Commentary

A turning point: The new World Health Organization guidelines for treatment of human immunodeficiency virus infection

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The world of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) has changed dramatically over the last 35 years. It was a blow to humanity when first described in 1981 as it was an inevitably fatal disease. The disease was expected to devastate the world in an unprecedented manner. In 1996, there was the first glimmer of hope when highly active antiretroviral treatment (HAART) was shown to suppress the viral replication significantly and improve survival. The question from those infected with HIV, changed from "Will I live?" to "How long will I live?" By the turn of the century, Indian pharmaceuticals had started producing generic anti-retrovirals that reduced the cost significantly and increased access drugs in the developing countries. Programs such as "3 by 5" initiative by the World Health Organization (WHO), President's Emergency Plan for AIDS Relief (PEPFAR) and UNAIDS provided a big push to scaling up antiretroviral therapy. In India too, a free anti-retroviral treatment program was launched by National AIDS Control Organization (NACO) in 2004 and was rapidly scaled up to become world's second largest program. Currently, it is estimated that almost a million people living with HIV (PLHIV) are receiving antiretroviral therapy, taking together both public and private sector patients. Moreover, one can confidently say that if a patient is diagnosed early, treated at the right time, and is adherent to treatment, then he or she can live a near normal life span. Thus, an invariably fatal disease has got converted into a chronic manageable medical disease. There is still no cure, but the tide has certainly turned. The question now is "How can I live better and can I be cured?"

UNAIDS has now set an ambitious target to end the AIDS epidemic by 2030.[1] To achieve this, a strategy termed 90-90-90 has been launched. The target is, by 2020, 90% of all people living with HIV should know their HIV status, 90% of all people with diagnosed HIV infection should receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy should have viral suppression.

The new WHO ART guidelines released on world AIDS day 2015 make two important recommendations.

- First, antiretroviral therapy should be initiated in everyone living with HIV irrespective of CD4 cell count. Though the strength of the recommendation in guidelines for adults more than 19 years of age and children <1 year is 'strong' and that for those between 1 year and 19 years is 'conditional', recommending prioritizing treatment for those with advanced disease (for want of evidence; this defies logic).
- Second, the use of daily oral pre-exposure prophylaxis (PrEP) is recommended as a prevention choice for people at substantial risk of HIV infection as a part of combination prevention approaches.

The immediate implication of the former is that all the inevitable sessions at HIV conferences on "When

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to start antiretroviral therapy" have finally been put to rest. The pendulum of the answer to this question had already started swinging in the direction of earlier initiation since 2013 and the threshold for starting therapy initially reached CD4 counts of 350 and then moved to 500 in 2013. This was because several studies showed an increased advantage with respect to reduced mortality, morbidity, incidence of tuberculosis and impact of prevention when treatment was started early. However, it was also being observed that untreated HIV infection, even at higher CD4 counts, was associated with several non-AIDS-defining conditions such as cardiovascular, renal, hepatic, malignant and neurocognitive disorders. There were cohort analyses which showed beneficial effects on these morbidities when antiretroviral therapy was initiated early. A recent large randomized control study demonstrated that for serodiscordant couples, antiretroviral therapy prevented transmission to the uninfected partners among homosexual couples.[2]

The TEMPRANO study showed that starting antiretroviral therapy at CD4 >500 in the absence of any of the existing clinical criteria for starting therapy reduced severe HIV morbidity.[3] The START study substantiated these findings and supported the new recommendations.[4] HPTN 052 clinical trial had already indicated that early antiretroviral therapy is highly effective in the prevention of sexual transmission of HIV[5] One of the major advantages of early initiation of antiretroviral therapy countries with a high burden of tuberculosis is the reduction in tuberculosis notification. Cost effectiveness models have shown that the costs of early initiation of antiretroviral therapy would be offset by subsequent reduced costs of future hospitalizations and improved quality of life, as well as costs saved due to reduction in number of new infections.

The second component of the recommendations is preexposure prophylaxis (PrEP) with tenofovir and emtricitabine. Several studies have demonstrated the efficacy of this strategy. The new recommendations no longer restrict this option to special populations. The most important precondition for the success of this strategy, however, is adherence to treatment. There is an urgent need to roll out demonstration projects to understand and sort out implementation challenges.

There are several challenges regarding implementation of these guidelines in the developing countries. Although the median CD4 count at the time of antiretroviral therapy initiation is increasing in almost all settings, it remains significantly lower than 350 cells/cmm. Retention in care is a contentious problem with high rates of loss to follow-up. Maintaining supply chains of antiretroviral therapy drugs for the additional numbers of people going on treatment, when many programs are currently struggling with the issue of frequent non-availability of stocks, remains the major concern for program managers. Long-term side effects of medications are an issue that will need close monitoring, though a lot experience has already accumulated from long-term treatment of many patients for nearly two decades. The problem of emergence of resistance to treatment, mainly due to non-adherence, is likely to be compounded when larger numbers of people who are currently completely asymptomatic will go on treatment. However, these issues are manageable. There is a need for wider availability of viral load and drug resistance testing, better drugs and more fixed dose combinations that will reduce the pill burden and offer safer options for treatment. Some of the latter are already in the pipeline.

The need of the hour is to embrace this chance to control and eventually eliminate this disease. This will require strong political will and robust programmatic support.

Frankly, when the medical fraternity in India first confronted AIDS in 1986–1987, we had never imagined that the pandemic unfolding in front of our eyes would see its end within our lifetime.

It now appears that the end of the menace of AIDS is not far off.

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