing new HIV infections. As the CD4 cutoff thresholds for ART treatment are increased, the

"community benefit" increases. In light of the growing access to ART in resource-limited settings and increasing evidence suggesting the clinical and prevention benefits of initiating treatment at higher CD4 cell counts, it is conceivable that, in the future, ART will be an integral part of both individual-level clinical treatment programmes as well as public health-based HIV prevention interventions. Additionally, data from 30 international studies and 16 cohorts of untreated adults found relatively low CD4 cell count levels after HIV infection and a fairly rapid progression to CD4 cell count thresholds such as 500, 350 and 200 [98]. The time to eligibility was variable and, in some settings, only a few years after HIV infection. From this perspective and assuming access to HAART, decisions whether to start at 200, 350 or 500 represent only a few years earlier in the course of a much longer life span.

21. What are the human rights implications of expanding access to ART?

It is well recognized that providing ART is part of rights access to health. The United Nations Commission on Human Rights recognised that "access to medication in the context of pandemics such as HIV/AIDS is one fundamental element for achieving progressively the full realization of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" [99]. This right is subject to both progressive and immediate realisation. The International Covenant on Economic, Social and Cultural Rights (ICESCR) stipulates the right to the highest attainable standard of health, including access to medicines, is subject to progressive realisation and resource availability [100]. At the same time, General Comment 14 of the UN Committee on Economic, Social and Cultural Rights (CESCR) declares that states have an immediate obligation to make essential medicines available and accessible throughout their jurisdiction [101]. Antiretroviral drugs are defined as essential medicines [102].

Implementing within a human rights framework is paramount as without community engagement and support expanding access to ≤ 350 and beyond will be impossible. It is critical that there be no coercion to be tested or take ART, with adequate support for individuals with questions and concerns. Human rights measures would also improve uptake of testing and treatment, and patient retention. Health programs should consider costing and implementing concrete measures to improve the human rights and community support context.

However, it will be a challenge to provide expanded HIV testing safely and acceptably in the face of HIV-related stigma, discrimination and potential human rights abuses. HIV treatment programmes are presently undermined by gender inequity and violence against women, stigma discrimination against people living with HIV, and the criminalization of or denial of existence by some governments of populations at increased risk of HIV. In addition, expanding HIV testing and provision of ART could be conducive to the promotion of coercive approaches among the general population by community leaders and health workers owing to potential conflicts of interest with HIV-positive individuals, as has been seen in countries like Lesotho where universal testing campaigns have been implemented [103]. Besides the obvious human rights concerns that such an approach presents, coercion also ultimately undermines public health goals. Successful treatment requires individual, which in turn requires a health provider-patient relationship as well as understanding of the purpose of testing and treatment. As stated at the WHO consultation, "individual's autonomy and responsibility depends on their access to and understanding of complete information on the intervention, including benefits and risks"[32].

For expanding access to ART for everyone with CD4 $\leq$350 cells per cubic mm in a generalised South African setting, preliminary projections have shown that the average annual costs for implementing public sector human rights and community support interventions were a small percentage (i.e. 1.4%) of total programme costs. Protection of human rights in expanded ART programmes is obligatory and human rights interventions may well determine the success or otherwise of the intervention. Ensuring robust human rights interventions and measuring their cost and impact is important for achieving universal access and treatment [104].

22. How would viable monitoring and evaluation systems be ensured while implementing expanded access to ART?

A monitoring and reporting system that is simple and standardised would be vital for surveillance of programme outcomes and ensuring reliable ART drug forecasting and supply. Without a robust system in place there will inevitably be drug and commodity ruptures as ART procurement and distribution is ramped up. Current monitoring and evaluation systems should be adapted to collect relevant information. Such indicators should allow monitoring not only of the policies adopted but also the processes by which policies are designed and programmes are implemented. Monitoring of the general health care system will

reveal the extent to which the scaling-up of HIV programmes has an impact on the health infrastructure, the migration of personnel, health care financing, and the delivery of health care generally. At least one or two indicators should ensure that access by vulnerable, marginalized, or other potentially underserved populations, including women, is monitored [105].

There is also the issue of ensuring and monitoring drug adherence in individuals who generally feel well. Monitoring adherence and the development of drug resistance would be important and could be done through sentinel surveillance using dedicated external human resources and funding. A point-of-care viral load test would be an indispensable tool for monitoring adherence and effectiveness [106].

The challenges of retaining patients might be higher in those who have not yet experienced AIDS symptoms. In a population-based cohort presenting for HIV testing at two South African HIV outpatient sites, nearly half of newly diagnosed HIV-infected persons had pre-treatment loss to care as defined by not following up with a CD4 count [91]. Understanding reasons for pre-treatment loss to care is critical for the development of focused interventions to increase the number of people who access and remain in HIV care. A systematic review of patient retention in ART programmes in sub-Saharan Africa has shown that loss to follow-up was the major cause of attrition on ART programmes, followed by death [92]. Using the successful DOTS model adapted by TB control programmes, Malawi has developed a system of quarterly ARV cohort and cumulative ARV quarterly analyses. Such quarterly analyses may be useful for countries in assessing ARV delivery, although the burden of work involved in calculating the numbers may become large once ARV delivery systems have been established for several years [107]. Better patient tracing procedures, better understanding of loss to follow up and earlier initiation of ART to reduce mortality are needed if retention is to be improved. Retention varies widely across programmes, and programmes that have achieved higher retention rates can serve as models for future improvements. In addition, developing reliable referral systems that document transfers is essential to evaluating overall programmatic effectiveness.

A systematic review of outcomes among patients lost from treatment programmes and estimated that about 40% of the lost to follow-up patients had died, with much of the mortality occurring in the first 6 months after being lost to follow-up [108]. Making efforts to get these patients back into care is important to the overall success of ART programmes, and developing ways to track and

locate lost patients is essential to proper programme evaluation [109]. To further evaluate programmes, when available, method such as cross referencing with vital registration systems [110, 111] or adjusting mortality estimates statistically should allow for better estimates of programme impact as well as appropriate targeting of resources towards patient retention [112-114].

23. Does WHO recommend use of ART for prevention of HIV and TB?

Based on the results of clinical trials and observational cohort studies that have conclusively demonstrated the benefits of earlier initiation of ART in decreasing AIDS related morbidity and mortality, the WHO has revised its guidelines in November 2009 to recommend ART for all people living with HIV with CD4 ≦ 350 cells per cubic mm and for all people living with HIV with TB irrespective of their CD4 count in resource limited settings.

While it has been well known since 1991 that effective ART can potentially contribute to the prevention of HIV transmission, only recently, the dramatic impact of ART on secondary HIV transmission from all routes has become better understood. The evidence clearly shows that successful viral suppression through ART can substantially reduce the risk of vertical, sexual and blood borne HIV transmission especially if combined with other evidence-based prevention interventions. Clearly, a significant impact on HIV transmission rates can be achieved as a secondary preventive benefit of ART by optimizing coverage among all those who need treatment based on existing treatment guidelines.

Optimizing coverage will also result in other prevention benefits, including lower rates of TB. In settings with a large burden of HIV and TB, studies show that ART may contribute to TB control in both HIV-infected and HIV-uninfected individuals. By reducing mortality rates, ongoing scale up of ART may accelerate progress toward the MDG TB control target of halving the 1990 mortality rate by 2015 [72].

WHO recommends that besides expanding ART to meet universal access targets, further research is needed to assess the feasibility, safety, acceptability, impact, and cost of innovations such as universal voluntary testing and immediate treatment approach, and broad consultation must address community, human rights, ethical and political concerns. Discussion will also be needed on ART for prevention in populations most at risk in epidemics of varying intensity [19].

24. What are the concerns of people living with HIV with earlier initiation of ART?

While the benefits of starting ART at CD4 ≤350 cells per cubic mm are recognized and strongly supported by people living with HIV, concerns have been raised whether broadening the criteria for treatment may result in some persons in urgent need of treatment being displaced by persons for whom treatment would be beneficial but not as urgent. Accordingly, in recommending a higher CD4 count threshold for initiation of ART, a guiding principle of the recent WHO guidelines is that those most in need of treatment should retain priority access [43].

Despite recent reductions in HIV incidence, the number of people needing ART continues to grow. Earlier initiation of ART has been linked to improved survival and reduced HIV□related morbidity. More expensive yet patient friendly ART regimens are increasingly used as preferred initial options due to fewer long□term side effects. In addition, improved access to antiretroviral therapy has increased demand for supportive laboratory techniques such as CD4+ cell and viral load monitoring. Incremental costs associated with these changes can be substantial leading to increasing concerns among people living with HIV regarding the feasibility and sustainability of expanding access to ART. In addition, during consultations with people living with HIV, concerns were voiced about the increased risk of adverse events, resistance to first-line ARVs, drug stock-outs, and non-availability of second-line regimens [43].

As the "end-users" and the intended beneficiaries of HIV treatment, people living with HIV must be able to express demand for treatment; overcome social, gender-based, economic, and political barriers to treatment access; possess enough treatment knowledge to be involved in their own health care decisions; and be active participants in sustained long term treatment and care. Treatment literacy, empowerment, and advocacy for people living with HIV are central to the potential impact of any global plans, resources, and delivery systems to ensure treatment access. HIV-positive individuals should be involved at all stages of development, implementation and evaluation of such programmes. With community engagement and availability of adequate resources, it would be feasible to scale up ART access to CD4 ≤ 350 and beyond.

WHO has recommended that countries should consider the following principles to guide decision□making while expanding access to ART [115]:

a. **"First, Do No Harm"** – Seek to maintain the current progress of treatment programmes without disrupting the care of those on

treatment or compromising people living with HIV at highest risk for poor outcomes.

b. **Access** – Ensure all eligible people with HIV are able to enter treatment services
c. **Quality** – Ensure that care achieves the highest standards possible within a public health approach.
d. **Equity** – Ensure fairness and justice in the distribution of treatment services.
e. **Efficiency** – Achieve the greatest health impact with the optimal use of available human and financial resources.
f. **Sustainability** – Understand the long□term consequences of changes with the vision of providing continued, life□long access to ART for those in need.
g. **Forward looking** □ Be mindful of the need to accelerate adoption of new evidence and new technologies into programming, and time to overcome delays to achieving implementation.

25. What are some of the scientific and technical issues relating to ART for prevention?

Important scientific and technical areas that merit consideration include:**Error! Bookmark not defined.**

- Optimum timing of initiation of ART
- Cost and cost-effectiveness of expanding access to ART,
- Incidence of resistance and adverse events with earlier initiation of ART,
- Strategies to improve treatment adherence,
- Strategies to achieve increased access to HIV counseling and testing including universal voluntary counseling and testing,
- The relationship of the stage of infection to efficiency of transmission,
- Behavioural disinhibition associated with expanded access to ART,
- The degree of therapeutic benefit to the individual with immediate initiation of ART.

26. What should be the future research agenda in the field of using ART as a tool for HIV prevention?

While expanding ART to meet universal access targets, there is a need for further scientific evaluation and discussion to define the requirements for public health decision-making on how to best use ART for prevention and control of HIV/AIDS. In November 2009, WHO held two ART for prevention stakeholders meetings to

explore human rights and ethical considerations, clarify research priorities and review feasibility and acceptability issues. Key areas of research in ART for prevention and in particular the WHO model requiring further consideration included the following [32]:

- the incidence and nature of drug resistance
- the epidemiological role of acute HIV infection
- human rights issues
- initiating complex medical regimens in individuals who may not need ART, increased and longer utilization of ART
- scaling up HIV testing and counseling
- financial requirements
- feasibility and acceptability of universal test and treat across diverse communities
- side effects associated with earlier initiation of ART
- adherence rates for people started on ART at higher CD4 counts
- stigma in affecting the feasibility and effectiveness of universal teat and treat
- the degree viral load suppression resulting from earlier initiation of ART
- the extent of residual HIV transmission, the frequency and magnitude of viral rebound.

WHO and its collaborators are currently engaged in further modeling on the impact of ART on TB, the relative importance of drug resistance and other assumptions, the effect of combination PrEP and 'test and treat', effects on PMTCT and an in-depth economic analysis of the various strategies. There are a number of planned field trials and analyses, including ongoing and planned work in Washington, District of Columbia; and the Bronx in New York City; Vancouver, British Columbia; San Francisco, California; Botswana; Uganda, Malawi and Kwa-Zulu Natal, South Africa [116]. Swaziland and China have recently announced efforts to use HIV testing and counseling and ART for prevention as part of their efforts to address HIV. Scientific and community opinion leaders have called for expansion of access to treatment during further research on ART as prevention.

However, developing and sustaining successful treatment programmes requires working respectfully with and strengthening the capacity of civil society organizations that are at the front line of treatment literacy, adherence

counseling, social support, and other work with persons and communities affected by HIV. Planning for and allocating resources to support civil society organizations should be central to any study of ART as prevention [117].

27. Are any countries recommending or considering expanding access to HIV testing and ART as a prevention measure?

ART in prevention of HIV and TB is an important issue for many countries struggling with significant HIV epidemics. Although information is incomplete it is fairly clear that Canada and the United States have adopted expanded access to HIV testing and counseling and ART as key elements of their prevention strategies. Specifically, Vancouver in British Columbia and San Francisco California are aggressively implementing high coverage of both interventions as prevention measures. Taiwan has offered free ART and increased access to HIV testing as part of its HIV response. More recently, Swaziland announced the funding of the DREAM project which is focused on prevention through dramatic increases in HIV testing and counseling efforts and ART coverage. China has also recently announced that it will work with Canada to adopt and implement interventions based on the experience in Vancouver British Columbia. Malawi has proposed using ART for all pregnant women living with HIV irrespective of immune status or CD4 count in an effort to reduce transmission to children and partners. Vietnam, with a concentrated epidemic including among injection drug users, is planning on expanding ART in line with WHO recommendations with a close evaluation of the impact on HIV and tuberculosis prevention. The list of countries adopting the WHO $\leq$350 guidelines is long and growing as more countries realize the potential benefits of starting earlier treatment.

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