

# ■ Harnessing the Secondary Preventive Benefit of Antiretroviral Treatment

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## Introduction

Despite remarkable advances in our understanding of the nature of HIV, after 27 years we still find ourselves struggling to address a devastating HIV pandemic.<sup>1</sup> Over 25 million people have died and an estimated 33.4 million people are living with HIV.<sup>2,3</sup> In 2008, about 68% of people living with HIV were in sub-Saharan Africa with around 35% in 8 countries alone.<sup>2</sup> HIV is the strongest risk factor for tuberculosis (TB) and an estimated 1.4 million people living with HIV developed TB causing 500,000 (26%) of total HIV-related deaths.<sup>4</sup> In 2005 and 2009 the G8 met in Scotland and Italy and committed to achieving Universal Access to HIV prevention, care and treatment by 2010.<sup>2,5</sup>

There has been an unprecedented investment in mitigating the HIV pandemic--UNAIDS estimates \$13.8 billion in 2008.<sup>6</sup> Despite this significant outlay of resources, our challenge is to not only sustain but expand our response to the HIV epidemic in the face of the worst economic crisis since the 1930's. The magnitude of the economic crisis is often hard to comprehend. Experts estimate that over \$14.5 trillion, or 33%, of the value of the world's companies has been wiped out and taxpayers will spend trillions in bailout packages and plans.<sup>7</sup> The economic disaster is being felt world-wide and has already impacted investment in international and national public health. The contraction and re-orientation in public sector investment demands leveraging existing international and domestic health sector resources, broadening backing for the health sector to include new

sources of support, and a more efficient use of existing funding. However, the bottom line is that Universal Access remains a dream for millions of people and faces serious technical, economic and political challenges on a number of fronts.<sup>2</sup> These challenges contribute to a growing concern that there may be a weakening of the longstanding G8 pledge to achieve Universal Access by 2010 and to deliver on the health related Millennium Development Goals by 2015.<sup>8,9</sup>

## Prevention and Treatment Gap

The discovery and use of ART represented a paradigm shift in the approach to the epidemic and has saved millions of lives. In the face of considerable scepticism, by end 2008, over 4 million people were on ART.<sup>2</sup> Despite this remarkable achievement, often in some of the harshest economic conditions in the world, in 2008 over 5 million needed treatment and there were over 2.5 million new infections.<sup>2</sup> Approximately 23 million people were waiting, mostly unknowingly, to become treatment-eligible, sicken or die. Using the lower 200 CD4 count eligibility criteria, the estimated coverage of antiretroviral therapy reached 42% in low and middle-income countries.<sup>2</sup> Although recent gains suggest that we have added an additional million on treatment in 2009, the coverage percentage would markedly decrease if we applied the new WHO recommendations for ART for those with <350 cells/mm<sup>3</sup>. Despite our current focus on limiting scarce resources to provide access to ART for people who are very ill, if we do

not markedly reduce HIV incidence it is unlikely that we will be able to meet Universal Access targets including the increasing demand for ART.

### **The Human Rights and Community Support Gap**

The HIV pandemic underscores the obvious lack of equity and human rights in current global public health conditions. The fact that millions of people live with the risk for HIV and have no access to HIV prevention, treatment and care represents a serious breach of the fundamental right to health care<sup>10</sup> and the potential for stigma and human rights violations exacerbates the problem.<sup>11</sup> Growing economic disparities will likely further contribute to the increasingly divergent approaches to HIV prevention, care and treatment that are seen between rich and poor countries.<sup>12,13</sup> Engaging the community as a meaningful partner in the design, implementation and evaluation of HIV programmes is critical for program success, particularly when the potential for stigma and human rights violations exist.<sup>11</sup> To achieve societal health goals, it is imperative to address the human rights and community support gap when considering the design and implementation of HIV and other health programmes.

### **Earlier Access to Treatment is Critical**

Although starting ART earlier is critical for people living with HIV, we do not know with certainty when to start people on ART after HIV infection. We do know that in sub-Saharan Africa people start very late at a median CD4 count of around 100 and despite progress with improving earlier access, mortality remains markedly higher when compared with resource rich settings.<sup>14,15</sup> Mortality risk is associated with starting late even for patients on ART and is associated with the time spent below 200 CD4+ cells per cubic mm.<sup>16,17</sup> Even after testing HIV positive and entering care while waiting to be eligible for ART, one South African study found that 25% of people die while on the waiting list.<sup>18</sup> One explanation is that patients with higher CD4 cell counts are being monitored too infrequently for the timely start of treatment.<sup>18</sup> Although mortality rates at higher CD4 levels are lower, they are not zero, and being infected with HIV may represent a significant impact on morbidity and mortality. In Zimbabwe, a study of post-partum women not

on ART showed that HIV mortality within 24 months postpartum was 54 times higher for those with CD4 cell counts less than 200 cells/ml, 5.4 times higher for 400-600, and the hazard even remained elevated at 6.2 for women with greater than 600 CD4 cell levels.<sup>19</sup> An analysis of North American cohort data showed a 94% increase in mortality for those who started treatment below CD4 a 500 CD4 count level when compared to those who started earlier.<sup>20</sup> Europe and North America cohorts including over 40,000 patients showed that starting treatment earlier reduced the risk of acquired immunodeficiency syndrome or death with those starting before reaching 350 having the most benefit.<sup>14</sup> 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 and the negative effects of letting CD4 counts drop too low.<sup>21,22,23,24</sup> Another argument for an earlier start is that ART has a significant role to play in preventing TB morbidity, transmission and mortality. A recent review concluded that ART reduces the risk of TB by 54-92%.<sup>25</sup> In a randomised clinical trial of 642 patients co-infected with HIV and tuberculosis in South Africa starting ART earlier during tuberculosis therapy reduced mortality rates by 56%.<sup>26</sup> 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 researches as CD4+ <500 CD4.<sup>16,17</sup> Recognising this, WHO recently revised its guidelines to recommend ART for all with <350 CD4 cells and for all patients with TB irrespective of their CD4 count.<sup>27</sup>

Trial data confirms earlier observational studies and also points in the direction of an earlier start. The CIPRA HT 001 randomised 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 ART earlier between 200 and 350.<sup>28</sup> In ACTG A 1564 survival curves demonstrated a 47% reduced progression or death in patients receiving immediate as opposed to deferred ART.<sup>29</sup> Analysis of data from the SMART trial and more recent work have suggested that starting earlier was more beneficial and found that HIV may be associated with serious non-AIDS defining events including cardiovascular, renal, and liver disease and non-AIDS malignancies.<sup>21,30,31</sup>

Scientific evidence increasingly suggests that HIV infection is likely a chronic inflammatory disease process which provides additional rationale for an earlier start of ART suppress viral replication. However opinions on starting at CD4 cell counts above 350 or even 500 remain divided. Apart from the subset analysis in the SMART trial, there are no data from randomised clinical trials to inform the optimal time to start ART in these patients and guidelines are largely based on evidence from observational studies.

Although some countries rely on clinical staging to determine eligibility for ART, most use surrogate markers such as CD4 count to determine an individual's immune status. However, a single CD4 count only represents a snapshot and people living with HIV will eventually need ART to stay alive. The question facing people living with HIV, clinicians and policymakers is how long to wait until a person is immunocompromised enough to be eligible for treatment. Data from 30 international studies and 16 cohorts of untreated adults found relatively low CD4 levels after HIV infection and a fairly rapid progression to CD4 thresholds such as 500, 350 and 200.<sup>32</sup> The time to eligibility was variable and in some settings was only a few years after HIV infection.<sup>32</sup> From this perspective and assuming access to ART, decisions whether to start at 200, 350 or 500 represent only a few years earlier in the course of a much longer life span while on ART.

In summary, results of clinical trials and observational cohort studies have now conclusively demonstrated that earlier initiation of ART is warranted, to decrease AIDS related morbidity and mortality. Furthermore, non-AIDS related morbidity and mortality has been shown to decrease with even earlier initiation of therapy. Guidelines written for high income countries now recommend starting treatment earlier before severe immunocompromised and use factors such as CD4 decline, viral replication, and discordant couple status as potential eligibility criteria even at higher CD4 counts.<sup>33</sup> The World Health Organisation, as a result of an exhaustive review of the literature as well as consultations with country programs and community representatives, recognises the importance of starting ART earlier and has replaced the 200/mm<sup>3</sup> with 350/mm<sup>3</sup> as the

CD4 cell count threshold for resource limited settings.<sup>27</sup>

### **HIV Counselling and Testing**

Regardless of when people should start ART, assuring universal access to prevention, care and treatment will entail that millions of people with HIV have access to learning their status. Despite remarkable efforts to expand access to HIV testing and counseling, an estimated 80% of people living with HIV in sub-Saharan Africa do not know their status and 90% are unaware of their partners status.<sup>2,34</sup> In Kenya, a leader in improving access for HIV counseling and testing, out of those found positive 57% of people eligible for ART by Kenyan CD4 count criteria do not know that they had HIV and a further 28% mistakenly thought they were HIV negative; only 16% actually knew their HIV status.<sup>35</sup> However, 92% of those who knew their status and were eligible were on ART.<sup>35</sup> HIV counseling and testing itself—particularly when it includes couples counseling—is a remarkably effective prevention intervention.<sup>36,37,38,39</sup> Community-based efforts, including home-based couples counseling and testing, have considerable promise to expand access to HIV testing and health care. In Western Kenya, a private sector company in collaboration with the Ministry of Health, local NGOs, and Centers for Disease Control Kenya was able to test 41,040 or 80% of the men and women between 15 and 49 during a seven day campaign.<sup>40</sup> In our efforts to improve the basic human right to health care through the expansion of HIV testing and counselling, we must also keep in mind the importance of ensuring that access is provided within a strong human rights framework that emphasises the Three C's: consent, confidentiality and counselling.<sup>41,42</sup>

### **Prevention is Clearly the Answer**

Stopping the HIV epidemic remains a significant challenge in most settings and there is a need to re-examine our current approaches to preventing the transmission of HIV. Combination prevention includes evidence-based interventions to address behavioral change, ART, other biomedical strategies, and structural, social justice and human rights interventions among others.<sup>43,44</sup> While this article focuses on ART as a biomedical prevention intervention, it is clear that biomedical prevention should

be viewed as part of a larger effort to optimise combination prevention. Of 37 randomised controlled prevention trials reporting on 39 interventions including vaccines, microbicides, and herpes suppression trials to prevent sexual transmission of HIV, only five reported a positive effect (defined as intervention significantly reduced the risk of HIV in the intervention arm compared to the control arm).<sup>45</sup> Only the three male circumcision trials, the vaccine trial and the STI study in Mwanza, Tanzania, over a decade ago and of limited generalisability, were effective.<sup>46,45</sup> The microbicide gel Pro 2000 trial showed no effect.<sup>47,48</sup> Pre-exposure prophylaxis (PrEP) is being assessed in ten ongoing or planned international trials and first results are expected in late 2010 or early 2011. PrEP is certainly promising, however, it will undoubtedly be difficult to give scarce ARVs to persons without HIV when many people are dying from lack of access to ART. Additionally, PrEP will also face operational challenges around the need to repeat HIV testing to ensure that only those without HIV receive mono or dual therapy. A vaccine may provide an important future intervention,<sup>49</sup> however, the overall grim situation has prompted many people to consider the potential prevention role of ART.<sup>50,51</sup> This situation has led to renewed interest in the potential value of ART for preventing HIV transmission.

### ***Harnessing the Secondary Preventive Benefit of Antiretroviral Treatment***

Scientific evidence increasingly supports using ART for the prevention of HIV transmission. This is a true game changer as it dramatically enhances the value of the Universal Access pledge from a compassionate life saving initiative, to a strategic investment aimed at drastically reducing the number of new infections. Prevention efforts focused on people living with HIV make sense as HIV transmission only occurs from people with HIV, viral load is the greatest risk factor for HIV transmission, and lowering the viral load is critical to interrupting transmission.<sup>1,52,34</sup> Viral load predicts the risk of sexual transmission of HIV-1 which is rare among persons with levels of less than 1500 copies of HIV-1 RNA per milliliter.<sup>52,53</sup> ART significantly lowers viral load and many observational studies have demonstrated its potential for prevention of HIV transmission.<sup>54,36</sup> Couples

counseling and ART in Uganda reduced HIV transmission by 98%.<sup>36</sup> A 2009 meta-analysis including 11 cohorts (5021 heterosexual couples) found zero risk of sexual transmission while on ART for HIV-1 ribonucleic acid below 400 copies (upper confidence limit of 1.27 per 100 years).<sup>55</sup> A recent randomised controlled study of genital herpes simplex virus treatment among long-term, HIV-serodiscordant heterosexual couples in Africa found a 92% reduction in transmission if the HIV-positive partner was on ART.<sup>56</sup> The proportion of couples who had unprotected sex actually decreased when the HIV-positive partner started treatment, allaying fears about the resumption of risky sexual behaviours.<sup>57</sup>

Further proof of concept that ART interrupts HIV transmission can be found in efforts to prevent mother-to-child transmission. Perinatal AIDS cases have been virtually eliminated in the United States most likely due to the implementation of guidelines for the universal voluntary HIV testing and ART for pregnant women for their own health and antiretroviral prophylaxis if therapy is not yet required, combined with elective caesarean section and complete avoidance of breast feeding and lastly HIV diagnosis and ART for newborn infants.<sup>58</sup> In 2008, the majority of the 430,000 new paediatric HIV infections were in sub-Saharan Africa where there is recent evidence that ART can be used to decrease transmission to one percent.<sup>59,60,61</sup> In fact the provision of antiretroviral therapy for all HIV-positive pregnant women with CD4 cell counts <350/ $\mu$ L can potentially prevent an estimated 75% of mother-to-child transmission of HIV.<sup>62,61</sup>

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 is associated with ART use.<sup>63</sup> Between 2004 and 2008, the number of HIV diagnoses in San Francisco fell by 45%, the average viral load amongst the HIV-positive population fell by 40%, and the actual HIV incidence fell by one-third between 2006 and 2008.<sup>64</sup> In Taiwan a reported 53% reduction in new HIV cases was associated with free access to ART.<sup>65</sup>

### **Modelling ART for Prevention of HIV Transmission**

Using models is a standard approach for public health authorities to better understand what we think we know and perhaps most importantly what we need to find out. Our model builds on previous work to focus on a generalised HIV epidemic setting largely driven by heterosexual sex and used data from South Africa, Uganda, Malawi and elsewhere.<sup>66,67,50,51,68,69</sup> It is inspired by earlier analyses suggesting that rapid scale-up of conventional ART approaches could significantly reduce mortality<sup>70</sup> and have a substantial impact on HIV incidence.<sup>67,50</sup> The model examines ART for all those with <350 as per current WHO recommendations and concludes that although it would not eliminate HIV it could save nearly 2.41 million lives.

Models are perhaps most useful when used to examine the potential impact of public health interventions and to discuss programmatic targets for maximal impact. Modeling 'test and treat' for Washington, D.C. concluded that the strategy could potentially decrease the number of new HIV infections there by as much as 26% over ten years and work in San Francisco suggests that incident infections could be reduced by 91%.<sup>71,72</sup> Scientists in Vancouver have reviewed scientific evidence and modelled data derived from their program and reached the conclusion that expanding access to ART could markedly reduce HIV incidence, decrease drug resistance, save lives, and be cost effective.<sup>50,63,73,74</sup> Other mathematical modeling studies have reviewed assumptions and to examined 'test and treat' in other contexts and have arrived at contrasting conclusions but a full discussion is beyond the scope of this article.<sup>71,72,75,76,77,78,79</sup> Models are sensitive to key assumptions and when including a different context or more pessimistic parameters the results are predictably less optimistic.<sup>75,76,77,78</sup> One modelling group using hypothetical assumptions raised the spectre of widespread resistance<sup>78</sup> but data from programs providing ART and population-based threshold studies suggest that these claims may not reflect the actual situation.<sup>80,81,82,83,74</sup> Resistance is of course a serious concern and WHO is working with partners to monitor the situation through the 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.<sup>84, 85</sup> Other authors have raised other issues including the potential importance of adherence, sexual disinhibition, and the acute phase.<sup>86,87</sup> Although modelling is important, program data, research studies and field trials will need to examine the key thresholds for program performance raised in the supporting information of the recent Lancet paper<sup>51</sup> and in subsequent articles by the modelling community.<sup>71,72,75,76,77,78,79</sup>

### **Ongoing Scientific Evaluation**

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 the prevention and control of HIV/AIDS.<sup>50,51,88,89</sup> In November 2009 WHO held two meetings bringing together stakeholders for a discussion of ART for prevention designed to explore human rights and ethical considerations, clarify research priorities and review feasibility and acceptability issues. WHO and its partners are 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 PMCT and an in-depth economic analysis of the various strategies, and a systematic comparison of different modes of providing testing and counseling, and of the ethical practices around testing and counseling. 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,<sup>90,91</sup> Vancouver, British Columbia,<sup>92</sup> San Francisco California,<sup>64</sup> Botswana<sup>93</sup> and Kwa-Zulu Natal, South Africa<sup>94</sup> Scientific and community opinion leaders have called for expansion of access to treatment and ongoing research on ART as prevention.<sup>50,88,94</sup> Funding opportunities are increasing and more data on this important topic will be made available in the near future.<sup>50,88,94</sup>

### **Time for a New Treatment Paradigm?**

In order to sustain and build upon the progress made to date, we need a shift in our response to HIV - a new prevention/treatment paradigm - that better acknowledges and maximises interconnectedness

and interdependence of conventional prevention and treatment interventions. The current response to HIV is often complicated and fragmented. Prevention, treatment, care and social support programs are often not integrated which translates into a lack of continuum of care and increased costs for programs and patients. A new approach needs to include a redoubling of efforts to deliver evidence-based, tailored interventions including community-focused prevention and community-based treatment services with affordable, simplified drugs and diagnostics focused on improving access to HIV care for the majority of people living with HIV. Two key opportunities now present themselves that have the potential to hasten and expand the twin goals of saving lives and preventing new HIV infections. Major efforts are required to radically simplify current ART through ARV regimens that will be easier to administer and take and have longer lasting impact. This will be critical in reaching the goals of Universal Access and will result in cost reductions. It is also increasingly clear that Universal Access to ART will have a

significant impact on HIV transmission.

Our challenge is to understand how best to use new information regarding the role of ART for a reinvigorated, more effective and sustainable global response to AIDS. The therapeutic concepts regarding earlier treatment are not necessarily novel as many researchers, clinicians, program managers and patients have been calling for earlier access – what is potentially new is a focus on simplification with accelerated expansion and full integration of treatment as a key aspect of HIV prevention efforts.

## Conclusion

HIV is an infectious disease and with the right interventions it can be controlled and possibly even eliminated. Without a considerable effort to achieve Universal Access, millions of people will die before accessing ART. ART has considerable benefit both as treatment and prevention and it is likely that it will be increasingly considered as a key element of combination prevention.

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