

## Preventing HIV transmission with antiretrovirals

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Three of the most extraordinary events in global health over the past 30 years have been the emergence of the pandemic of HIV/AIDS, the development of antiretroviral therapy (ART) capable of arresting HIV progression and reducing mortality, and scale-up of therapy in low- and middle-income countries. By the end of 2007, approximately 3 million people were accessing ART in resource-constrained settings,<sup>1</sup> an unimaginable achievement a few years previously, yet one whose expansion and sustainability are threatened by resource constraints and competing priorities. Adding complexity are scientific uncertainties – where is the pandemic going, what is the best way to use ART for individual health and what role can ART play in HIV prevention?

By the end of 2007, an estimated 33 million persons were living with HIV and 2.7 million had become newly infected that year.<sup>2</sup> Sub-Saharan Africa has 67% of all estimated infections. At the risk of oversimplification, two broad patterns have emerged globally: HIV affects the general population in sub-Saharan Africa but elsewhere is largely concentrated in specific groups at risk. Eight countries in southern Africa have an adult HIV prevalence of 15% or above.

Although the annual incidence of HIV infections globally peaked around the mid-1990s,<sup>3</sup> the absolute number of people living with HIV in Africa continues to increase as a result of persistent high incidence and population growth rate. Universal access remains a remote aspiration unless HIV transmission is substantially and rapidly reduced.

While treatment and prevention seem different concerns, recent research suggests earlier initiation of therapy may provide individual as well as public health benefit. Industrialized country guidelines mostly advocate starting ART in asymptomatic individuals when the CD4+ count falls below 350/ $\mu$ l.<sup>4</sup> WHO's 2006 guidelines are permissive in this regard but are often interpreted as more conservative, and understood to advise initiation at CD4+ counts below

200/ $\mu$ l.<sup>5</sup> Two observations are that, irrespective of guidelines, the majority of persons with HIV are diagnosed late with advanced disease; and that the optimal time to start has never been definitively established through randomized controlled trials.

Recent observational studies showed improved survival in persons starting ART earlier compared to those deferring treatment (the thresholds examined against higher CD4 counts were  $\leq 350$  CD4+ cells/ $\mu$ l; and  $\leq 500$ / $\mu$ l).<sup>6,7</sup> Experience in South Africa showed a greatly increased risk of death with increased time lived at CD4+ counts below 200/ $\mu$ l,<sup>8</sup> and increasing tuberculosis incidence with time lived below 500/ $\mu$ l.<sup>9</sup> WHO will be reviewing evidence and revising guidance on ART use, including when to start, for adults and children later this year, but there are many advocates for earlier therapy.

There is little doubt that ART has preventive effects; what is uncertain is how best to apply it and combine it with other evidence-based prevention interventions for maximal synergy and benefit. For HIV-negative persons, guidelines already exist concerning use of ART for post-exposure prophylaxis,<sup>10</sup> and results of randomized controlled trials of pre-exposure prophylaxis will soon become available. It is the treatment of persons who are already infected, however, that may have the widest impact. The rationale seems simple: transmission only occurs from infected persons who are numerically far fewer than HIV-negative susceptible persons; viral load is the greatest risk factor for all modes of transmission; ART lowers viral load; prevention of mother-to-child transmission offers proof of concept; and there is observational evidence of reduced transmission from discordant heterosexual couples when the index partner is on ART.<sup>11,12</sup>

Several papers have proposed expanded use of ART as a means of limiting HIV spread<sup>13,14</sup> and further impetus to this discussion was given by a mathematical model published by WHO

scientists in late 2008.<sup>15</sup> Their paper reported that in an HIV/AIDS epidemic of southern African severity, universal voluntary HIV testing on an annual basis followed by immediate ART could reduce HIV incidence by about 95% within a decade, with cost-saving over the medium term. Formidable challenges to such an approach include conducting the necessary research; operational and financial feasibility; ethical and human rights challenges, acceptability; and the potential for drug resistance and toxicity.

Widespread early therapy for HIV is intellectually compelling because it targets viral load, the major biological risk factor for transmission and disease progression. Delaying treatment until HIV has inflicted severe damage on the immune system and further transmission occurs is a different practice to the approach of other infectious diseases such as tuberculosis. Earlier diagnosis and treatment offer opportunity for "positive prevention" emphasizing other health interventions, as well as enhancement of sexual and reproductive health and rights of persons living with HIV.<sup>16</sup> Nonetheless, the world requires evidence before policy development on ART for HIV prevention can be envisaged.

WHO will organize a consultation in late 2009 to examine research priorities, operational considerations and ethical and human rights concerns around the use of ART for HIV prevention. Additional questions other than impact in generalized epidemic settings include relevance to concentrated epidemics, impact on tuberculosis incidence, prevention of mother-to-child transmission and cost implications.

At a time when other avenues of HIV prevention research, including vaccine evaluations, have given discouraging results, how to use ART for the greatest simultaneous therapeutic and prevention benefit is perhaps the most pressing question in HIV research. ■

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