

**PEPFAR Scientific Advisory Board Recommendations for
the Office of the US Global AIDS Coordinator:
Implications of HPTN 052 for PEPFAR's Treatment Programs**

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INTRODUCTION

Development of Recommendations

To ensure that PEPFAR remains at the forefront of science-driven programs, the Office of the Global AIDS Coordinator (OGAC) convened the PEPFAR Scientific Advisory Board (SAB) following the announcement of the results of the HIV Prevention Trials Network (HPTN) 052 study in mid-2011. Members of the SAB convened by phone to discuss the trial with the Principal Investigators and formed a subcommittee to further discuss the science of the trial, to begin to put it into the context of existing information on HIV prevention and treatment, and to discuss implications for PEPFAR's HIV programs. While the initial focus of the group was specifically on the implications of the results of HPTN 052, the expert group decided to expand their scope to also address closely related treatment issues.

The 052 subcommittee developed a set of recommendations and presented them to the larger SAB on September 14-15, 2011, at the full SAB meeting held in Washington, DC. Extensive discussions at the meeting led to consensus regarding six recommendations.

The objective of this document is to present the six recommendations, along with key considerations. For each recommendation, the SAB has written a detailed explanation of the full scientific rationale, public health impact, resource implications, implications for PEPFAR, gaps in knowledge, and an examination of implementation issues that cross-cut many of the recommendations. These are the recommendations of the SAB to Ambassador Goosby and OGAC, for their use as they develop future policies and guidance for PEPFAR programs.

RECOMMENDATIONS

Summary and Key Considerations

On the basis of existing scientific evidence, the SAB recommends that PEPFAR act on the following six recommendations:

- 1. Accelerate the support of the scale-up of antiretroviral therapy (ART) to all HIV-infected individuals with CD4+ cell count <350 cells/mm³, irrespective of World Health Organization (WHO) disease stage for treatment and prevention (Goal: 90% coverage)**
- 2. Offer ART to all patients with HIV-related tuberculosis (TB), irrespective of CD4+ cell count and integrated during TB treatment**
- 3. Endorse WHO guidelines for prevention of mother-to-child transmission (PMTCT) in pregnant and breastfeeding women with a CD4+ cell count >350 cells/mm³, with a preference for Option B (ART throughout pregnancy and breastfeeding) where locally appropriate**
- 4. Support the use of ART in specific populations with CD4+ cell counts >350 cells/mm³ in order to prevent transmission to others based on the results of HPTN 052. The benefit of this intervention has been demonstrated for heterosexual discordant couples. Careful evaluations, including assessment of benefit/risk/impact/feasibility and modeling exercises are urgently needed to identify populations that should be prioritized for this intervention, given local conditions**
- 5. Intensify efforts to establish effective programs for engaging key affected populations in HIV prevention, care, and treatment programs. Particular efforts should be undertaken to ensure key affected populations eligible for treatment receive ART in an enabling environment that supports their human rights**
- 6. Seek and secure sufficient resources to implement the recommendations, given the scientific basis for, and potential impact of, their implementation**

Key considerations that arose during the deliberations of the SAB and that should be noted when considering the detailed recommendations include:

External Generalizability

The SAB generally consider the results of 052 to have high external generalizability, (i.e. most members considered the results to be applicable to any heterosexual couple, and perhaps applicable to sexual transmission in general). It was also recognized that the results were generated in a study setting, so effectiveness in program conditions could vary. However, members did not expect substantial variation in the program setting, in part because adherence rates tend to be high among those on treatment in PEPFAR programs.

Prioritization

The first four recommendations are listed in order of priority, as defined by the SAB. Recommendations 5 and 6 are of a more general and cross-cutting nature. The SAB made particular reference to the importance and precedence of Recommendation 1 over the other recommendations. Achieving the ambitious treatment goal of 90% coverage for all HIV-infected individuals with CD4+ cell count <350 cells/mm³ would *de facto* cover those individuals most in need of treatment and would prevent transmission for a substantial proportion of special populations included in the subsequent recommendations (i.e. those with HIV-related TB,

pregnant women, discordant couples, and other key persons most at risk). However, the SAB recognized that these recommendations are not meant to be applied blindly. Rather, they will be applied in close consultation with in-country leadership and with appropriate attention to local epidemiology, capacity, and prioritization.

Normative Guidance

Recommendations 1-3 and 5 are supported by current WHO treatment guidelines. Recommendation 4 is not currently addressed in WHO guidelines. WHO is currently considering how best to respond to new data on treatment as prevention and will likely release a new series of guidelines over the next 1-2 years.

Local Adaptation

Implementation will need to be adapted for the local epidemiologic context and conditions on the ground. For example, PEPFAR programs in countries with very low treatment coverage even at a CD4+ cell count threshold of 200 or 250/mm³, or low median CD4+ cell count at ART initiation, should concentrate resources on Recommendation 1 for the near and medium term, and may not realistically be able to address the others.

These recommendations should, of course, only be considered if they are aligned with national guidelines and based on their relative impact in a given epidemiologic context. For example, offering ART to people at higher CD4+ counts must be consistent with national guidelines and of interests of the Ministry of Health. Key affected populations for transmission will differ across countries. Some countries might offer treatment to specific key affected populations with CD4+ count greater than 350/mm³ but this will depend on local coverage, the quality and availability of programs for these populations, and the extent to which HIV infection in key affected populations contributes to the local epidemic.

Focus of Efforts

The SAB devoted considerable attention to the tensions that exist around groups for whom earlier treatment may be justifiable. On one hand, modeling suggests that actively seeking and offering treatment to individuals most likely to transmit to multiple partners *could* have a larger impact on the epidemic than treating those who have already accessed the care continuum but who are less likely to transmit to multiple persons. On the other hand, it was also recognized that by the time an individual or couple has made it through the testing and care cascade, missing the opportunity to intervene would be ignoring the programmatic investments that have already been made. Furthermore, there may be imperatives held by individual clinicians to their patients that argue for targeting individuals already in that relationship. The SAB agreed that both approaches needed to be employed, as locally appropriate.

Strengthening Retention and Adherence

Viral load suppression is the *sine qua non* of treatment as prevention, and thus, retention in care and adherence to ART is an urgent priority. To accomplish this, all the steps in the implementation cascade, from testing to care and retention in care, need to be delineated, and efficient and effective evidence-based strategies identified for each step. Special approaches need to be considered when implementing the cascade among key affected populations and those with multiple partners because issues related to stigma and discrimination present significant challenges. As part of this, strategies must be evaluated and used to:

- Substantially increase testing and voluntary knowledge of serostatus (including repeat testing for those who test negative)
- Scale up linkage from HIV testing to HIV care and retention in HIV care

- Improve the monitoring, retention, and follow-up of individuals in HIV care, not eligible for ART
- Improve follow-up of HIV-infected women through and beyond delivery

Trade-offs and Resources

The SAB did not explicitly evaluate treatment as a prevention intervention relative to other prevention modalities. Other evidence-based prevention methods and combinations of such methods remain an essential part of PEPFAR programming. These recommendations should not be interpreted as superseding PEPFAR's support for other effective combination prevention activities. In fact, implementation of these new recommendations will require strong linkages to other prevention programs, along with accelerated HIV counseling and testing scale up.

Although these recommendations were made in light of the new scientific evidence, implementation will ultimately depend on the availability of resources. In the current budgetary environment, the extent of scale up of treatment, as with the scale-up of other effective combination prevention interventions, will likely depend in part on reallocation from interventions of less impact, such as prevention interventions not prioritized in the August 2011 PEPFAR Prevention Guidance. Tradeoffs will be required at the country level, where programmatic investment decisions are made, and at the headquarter level, as PEPFAR balances investments across countries with variable internal resources, burdens of HIV disease, and rates of coverage.

Further economic and epidemiologic modeling is needed to refine projections of the expected resource needs for operationalizing these recommendations, and the expected public health impact of implementation. The SAB recognizes that conducting these analyses is an essential component of ongoing U.S. government due diligence, and that they will be conducted by OGAC in the policymaking context.

Ethical Issues

The SAB prioritized Recommendations 1 through 4 based on the ethical goals of maximizing benefit to the individual while also maximizing benefit to public health through reduced transmission. The issue of prioritizing treatment as prevention raises many complex questions. Under conditions of constrained resources, tradeoffs are inevitable and are not new in public health. Providing ART to a person with a relatively high CD4+ cell count because he or she is likely to transmit HIV to one or more sexual partners may result in denying ART to another person with a low CD4+ cell count, where ART is clinically indicated for benefit. At the same time, not providing ART to a person with a high CD4+ cell count who wants ART and knows that taking it can effectively reduce transmission is far from ideal. Although there are different theories regarding the best way to ethically allocate inadequate and scarce resources, in ways none are completely satisfactory. The "least bad" allocation of resources depends not only on the principles emphasized, but may depend heavily upon the local situation. Populations most at risk for transmission will differ across countries; some countries might offer treatment to specific key affected populations with CD4+ counts greater than 350/mm³, but this will depend on local coverage and the extent to which these populations drive the local epidemic. Deliberation about the ethical trade-offs, as well as stringent attention to human rights, should guide difficult decisions about allocation of ART.

Knowledge Gaps

The recommendations included below represent best efforts to distill current evidence and experience. However, the process also identified several key knowledge gaps where there is

great urgency for research to identify answers to the key questions of paramount importance to advancing the efforts to control the HIV epidemic.

These considerations and others appear throughout the detailed recommendations that follow.

Full Recommendations

RECOMMENDATION 1: The SAB recommends that PEPFAR accelerate the support of the scale-up of ART to all HIV-infected individuals with CD4+ cell count <350 cells/mm³, irrespective of WHO disease stage for treatment and prevention. (Goal: 90% coverage)

Scientific Rationale:

The HPTN 052 study confirmed the efficacy of ART for prevention of HIV in discordant couples. In the multi-country study, 1763 HIV-infected partners with CD4+ cell count between 350-550 cells/mm³ within discordant relationships were randomized to either early ART initiation (at randomization), or to delayed ART initiation (at CD4+ count between 200-250 cells/mm³ or after an AIDS defining illness). Their HIV-uninfected partners were followed to detect HIV transmission. Over 1.7 years of follow-up, the risk of transmission in the early arm was significantly lower as compared to the delayed arm (1 versus 27 linked HIV infections, respectively, $P < 0.001$) [1]. The HPTN 052 study did not compare efficacy of ART use for prevention in patients with lower CD4+ cell count (<200 cells/mm³), as delaying ART in this group of patients, who are eligible for treatment for their own health, would not be ethical. However, it seems certain that the prevention efficacy observed in the population studied in HPTN 052 would be anticipated in those with CD4+ cell count <200 cells/mm³ [2, 3], as long as viremia is suppressed.

In fact, use of ART in patients with lower CD4+ cell counts would be expected to have an even more profound effect on HIV transmission to sexual partners because the efficiency of transmission is greater at lower CD4+ cell count. HIV transmission risk has been noted to be associated with CD4+ cell count. Donnell *et al* [2] demonstrated a gradient in risk of linked HIV transmission, with the highest rates noted in the lowest CD4+ cell count stratum for HIV-infected individuals (8.79, 2.79, 1.70 and 1.82 linked transmissions per 100 person years in individuals with CD4+ count of <200, 200-349, 350-499 and >500 cells/mm³, respectively). By dichotomizing the risk of linked HIV transmission by CD4+ count to <350 cells/mm³ and to ≥ 350 cells/mm³, a rate of 3.14 and 1.77 transmissions per 100 person years, respectively, was demonstrated. In HPTN 052, it was noted that most of the transmission events observed occurred when the index case had CD4+ cell count >350 cells/mm³, but this simply reflected the study design, in which subjects were recruited with a CD4+ cell count between 350-550. At the time of unblinding, only 181 out of 886 subjects in the delayed arm had experienced a decrease in CD4+ cell count requiring (per study protocol) their initiation onto ART.

In terms of individual benefits to the person receiving ART, treatment has been associated with significant benefits in individuals with CD4+ count <350 cells/mm³. A single-country (Haiti) randomized clinical trial, which enrolled 816 HIV-infected patients with CD4+ count between 200 and 350 cells/mm³ (median: 281 cells/mm³), demonstrated that immediate initiation of ART at enrollment was associated with significantly fewer deaths compared to patients who delayed ART initiation until a CD4+ cell count of <200 cells/mm³ or upon diagnosis of an AIDS event (6 versus 23 deaths, $P = 0.001$) [4]. Early initiation of ART was also associated with fewer incident TB cases (18 versus 36 events). Of those who initiated therapy in the delayed arm, the median CD4+ cell count at ART initiation was 166 cells/mm³, substantially below the current WHO-recommended threshold for ART initiation of 350 cells/mm³.

The HPTN 052 study also provided evidence of benefit of use of earlier ART initiation. In the 1,763 HIV-infected partners, early ART initiation was associated with significantly fewer composite clinical endpoint events compared to delayed ART initiation [1]. There were

significantly fewer primary composite treatment endpoint events—WHO grade 4 events, severe bacterial infections, pulmonary TB or death—in the early ART group versus the delayed group (40 versus 65 events in the early and delayed groups, respectively [P=0.01]). The difference was driven entirely by the incidence of extrapulmonary TB events (3 versus 17 events in early versus delayed ART arms, respectively). Participants in the early versus delayed ART groups had significantly more frequent adverse grade 3 or 4 laboratory abnormalities (P<0.001) but no difference was noted in grade 3 or 4 clinical adverse events (P=0.64).

There remains substantial uncertainty in terms of the benefit/risk balance for initiation of ART at CD4+ cell count >350 cells/mm³ in resource-limited countries. Beyond the data from HPTN 052, where only 886 individuals who presented with CD4+ counts > 350 were put on treatment (but had no adverse consequences) [1], the SAB knew of no other clinical trials or observational data from resource-constrained countries to inform this issue. Findings from one observational study from resource-rich countries showed that early ART in patients with higher CD4+ cell count (CD4+ cell count >350 cells/mm³) was associated with fewer deaths [5], whereas three other studies conducted in resource-rich countries did not demonstrate such a benefit [3, 6, 7]. Hence, available data confirm the benefits associated with ART initiation for individuals with CD4+ cell count <350 cells/mm³, with a paucity of data for clinical benefits for individuals with CD4+ cell count >350 cells/mm³, particularly in resource-limited settings.

Public Health Impact:

Based on the evidence provided above, there are substantial data in support of the use of ART in HIV-infected patients with CD4+ cell count of <350 cells/mm³ in terms of both prevention of morbidity and mortality as well as for the decrease in risk of transmission to an HIV-discordant partner. This motivates the target of 90% coverage as the goal for this recommendation.

However, achievement of this important public health impact is hindered by the fact that initiation of ART in resource-limited countries occurs largely at CD4+ cell counts below 200 cells/mm³, despite current recommendations by WHO that support initiation of ART at <350 cells/mm³ [51]. This is either due to late diagnosis of HIV or failure of those found to be HIV-infected to be linked to HIV care programs.

Public health impact will also vary based on prioritization at the country level. Consistent with WHO guidelines and the current PEPFAR 5-year strategy, many countries have recommended prioritization of pregnant women, those with HIV-related TB, and the sickest. Further prioritization may be necessary with constrained resources and these decisions are best made at the local level.

Resource Implications:

Achievement of this recommendation with 90% coverage will require expansion of several services within PEPFAR-supported programs, including:

- The expansion of HIV testing in order to identify those with HIV infection. This includes expansion of HIV testing, particularly in settings where the yield of HIV-infected individuals will be high. Of utmost importance will be informing individuals identified with HIV infection of the importance of long-term engagement in care.
- The expedited linkage of those with HIV infection to HIV care settings. Availability of point of care CD4+ count testing may enable more streamlined counseling prior to referral and linkage to HIV care, and has been shown to enhance retention in ART

programs [8]. Linkage of HIV-infected individuals to a nearby HIV care site and the provision of transportation and other support may enable retention in care.

- Appropriate initial and ongoing clinical and CD4+ count staging, including for those not yet eligible for ART in order to ensure prompt initiation of ART once they reach eligibility criteria.
- The achievement of high retention rates in programs.
- For those found to be eligible for ART initiation, a streamlined and accelerated process is needed to ensure timely initiation of ART. Appropriate clinical and support services are needed to enable monitoring of such individuals for response, failure, side effects, immune reconstitution inflammatory syndrome (IRIS), pregnancy, and adherence, among others.
- The achievement and maintenance of high ART adherence with sustained viral suppression in individuals.

Financial resources for implementation of this recommendation will vary greatly depending on the setting. In addition to the near-term resource estimations that OGAC will conduct in the policymaking context, using the best cost data available for countries, there is a need for local cost studies to determine the costs of achieving this goal with buy-in from government and donor stakeholders.

Implications for PEPFAR:

Focusing on the timely initiation of ART among HIV-infected individuals with CD4+ cell count <350 cells/mm³ offers the opportunity to bring prevention and treatment efforts together and, possibly, streamline programs in the field.

Of paramount importance is an expansion of efforts to test and identify HIV-infected individuals. These efforts should be ambitious, but also targeted to settings that are likely to result in a high yield of previously unidentified HIV-infected persons (e.g. provider initiated testing at healthcare facilities), and should be tailored to fit the epidemiology and HIV response of individual countries.

Once HIV-infected individuals are identified, the priority is to follow them as they move through the care cascade, with collection of appropriate indicators to assess achievement of this objective.

Particular attention and priority should be given to HIV-infected individuals already enrolled in care to enhance their retention and to enable prompt initiation of ART once eligible. CD4+ cell counts should be monitored and documented annually at a minimum, and at more frequent intervals (e.g. every 6 months) as CD4+ count approaches the 350 cells/mm³ threshold. The frequency of CD4+ cell monitoring may also be an appropriate indicator for quality of services. Another indicator of the success to promptly initiate ART upon eligibility is the change in the median CD4+ cell count at ART initiation over time.

For HIV-infected individuals found to be eligible (CD4+ count <350 cells/mm³), initiation of ART should be achieved within no more than 4-6 weeks to permit time for appropriate assessment and counseling. Such a timeframe would need to be minimized in specific situations, such as pregnancy, advanced HIV disease, patients with HIV-related TB etc.

Gaps in Knowledge:

There are substantial knowledge gaps regarding implementation of rapid and effective scale up of ART coverage for patients with CD4+ count <350 cells/mm³. These include implementation science to identify effective methods for expansion of HIV testing and linkage from HIV testing to HIV care, as well as methods to optimize retention in HIV care and prompt initiation of ART upon evidence of eligibility. The challenge of retaining patients in care (particularly for those not yet eligible for ART) will require identification of innovative approaches.

Finally, in order to determine with confidence the clinical impact of ART in HIV-infected patients with CD4+ counts >350 from resource-limited countries, more evidence is needed to ascertain the benefits versus risks of such treatment for the individuals receiving ART.

RECOMMENDATION 2: The SAB recommends that PEPFAR offer ART to all patients with HIV-related TB, irrespective of CD4+ cell count and integrated during TB treatment.

Based on Recommendation 1, all patients with HIV-related TB with CD4+ counts below 350 cells/mm³ should be offered ART. Recommendation 2 extends the provision of ART to patients with HIV-related TB who have CD4+ counts above 350 cells/mm³.

Scientific Rationale:

TB is an important contributor to HIV-related morbidity and mortality: TB is the most common serious infectious complication associated with HIV infection in Sub-Saharan Africa. As the HIV epidemic has matured in Sub-Saharan Africa, there has been a dramatic increase in the incidence of TB, including extra-pulmonary TB. TB is also the most common cause of mortality among patients with HIV disease in developing countries [9, 10]. The development of TB in HIV-infected individuals has been shown to accelerate the course of HIV disease and adversely affect HIV outcomes [11].

TB-HIV patients have poorer clinical outcomes than HIV-negative TB patients: HIV and TB pose major public health challenges, both independently and, to a greater extent, when combined. TB can occur even at high CD4+ levels and patients with concurrent TB disease and HIV infection, with CD4+ counts above 350 cells/mm³, have poorer clinical outcomes from TB than those who have TB disease without HIV infection. HIV has a substantial deleterious impact on tuberculosis outcomes. In the presence of HIV, tuberculosis is associated with substantially higher case fatality rates regardless of initiation, or in the presence, of effective tuberculosis chemotherapy [9, 10].

Initiation of ART during TB treatment improves outcomes: Initiating ART during TB treatment has been shown to reduce mortality by 56% compared to ART initiation soon after TB treatment [12]. In the SAPIt (**S**tarting **A**RT at three **P**oints **i**n **T**B) trial, the mortality rate in the 429 patients who initiated ART during TB treatment was 5.4 deaths per 100 person-years compared to the mortality rate of 12.1 deaths per 100 person-years in patients who initiated their ART after completion of TB treatment (HR= 0.44; 95% confidence interval, 0.25 to 0.79; P = 0.003). This study included patients with CD4+ cell counts up to 500 cells/mm³. Based on this finding, in December 2009, advice from WHO recommended the provision of antiretroviral therapy as soon as possible during TB treatment for all individuals with HIV-related TB.

Initiate ART within the first 12 weeks of TB treatment: The SAPIt and ACTG5221 trials demonstrated that initiation of ART as soon as possible after starting TB treatment in TB-HIV co-infected patients with severe immunosuppression (CD4+ cell counts below 50 cells/mm³) improves survival substantially. However, in patients in the SAPIt trial with CD4+ cell counts above 50 cells/mm³, initiating ART about 8-12 weeks after TB treatment initiation was associated with 2.2-fold lower rate of IRIS and fewer antiretroviral drug switches due to adverse events without increasing AIDS incidence or deaths [13]. In the ACTG A5221 study [14], among patients with CD4+ T-cell counts < 50 cells/mm³, 15.5% of patients in the earlier-ART group versus 26.6% in the later-ART group had an AIDS-defining illness or died (95% CI, 1.5 to 20.5; P = 0.02). Data from the Cambodian Early versus Late Introduction of Antiretroviral drugs (CAMELIA) [15] study reported a 34% lower mortality (P<0.01) among patients with HIV-related TB with a median CD4+ count of 25 cells/mm³ who initiated antiretroviral therapy within two weeks of anti-tuberculosis therapy compared to patients who waited eight weeks to initiate antiretroviral therapy. In summary, patients with CD4+ cell counts below 50 cells/mm³ derive the greatest benefit if they start ART as soon as possible after starting TB treatment while those

with CD4+ cell count ≥ 50 cells/mm³ can defer ART initiation until the start of the continuation phase of tuberculosis treatment. ART initiation should not be delayed beyond the first 12 weeks after the start of TB treatment.

Patients with HIV-related TB have increased risk of repeat TB: HIV-uninfected individuals with TB have a 10-20% lifetime risk of developing tuberculosis disease following TB infection, whereas TB/HIV-infected individuals have an annual risk of developing TB disease that can exceed 10%. Recurrent TB accounts for the majority of TB cases in countries with a high TB incidence rate [16]. HIV infection increases the risk of recurrence following successful treatment of tuberculosis. Risk factors for recurrence of HIV-associated tuberculosis are initial treatment regimens with less than six months of rifampicin, post-tuberculosis scarring, cavities, and low CD4+ counts [17-19]. One study of South African gold miners demonstrated that TB recurrence was five times more likely in HIV-infected than HIV-uninfected people [20].

Patients with HIV-related TB have a higher risk of transmitting HIV: Patients with HIV-related TB with CD4+ >500 cells/mm³ have been observed to have significantly higher mean plasma viral loads than HIV-infected patients without TB [21], making them more likely to transmit HIV to their partners. Although higher plasma viral loads may be noted with other opportunistic infections (OIs), TB may be different (in addition to the magnitude of the global disease burden) in that it can occur at high CD4+ levels.

Public Health Impact:

The benefits of providing ART to all patients with HIV-related TB, irrespective of CD4+ count, include reduced morbidity and mortality as well as reduced HIV transmission to partners and repeat episodes of TB. The integration of HIV and TB treatment has substantial potential public health as well as health systems benefits.

Resource Implications:

Tuberculosis presents a huge diagnostic challenge, especially in the presence of HIV. Patients with TB and HIV present particular challenges for the diagnosis of TB because patients can 1) have paucibacillary TB and are often sputum smear for acid-fast bacilli negative, or 2) have extra-pulmonary TB. The difficulty in diagnosing such patients, especially in those with HIV-related TB, compromises control and therapeutic efforts. There is a need to improve diagnostic technologies to obtain a timely diagnosis of TB. Newer technologies like GeneXpert could make an impact on this but the technology remains expensive. Implementing GeneXpert will require substantial resources for equipment, staff, training, reagents and maintenance, but is highly cost-effective in most settings.

To have the greatest impact, every TB service will need to provide the full array of HIV services. Every TB patient will need to receive HIV testing and counseling and those found to be HIV-infected should have a CD4+ count, if available. Estimates of the proportion of TB-HIV patients who have CD4+ cell counts greater than 350 cells/mm³, range from 11% to 30%. Thus, if all patients with HIV-related TB are initiated on ART regardless of CD4+ cell count, this would increase the demand for treatment, thereby requiring additional resources for the additional health service capacity.

However, expanding treatment of TB-HIV co-infected patients will produce some long-term cost savings due to decreased repeat episode TB cases in addition to reduced HIV transmission to sexual partners.

Implications for PEPFAR:

Offering ART to all patients with HIV-related TB places the integration of TB and HIV firmly on the PEPFAR agenda and identifies it as a high priority. Due to its substantial public health impact and survival benefit, it represents substantial gains in healthy person-years of life. PEPFAR programs providing TB-HIV treatment may benefit from standardized simplified treatment regimens for TB-HIV integration. PEPFAR may also need to develop training programs for all providers, including nurses, doctors and clinicians who currently provide TB services, on how to integrate the TB services with HIV care and how to ensure ongoing monitoring, management of IRIS, common adverse events, as well as how to maintain high levels of adherence.

Gaps in Knowledge:

There is a lack of data on the optimal ART regimen for patients receiving treatment for drug-resistant TB. Interactions between non-nucleoside reverse transcriptase inhibitors (NNRTIs) and rifampicin as well as protease inhibitors (PIs) and rifampicin also need further investigation to establish if their dosage should be increased in the presence of rifampicin. The overlapping toxicities of ART and antituberculosis regimens need to be assessed, particularly among pregnant women. In addition, the management of IRIS events also needs further study.

RECOMMENDATION 3: The SAB recommends that PEPFAR endorse WHO guidelines for PMTCT in pregnant and breastfeeding women > 350 cells/mm³, with a preference for Option B (ART throughout pregnancy and breastfeeding) where locally appropriate.

Scientific Rationale:

Transmission occurs from mother to child: HIV viral load is the most critical factor in HIV transmission. Numerous ecological and clinical studies have shown that HIV transmission from an infected woman to her child in utero, peripartum, and/or during breastfeeding can be reduced to less than 1% when the woman is virally suppressed [22, 23]

Highest viral load occurs in pregnant women with the lowest CD4+ cell counts: Opportunities to offer HIV counseling and testing to all individuals in high prevalence areas should not be missed, especially to women who are pregnant. ART should be offered without delay to all who have a CD4+ cell count <350cells/mm³ (as per Recommendation 1). Using data from a Zambian cohort, Kuhn et al found that implementation of this CD4+ cell count cutoff for ART initiation in pregnant and lactating women would reduce maternal deaths by 92% and would prevent 88% of perinatal and postnatal infections [24].

Fertility rates are high: The aggregate total fertility rate in sub-Saharan Africa is > 5 births per woman [52], and women are most fertile between the ages of 18 and 40 years. Because women on ART while breastfeeding, typically for 12-18 months, may become pregnant again, Option B will allow more women to have early and sustained exposure to ART during pregnancy.

Complexities in current Prevention of Mother-to-child Transmission (PMTCT) guidelines: Current strategies for PMTCT for women with CD4+ cell counts >350 cells/mm³ consist of WHO Option A or B, both of which require repeat episodes of commencement and stoppage of ART regimens among women with subsequent pregnancies. While these options are more effective than other options, such as provision of single-dose nevirapine to the mother and infant, they are complex. Option A is especially complicated and requires many changes in regimen throughout pregnancy and post-delivery. Ultimately, the diversity of options in current guidelines and the requirement for staging by CD4+ cell count increases the complexity of service delivery and may result in impediments to scale up of mother-to-child transmission strategies. The SAB recommends that PEPFAR adopt a preference for Option B in order to simplify programs and to allow for the realization of the transmission benefits of treatment for the women's negative sexual partners.

Women present for ANC late: Women often present for antenatal care at 24 weeks or even later. This allows for transmission during early stages of pregnancy. After HIV diagnosis, there is typically a delay before starting ART and then at least 4-8 weeks before viral load is suppressed. Data from a study in Gugulethu, Cape Town, involving 265 pregnant women, where the mean time on ART prior to delivery was 7.6 weeks, showed that every week a pregnant, infected woman was not on ART increased HIV vertical transmission by 20% and that there was no HIV transmission among women who received more than 8 weeks of therapy [25]. Data from Zambia confirms that the greatest transmission prevention benefit is incurred in women who are treated with ART within 13 weeks of delivery [26]. This recommendation will encourage earlier testing and presentation for PMTCT services in women in their first pregnancy.

Impact on Individual Health and Population Health:

Improved survival and outcomes in mothers: Recent data from Denmark and Uganda suggest that ART can restore longevity to pre-HIV periods [27, 28]. Treatment of women in their

reproductive years will improve survival particularly in women with lower CD4+ counts. The impact in pregnant women with a higher CD4+ count (i.e. >500 cell/mm³) is less clear. Survival of mothers, especially during the formative years of their offspring, is very important for the wellbeing and survival of their offspring.

Reduced transmission rates: Reduction in transmission of HIV to infants will reduce HIV mortality in pediatrics and the need for ART in children and adolescents. In addition, recent data show increased risk of transmission from infected women to an HIV-negative partner during pregnancy [29]. These data, combined with data from HPTN 052, suggest that Option B may have an added prevention benefit over Option A for women in discordant partnerships.

Associated Risks and/or Challenges

Antiretroviral Drug (ARV) Regimen Issues: Currently, there are limited options for ART in pregnancy, especially in the first trimester (in current or repeat pregnancies) and at higher CD4+ cell counts. WHO recommendations for PMTCT currently include the following:

Late Stage Presentation (CD4<350):

For women presenting at late stages (CD4<350), full treatment with ART is recommended by WHO with the following regimens.

Mother	Exposed Infants (mothers on ART)
<p>Preferred</p> <ul style="list-style-type: none"> • AZT + 3TC + NVP or • AZT + 3TC + EFV <p>Alternative</p> <ul style="list-style-type: none"> • TDF + 3TC (or FTC) + NVP or • TDF + 3TC (or FTC) + EFV 	<p>Preferred</p> <ul style="list-style-type: none"> • NVP for 4-6 weeks or • AZT for 4-6 weeks

Nevirapine-based regimens are recommended for women in the 1st trimester.

Earlier Stage Presentation (CD4>350):

For women presenting at earlier stages of HIV (CD4>350), WHO recommends the following treatment options within Option B.

Option B
<p>Mother</p> <ul style="list-style-type: none"> • Triple ARV (from 14 wks until one wk after all exposure to breast milk has ended) • AZT + 3TC + LPV-r • AZT + 3TC + ABC • AZT + 3TC + EFV • TDF + 3TC (or FTC) + EFV <p>Infant</p> <p>All exposed infants</p> <ul style="list-style-type: none"> • AZT for 4-6 weeks OR • NVP for 4-6 weeks

For those starting ART at earlier stages of HIV (CD4+ count >350 cells/mm³), efavirenz- based regimens are recommended due to concern regarding hepatotoxicity that is noted with the use of nevirapine at higher CD4+ cell counts among HIV-infected pregnant women. However, efavirenz is currently contraindicated for use in the first trimester due to concerns regarding teratogenicity. For pregnant women initiating ART during the first trimester of pregnancy at these higher CD4+ T cell counts, ART options include a protease-based option such as lopinivir/ritonavir. Lopinivir/ritonavir is a difficult agent to tolerate in the first trimester due to gastrointestinal side effects, including nausea and vomiting. Alternatively, abacavir can be used, but this has the disadvantage of being costly and is not widely used due to its side effect profile and to concerns about the efficacy of triple nucleoside regimens.

As with the use of ART in other circumstances, consideration must be given to the challenge of adherence particularly in young healthy women. Poor adherence during and after pregnancy may compromise regimens that are available later in time. Studies have suggested that adherence and ART program outcomes may be lower in the post partum period compared to the pregnancy period, and that pregnant women may have poorer outcomes than other ART patients [30,31].

Public Health Impact:

Treatment of HIV-infected pregnant women and continuing ART after delivery and breastfeeding will reduce risk of transmission in discordant couples for those with CD4+ cell counts between 350-550 cells/mm³ according to HPTN 052. In individuals with higher CD4+ counts the impact is as yet unknown, although treatment of HIV-infected pregnant women at the time of pregnancy will reduce transmission risk to any HIV-negative partners. For sero-discordant couples who wish to conceive, this recommendation should also reduce transmission to negative partners during vaginal insemination.

Antenatal care is a very effective way to screen women for HIV given that prevalence tends to be higher in this demographic than in the general population.

Resource Implications:

Women will present during antenatal clinics (ANC) at all CD4+ cell counts, including >350 cells/mm³. This recommendation will therefore increase the number of individuals who will receive ART and thus the costs of running treatment programs. However, there is potential cost savings in the infections that will be prevented.

Implications for PEPFAR:

Women of child-bearing age should be encouraged to plan pregnancies and get HIV tested before conception. Those who are HIV-infected and pregnant and who are seen in any PEPFAR-supported program should be screened for ART eligibility, either clinically, and/or through CD4+ cell count. Women should be encouraged to attend antenatal services early if pregnancy is suspected. Women testing HIV positive in ANC programs will be offered the preferred PMTCT regimen, preferably as part of the ANC service. Linkage to ongoing care and treatment for all HIV-infected pregnant women before and after delivery and for their HIV-exposed newborns is critical. Providing these services within the maternal and child health (MCH) setting is ideal and active referrals and follow-up to ensure attendance are important.

Knowledge Gaps:

There is an urgent need to increase the options for pregnancy-compatible ART options to allow

for easier implementation of Option B. This includes reviewing drugs currently labeled as category B or even C drugs.

Countries are currently implementing Option A, Option B, or Option B+ (ART for all pregnant women for life). It is critical that key questions are answered to inform future decisions about best options for HIV-infected pregnant women from a public health perspective. These questions relate to logistics, cost, feasibility, acceptance, adherence, toxicity, resistance, birth outcomes etc. This will allow for evidence-based decisions for the next revisions of the WHO recommendations.

Implementation science is needed on how to best reach all pregnant women with PMTCT services, including access to ART for women who need it, improvements in adherence and retention during pregnancy and breastfeeding, and better links between PMTCT and HIV care and treatment services.

RECOMMENDATION 4: The SAB urges PEPFAR to support the use of ART in specific populations with CD4+ counts >350 cells/mm³ in order to prevent transmission to others based on results of HPTN 052. The benefit of this intervention has been confirmed for heterosexual discordant couples, and now careful evaluations, including the assessment of benefits, risks, impacts, feasibility, and modeling exercises are urgently needed in order to identify populations that should be prioritized for this intervention, given local conditions.

Scientific Rationale:

Every sexual HIV transmission event *de facto* involves encounters between HIV infected and uninfected individuals. In many cases these encounters occur within stable discordant couples and a substantial number of couples live in serodiscordant relationships. In these couples, the index case (infected participant) is equally likely to be a man or woman [32], and HIV transmission risk persists for couples over the duration of their relationship, although the risk is highest when one partner first acquires HIV [1, 32-36].

As noted previously, several observational studies and one randomized controlled trial have demonstrated that suppressive ART provided to an index case can prevent sexual transmission of HIV to their HIV negative partner [1, 2, 37-40] from either (or both) the direct impact of ARV and from couples' counseling. Couples enrolled in HPTN 052 also received repeated optimized counseling that focused on safer sex behavior, including condoms, and adherence of the index case to ART when offered. Such counseling likely contributed to the reduced HIV incidence. In a multivariate analysis, baseline condom use was associated with a reduced risk for transmission – specifically, those couples that reported 100% condom usage at baseline also had a lower risk for acquiring HIV [1]. In early studies from Africa and Thailand, 8-11 % of HIV negative partners ultimately acquired HIV infection. With the advent of couples HIV counseling, transmission risk in the absence of ART has decreased substantially [1, 41]. In HPTN 052, HIV transmission in the delayed arm of the study was 2.2 for every 100 person years [1].

Impact on Preventing New Infections/Public Health:

Focusing on recognized serodiscordant couples has several advantages. It allows a ready means to expand HIV testing. Given the risk for HIV transmission, the HIV-negative partner has substantial benefit from his/her partner's therapy. Preliminary evidence demonstrates good adherence to ART when the couple is focused on the therapy of the index case [1]. However, it is also clear that numerous HIV-infected people who do not identify as part of a discordant couple may represent a higher risk for HIV transmission than people in a stable relationship. Suppression of viremia might be most important in people who are most sexually active, such as sex workers (see Recommendation 5 on key affected populations). The recommendation to treat all HIV-infected people with CD4+ count <350 (Recommendation 1) can be expected to have great public health benefit. Treatment of select populations of HIV-infected people at CD4+ count greater than 350 /mm³ can have similar benefits.

Impact on Individual Health and Population Health:

As noted earlier, subjects receiving early ART (median CD4+ count 446/mm³ at initiation of therapy) had a prompt and sustained rise in CD4+ cell count, whereas those in the delayed ART group, who had a lower CD4+ count (median level 226/mm³ at initiation of therapy), did not return to a CD4+ count greater than 500/mm during the follow-up period [1]. Participants who received early ART also experienced reduced episodes of extrapulmonary tuberculosis [1], not unlike the reduced incidence observed with use of isoniazid (INH) prophylaxis [42].

Associated Risks and/or Challenges:

ARVs are a limited resource in many settings. The decision to treat people with CD4+ counts higher than current WHO guidelines needs to be weighed against the risk of not providing ART to patients with advanced HIV. The HPTN 052 couples management strategy was rigorous and restricted to a controlled setting, which was necessary for proof of concept. As programs are implemented, implementation science studies are needed to determine the best ways to apply the results from HPTN 052 to settings with less monitoring of adherence and less frequent counseling on safe sex. Similarly, there is interest in assessing the possibility of behavioral disinhibition or risk compensation and whether adherence levels in couples can be achieved in other settings. Potential adverse effects of earlier ART, as referenced, must also be considered.

20% of HIV transmissions in HPTN 052 were unlinked [1, 43]. Celum *et al.* reported an even greater proportion of unlinked cases of HIV transmission [36]. In HPTN 052, unlinked transmission events were associated with multiple sexual relationships by the HIV-negative partner at baseline that did not end in spite of couples counseling [43]. Therefore, it is essential that any counseling package include key messages for the negative partner regarding the risks of acquiring HIV outside of the primary relationship, particularly where HIV status may be unknown.

Resource Implications:

Of paramount importance is an expansion of efforts to test couples and identify those who are discordant. This will require a ramp up in test kits, personnel, and treatment for positive partners. These efforts should be ambitious, but also targeted to settings that are likely to result in a high yield of discordant couples (e.g. provider initiated testing at healthcare facilities). Of utmost importance will be informing the discordant couple of the importance of long term engagement in care for the infected partner.

Implications for PEPFAR:

The results of HPTN 052 reinforce the current guidelines of initiation of ART to all patients before CD4+ count falls below 350 cells/mm³. This would clearly include people in discordant relationships. In addition, the substantial risk associated with HIV transmission in couples in which the infected participant has a high CD4+ count suggests that ART be offered to all HIV-infected participants in discordant relationships, and perhaps to HIV-infected subjects at greatest risk for heterosexual transmission, regardless of CD4+ count. Couples counseling used in HPTN 052 is a specialized activity that, in and of itself, can reduce HIV transmission and should remain a core program component, and that is already recommended in PEPFAR guidance.

Special Considerations for Childbearing:

Safe Conception: For HIV-negative women in a serodiscordant relationship with an HIV-positive male sexual partner, *in vitro* fertilization techniques used in resource-rich countries [44] are typically not available in resource-constrained countries. Based on a recent study, ART treatment for the male, and time-limited use of pre-exposure prophylaxis (PrEP) for the HIV-uninfected female during attempts at conception, would be expected to reduce the risk of HIV acquisition by the woman [45]. This combination would be expected to reduce the chance for HIV transmission to a very low level, and appears the best recommendation currently available. For HIV-negative men wishing to conceive with HIV-positive women, simple insemination methods may reduce HIV acquisition risk.

Gaps in Knowledge:

HPTN 052 results are largely restricted to stable heterosexual couples. The degree to which ART can suppress the transmission of HIV resulting from anal intercourse and in men-who-have-sex-with-men (MSM) couples is unknown, although informed by considerable work in rhesus macaques [46, 47] and observational data sets [48]. The degree to which condoms and counseling are required in a real-world setting is also unknown. Perhaps most importantly, the HIV-infected population in which treatment would offer the greatest concomitant clinical and public health benefit is unknown and depends on the local epidemiological context (note that in Recommendation 5, we offer special considerations for key affected populations). While HPTN 052 was by design, focused in discordant couples, additional assessments of benefit, risk, impact, and feasibility, including modeling, and a particular focus on gathering further empirical data are required to determine the greatest overall benefit of ART. Specific questions include:

- To which specific population should early ART for prevention be directed?
- What are the clinical benefits and risks to be anticipated?
- How many cases of TB will be prevented?
- How important is preservation of high CD4+ count?
- How many new individuals with HIV will be detected through couples testing?
- Will ART be diverted from sicker to healthier HIV-infected people?
- How much monitoring and adherence counseling is required in a “real-world” setting?

RECOMMENDATION 5: The SAB recommends that PEPFAR intensify efforts to establish effective programs for engaging key affected populations in HIV prevention, care and treatment programs.

Scientific Rationale:

Members of key affected populations, including, but not limited to, injecting drug users (IDU), MSM, and commercial sex workers (CSW), are not only at very high risk of becoming infected with HIV, but if they do become infected, they are often at very high risk of transmitting the virus to others. Thus, there is an extremely strong rationale for providing effective HIV prevention and care services to key affected populations.

HPTN 052 was conducted among stable heterosexual couples, but many SAB members believe the external validity of the results (i.e. the suppression of viral load reduces HIV transmission) should apply to other transmission settings, including multiple heterosexual partners, same-sex partners and persons who share drug injection equipment. At present, it is not possible to estimate an effect size for treatment as prevention for different key affected populations, but the HPTN 052 results justify including treatment as prevention as one intervention to reduce HIV transmission among key affected populations.

Public Health Rationale—Combined Prevention and Treatment Programs:

It is important to emphasize that there are a number of HIV prevention interventions for key affected populations for which there is substantial evidence of effectiveness. These include providing the means for reducing risk behaviors such as access to sterile injecting equipment, distribution of condoms, and provision of treatment for substance dependence. Treatment as prevention for key affected populations must be considered within this broader framework of multiple interventions to reduce HIV transmission. The specifics of an optimal set of combined programs will necessarily vary with the particular population at risk and the particular epidemiological setting.

Associated Risks and/or Challenges:

While HIV prevention and care programs for key affected populations need to be adapted to the local situation, there are a number of general issues that need to be addressed for PEPFAR to have success in reducing HIV transmission among key affected populations.

The policy environments in many countries are hostile towards key affected populations: This makes it more difficult to provide services and conduct research with these groups. Providing services to key affected populations may require that public health agencies work through community-based organizations rather than have public agencies attempt to directly provide services. Building capacity for these groups will likely be critical, particularly in adverse policy contexts. Productive working relationships between public health agencies and community-based organizations are especially critical in areas where community-based organizations are likely to be the most effective means of delivering services to key affected populations and in linking individuals from community-based outreach and prevention services into treatment and care.

Coverage of existing evidence-based interventions for these populations is markedly low: Among IDU in the five largest IDU-driven epidemics (Russia, China, Ukraine, Vietnam and Malaysia) IDU account for some 67% of all HIV infections, but for only 25% of persons with HIV receiving ART [49]. Coverage of IDU with core prevention services, including needle and

syringe exchange (NSP) and medication-assisted therapy/opioid substitution therapy (MAT/OST) was even lower, with no country among these five reaching 5% coverage of IDU with MAT/OST (range 0-3%) [49]. Among MSM, a recent estimate is that between one in 10 and one in 20 MSM worldwide have access to the most basic set of prevention services, including receiving at least one condom/per year and one message to seek HIV testing [50]. Coverage data on sex workers globally are not available, but are also known to be problematic in those settings where data has been collected.

New research findings, with particular attention to the findings of HTPN 052: Implementation of these findings into public health practice may be of greatest benefit for key affected populations. However, because these groups are often considered difficult-to-reach populations and because they are often heavily stigmatized and/or criminalized, public health officials may exclude many members of key affected populations from programs such as those based on HPTN 052. Thus, the work required to optimally target these new interventions to those most at risk may remain undone. Because these individuals are at high risk of HIV acquisition and transmission, including to lower-risk sex partners, their exclusion from new preventive interventions could undermine efforts to control HIV at population levels—those most at risk must be engaged if real gains are to be made in HIV control.

Many public officials lack an understanding of the need for a human rights approach in HIV/AIDS work with key affected populations: It is imperative that there be increased understanding of the central need for a of a human rights approach to HIV/AIDS work with key affected populations.

These populations are most at risk for HIV infection, but also most at risk for exclusion from HIV prevention, treatment and care. The legal, social, and political barriers to care faced by MSM, IDU, and sex workers are many and varied. But the fundamental human rights principle of non-discrimination based on status or membership in a stigmatized group should be a core principle for PEPFAR and for the next phases of the HIV response. Here the public health, medical, and human rights imperatives are shared: these are people in need of services, and the denial of those services will extend the HIV epidemic. This is true in generalized epidemics, where key affected populations are often hidden but are still critical populations, and in concentrated epidemics, where these individuals are not only the most at risk, but they are the majority at risk, and yet they can still be underserved.

Prioritizing Treatment as Prevention for key affected populations

There are a number of principles that can be utilized to guide such decisions with respect to members of key affected populations.

First, particular efforts should be undertaken to ensure individuals in key affected populations that are eligible for treatment receive ART in an enabling environment that includes evidence-based prevention services for those not infected and supports the human rights of all persons with or at risk for HIV infection.

Second, there should be no discrimination against individuals in key affected populations for providing ART when clinically appropriate (at CD4+ cell counts <350, as suggested in Recommendation 1).

Third, if there are a number of evidence-based HIV prevention interventions for key affected populations, including condom distribution, legal access to sterile injecting equipment, and

treatment for substance dependence, these should be implemented either along with, or before implementation of treatment as prevention for key affected populations.

Finally, if a society has the resources to implement treatment as prevention, there should not be discrimination against members of key affected populations in receiving treatment as prevention.

Resource Implications:

PEPFAR must prioritize reaching key affected populations with care and treatment services, and therefore must commit additional resources for these activities. Actual resource requirements will vary by local condition, and PEPFAR should assess these needs as a next step.

Implications for PEPFAR:

Public health officials in many PEPFAR countries need to strengthen their technical expertise and knowledge of the specific issues around working with key affected populations. These technical issues include such key components of programming as needle and syringe programs for IDU, MAT for opioid dependent patients, best practices for reaching hidden populations of MSM, building social capital for people who sell sex, and couples-based counseling and treatment approaches for couples and families within key population risk groups. In many PEPFAR countries, technical capacity for addressing the needs of MSM is particularly limited. There are also clear needs for enhancing technical knowledge, including the skills needed to conduct research with key affected populations, to adapt evidence-based programs for these populations according to local situations, and to evaluate the effectiveness of these programs. In the coming era of combination prevention, “seek, test, and treat” approaches, and of ARV treatment as prevention, it will be critical to strengthen the capacity of community and clinic partners to provide ARVs to key affected populations in settings they use. This will help ensure access, protect dignity and non-discrimination, and maximize the prevention benefits of treatment for high incidence and prevalence populations too often excluded from treatment and care.

Implications for PEPFAR:

As stated above, HPTN 052 took place among discordant, heterosexual couples, and research is needed regarding the treatment for prevention benefit for anal intercourse, which is more common among MSM. In addition, the added issues of stigmatization and discrimination make implementation science among all key affected populations particularly challenging. The best ways to encourage testing and consequent retention in the care and prevention cascades are not well known, and are likely to vary depending on the social and epidemiological context. Understanding barriers to adherence and retention are essential to achieve the maximal benefits from treatment, and to prevent adverse consequences, including the development of resistance as well as transmission

Gaps in Knowledge:

While there is great variation among PEPFAR countries, there are a number of gaps in knowledge that would need to be addressed before the results of HPTN 052 could be effectively implemented to substantially reduce HIV transmission among key affected populations. These include:

1. Basic epidemiology of HIV among local key affected populations: size of the populations, current HIV prevalence, trends in HIV prevalence, rates of risk behaviors,

and linkages between these populations and other groups in society.

2. Methods for successfully engaging key affected populations in HIV prevention, care, and treatment: needed changes in policy environment, changes in law enforcement practices, training of health agency staff and health care providers, establishment of community based organizations.
3. Scale and effectiveness of current HIV prevention, care, and treatment services for key affected populations and how those might be improved.
4. Identification of subgroups most likely to benefit from treatment as prevention.

RECOMMENDATION 6: Given the scientific basis for and potential impact of these recommendations, the SAB recommends that PEPFAR seek and secure sufficient resources to implement the recommendations

Scientific rationale:

Three sources of evidence support the implementation of the SAB's recommendations: 1) scientific data (about which the Board spent the majority of the SAB meeting discussing); 2) model-based estimates for the number of HIV infections averted over time with expanded access and penetration of testing and care, and increased adherence and retention; and 3) economic analyses of the relative costs of implementation under varying conditions in a population. The latter two analyses indicate that substantial population benefits accrue with expanded HIV interventions over time. Over the next 10 years, we anticipate substantial reductions in the implementation costs, despite increased survival of increasing populations of HIV-positive persons.

Generally, existing data [53] suggests that reasonable decreases in per-patient treatment cost, combined with the benefits of increased access to treatment (including prevention benefits), means that the sustained implementation of increased levels of treatment would be cost-effective. Within 10 years, expanded HIV testing and ARV treatment is associated with reduced total costs associated with HIV: the number of infections averted rises, mortality decreases, penetration of HIV programs expands, and the total costs of treatment delivery fall. The additional benefits of enhanced national productivity associated with these improvements on the quality of life have not yet been calculated.

Over the last 7 years, there have been substantial reductions in the costs per patient year of treatment. From a cost of about \$1100 USD in 2004, current estimated PEPFAR costs per patient year of treatment are about \$436 USD. Considering all sources of funds (i.e. country support, Global Fund, etc.), the full expenditure per patient is an estimated \$812 per patient year and has shown similar sharp declines over time. 59% of these full treatment costs are offset annually through the savings that accrue from averted morbidity and mortality of treatment patients, averted orphanhood, and averted sexual and vertical infections that result from effective ART. These savings accrue over time, as treatment is sustained. Most likely, continued cost reductions of ARV treatment will be realized as re-engineering of medication delivery systems (dose, delivery modality [pills, patch]), clinical monitoring, laboratory monitoring and decentralization of care continue. Using country-level data as a prototype example (Kenya), the costs of expanding coverage of HIV testing and ARV treatment increases over time for about five years, with relatively small incremental costs. However, after five years, a steady state emerges for costs, as the number of infections averted increases, and treatment costs decrease, resulting in a net reduction of financial needs for HIV treatment services. In addition, the current benefits of 2.2 quality of life years saved for each year that an HIV-infected patient is provided treatment may increase as the penetration of HIV testing, ARV treatment, and adherence rises in a population, and lowered transmission in the population reduces incidence.

In addition to general benefit, this recommendation specifically enhances Recommendations 1 and 4 for the reasons stated below:

Recommendation 1: Results suggest that with a sharp step-up in ART coverage in a hyper-endemic setting, between 60 and 90 HIV infections may be averted annually per 1000 persons treated by ARV, provided treatment is promptly initiated when the CD4+ cell count among persons infected with HIV falls below 350 cells/mm³ and retention in care at all stages is high

[54]. Over time, the benefits of earlier treatment would accrue if the higher coverage level is maintained, leading to increasing numbers of infections averted [54].

If the recommendations of the SAB indicating provision of treatment to infected persons with CD4+ cell counts >350 cells/mm³ in a recognized discordant partnership are adopted (Recommendation 4), models suggest that an additional average of 3,000 person-years of treatment may be required per 1,000 individuals who are part of a discordant relationship (in addition to the person-years of treatment required if ART were initiated at a CD4+ <350). This translates into between 62 and 232 extra HIV infections being averted, depending on the behaviors of those receiving treatment, resulting in an overall increase in the numbers of infections averted per year of treatment to between 21 and 77 per 1000 individuals. A consortium of epidemiologists and modelers will meet to review these and related model estimates in November 2011.

Public Health Impact:

The SAB's recommendations are likely to result in substantial benefits to the individual, family, community, and country in terms of quality of daily life, reductions in future HIV infections, and, eventually, the economic costs of the HIV epidemic. However, the actual benefits will be substantially reduced if there is not broad implementation, uptake, and adherence. The sensitivity of these modeling analyses to the potential impact of these contextual factors is relatively low based on existing data. However, there have only been a few prototype models.

Resource Implications:

The SAB's recommendations will require expanded resources to as yet unknown levels, over the next five years. Once at that level, HIV funding needs may approach a steady state, given achievement of high coverage and decreases in the number of new infections. Further modeling is required to identify any potential decreases in required funding levels over time. Future SAB recommendations will also need to address the importance of solid monitoring of PEPFAR's implementation on the ground.

Gaps in Knowledge:

Both modeling and cost analyses are sensitive to their assumptions. Each recommendation proposed and future analyses require that we confirm these expectations. Ongoing analyses are focusing on:

- Estimating the cost of expanded access for five years directly linked to anticipated outcomes.
- Prioritizing and targeting funding to the subpopulations most likely to transmit the HIV virus.
- Strengthening health systems' infrastructure, ability to improve iteratively based on feedback from monitoring and quality improvement.
- Identifying the global costs for scaling up the recommended testing and ARV services required to move from a steady state of costs to reductions in HIV services, a point that most likely cannot be feasibly reached in less than 10 years.
- Moving from modeling country-level data to the global impact of testing and care including sensitivity analyses that vary assumptions of uptake, retention, and adherence for the population, region, and health system.

CONCLUSION

Over the last year, there has been a tangible and renewed sense of excitement and invigoration in the HIV/AIDS field due to critical new data emerging in studies, culminating in the prevention impact of treatment demonstrated in HPTN 052. This study has been described by many of our colleagues as a “game changing strategy for epidemic control.” We now have definitive evidence of treatment as prevention, along with other important and effective combination prevention tools. Finally, the prevention versus treatment dichotomy has disappeared, and we can consider a unified strategy for epidemic control where efforts to expand treatment can be justified not only as important for individual health, but also as a very strong preventive modality. The purpose of the SAB was to think through the science and the practical applications and implications of these findings.

The discussions at the SAB meeting on the initial recommendations, developed by a smaller sub-committee, were lively and involved many different opinions and points of view. Through these two days of intense discussions, issues surrounding the recommendations, study findings, and policy implications were explored in detail. By the end of the meeting there was general consensus on the six recommendations.

The SAB recognizes that programmatic decisions are complex and involve many issues, including science. The hope is that these recommendations will help inform Ambassador Goosby and OGAC as they develop future policies and guidance for PEPFAR programs. The opportunity is there for PEPFAR to capitalize on these scientific advances and change the course of the HIV epidemic.

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APPENDIX A

PEPFAR Scientific Advisory Board Members

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APPENDIX B

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