Editorial

Expanding the Scope of Antiretroviral Therapy for HIV Infection

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The 2010 Global Report on AIDS contains some welcome news: the number of annual AIDS-related deaths has continued to decrease from a peak of 2.1 million in 2004 to an estimated 1.8 million in 2009.[1] This is mainly attributable to the huge expansion in access to anti-retroviral therapy (ART). ART, usually a combination of 3 drugs that block HIV replication, effectively prevents or reverses damage to the immune system and thereby decreases the risk of developing opportunistic infections and progression to AIDS and death. As a result of major international funding efforts, more than 5 million people – mostly living in low and middle income countries – are now receiving treatment, 1.2 million of whom started treatment in 2009 (a 30% increase in a single year). In most settings, ART is reserved for patients who have reached a moderate to advanced stage of disease – usually defined by a CD4 T-cell count below 350 cells/mm^3. Given the remarkable success of ART at an individual and population level, there is understandably a great deal of interest in further expanding the use of this treatment – not only to treat individuals at earlier stages of disease, but also to treat uninfected individuals in order to prevent them acquiring HIV infection. The rationale for these proposed approaches is outlined below.

Firstly, why not treat people at an earlier stage HIV disease? Previously, there were (legitimate) concerns about cumulative drug toxicity and possible impact of that on long-term treatment adherence and consequent development of drug resistance. However, as new drug combinations have been developed that have better tolerability and safety profiles, these concerns have abated. Accompanying the increasing confidence in safety, there has been growing awareness that the range of possible benefits of early ART for the individual may be greater than previously recognised. Until relatively recently, the perception was that most of the morbidity and mortality from HIV disease was attributable to opportunistic infections and malignancies associated with advanced stages of HIV disease – and that there was therefore little to be gained by treatment earlier in the course of disease. However, a landmark clinical trial – SMART – revealed a surprising finding that revolutionised the way that HIV disease is viewed.[2] In this trial, patients with a CD4 T-cell count above 350 cells/mm^3 (mostly on ART) were randomised to continue treatment or to interrupt ART and only restart when the CD4 count fell below 250 cells/mm^3. The treatment interruption arm did worse than the continuous treatment arm, but the real surprise was that this was driven not by an excess of traditional AIDS-defining opportunistic infections, but rather by a higher incidence of cardiovascular, renal, hepatic and other diseases occurring in patients with relatively high CD4 T-cell counts – conditions that hitherto had not been recognised as complications of HIV disease. This revelation about the broader spectrum of HIV disease at higher CD4 T-cell counts together with the perceived long-term safety of ART, has led many to advocate initiation of ART at an earlier stage of disease. The US guidelines have now shifted – controversially – to recommend initiation of treatment in all patients with CD4 cell counts below 500 cells/mm^3.[3]

However, there are a number of concerns with expanding treatment to individuals with early stage of HIV disease. Firstly, there is no evidence to date from any large-scale randomised controlled trial that quantifies the benefit (if any) of starting treatment early in the course of HIV disease. Such a trial has recently started – the START trial will randomise 4000 patients with CD4 counts above 500 cells/mm^3 to start treatment immediately or to wait until the CD4 count drops below 350 cells/mm^3 and will provide an answer to this question in 2016. The second caveat is that even if there is a net benefit for the individual of treating their HIV disease early, such a benefit may be small and with the high cost of ART drugs may not be viewed as cost effective. In resource-limited settings especially, it may well be that greater good is achieved by focusing resources on treating a higher proportion of the patients with moderate to advanced disease rather than seeking to extend early treatment to a much larger pool.

More ambitious still, some are now advocating a strategy of massive expansion of ART to the entire HIV infected populations. The rationale is that, aside from potential benefits to an individual, ART also dramatically decreases the risk that an infected individual will transmit the virus to others. Mathematical modelling has suggested that a strategy

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of aggressive HIV testing to identify the majority of HIV infected people in a community followed by immediate treatment of all infected individuals could eliminate HIV transmission in that community and might ultimately be the best way to combat the epidemic.[4] Although there are a number of attractions of such a "test and treat" approach, there are also major problems associated with it – not least the barriers to widespread HIV testing, the lack of proven benefit (until the START trial is completed) of early ART for individuals, the possibility of poor adherence to therapy in people who feel well, and the ability to secure the necessary funding to implement such a strategy given that many ART rollout programmes are struggling to treat all those with moderate to advanced HIV disease. In resource-limited countries, only 35% of the people who need therapy according to current WHO guidelines (starting with CD4 T-cell count below 350 cells/mm^3) are receiving it.[1]

Moving beyond treatment for HIV infected individuals, there is a great deal of interest in the possibility of giving ART as prevention to HIV uninfected individuals at high risk of contracting infection. A recent trial of a combination of 2 ART drugs taken as pre-exposure prophylaxis demonstrated a 44% reduction in the risk of HIV acquisition among HIV uninfected men who have sex with men.[5] Further trials of ART as prevention in diverse at-risk populations are currently underway and may provide additional evidence of the efficacy of this approach. Using ART topically – as a vaginal gel microbicide – has also been recently shown to be of value, giving a 39% reduction in the risk of a woman contracting HIV infection in South Africa.[6] Further studies to develop topical ART for HIV prevention are planned.

In summary, ART continues to have major impact on HIV/AIDS at an individual and population level but there is potential for further expansion of its scope in coming years – to treat people earlier in the course of their infection as well to use primarily for purposes of HIV prevention. Unfortunately, even with declining incidence of HIV infection and the substantial current investment in and expansion of ART access, the rate of new infections still considerably outpace the rate at which new people are started on ART. Hence it is inevitable that financial considerations will play an important part in determining how widely ART is used in the future.

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