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Commentary

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Initiating Antiretrovirals in a Resource-Constrained Setting: Does One Size Fit All?

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Introduction

The World Health Organization (WHO) aims to provide antiretroviral therapy (ART) to at least 3 million patients in resource-limited settings by the end of 2005, an initiative referred to as "3 by 5." The program uses a CD4+ cell count of 200 cells/microliter (mcL) for initiating treatment as a cutoff in asymptomatic individuals.[1] Some issues need to be addressed when applying the program in resource-constrained countries such as India.

Limitations of WHO-Recommended Regimen Applied in India

Reduction in viral load might reduce transmission of HIV.[2] The combination of drugs primarily used in the WHO-approved regimen are nevirapine, lamivudine, and stavudine. This is the cheapest generic formulation in India that has the advantage of combining all 3 drugs in 1 pill. The cost of this combination is less than $1 per day. However, in the free treatment program, the number of patients who would require these medications worldwide will increase rapidly. Worldwide, 16,000 individuals get infected daily and each would, sooner, rather than later, require ART. In India, all of the 5 million-plus patients would be candidates for treatment. Do we have resources to provide medication even at less than $1 per day?

It is notable that although nevirapine-based regimens have been shown to do as well as other regimens, the drug has never been the "most preferred" in most international guidelines.[3] The other issue is one of resistance with nevirapine, as a single amino acid substitution in the reverse transcriptase gene can result in resistance to the whole nonnucleoside reverse transcriptase inhibitor (NNRTI) class of drugs.[4] Once resistance develops the transmissibility of the virus decreases, but what are the options for those who develop resistance? In most instances, anyone who develops resistance today has few options because alternative regimens are far too costly. Because no baseline nevirapine resistance rates in treatment-naive patients are available in India, there is no knowledge about the percentage of individuals who are unlikely to respond to the ART offered by the 3 by 5 initiative in the first instance.

Can Treatment Be Deferred?

Are we treating patients when they can do without ART? Can we defer treatment in asymptomatic patients? Perhaps we can. Western cutoffs to initiate ART may not be appropriate, as some studies have shown lower CD4+ cell counts in apparently healthy Indians. In one study, the range of CD4+ cell counts in healthy Indians started from just over 300 cells/mcL.[5] Another study carried out in 200 healthy Indians showed that CD4+ cell counts ranged between 304 and 1864 cells/mcL.[6] A modest decline early in the course of disease might qualify the patient for initiation of ART. Can we wait longer until "chronic immune failure" develops, as early initiation means that patients lose their only therapeutic option much faster? Another issue relates to pitfalls in using guidelines where CD4+ cell counts decide treatment. Does one size fit all? Thus, while cytomegalovirus (CMV) infection develops most often with CD4+ cell counts < 50 cells/mcL, does everyone with a CD4+ cell count < 50 cells/mcL develop CMV disease? Surely no. Do we, then, treat everyone on the basis of a CD4+ cell count that tells us that an individual with CD4+ cell count < 200 cells/mcL is at heightened risk for opportunistic infections (OIs), even though a fraction do not develop OIs?

The crucial issue is: Are we treating patients in resource-constrained settings far too early and running the risk of exhausting their therapeutic options much earlier rather than starting therapy later and providing a longer survival on the same regimen and resources? It could be argued that deferring therapy for too long would compromise the patient's ability to recover pathogen-specific immune responses. However, is a patient with advanced immunosuppression with a CD4+ cell count of 175 cells/mcL, but free of OI, an ideal candidate to initiate ART when all he has by way of therapeutic options is the first regimen that the WHO provides? Perhaps no. Therapeutic options in the underprivileged begin and end with the first and only regimen. In addition, early treatment would result in earlier resistance to nevirapine. Can we use the available agents more judiciously to prolong survival? If not everyone with a CD4+ cell count < 200 cells/mcL develops OI, should everyone then be made to take ART when we do not know the risk of developing OIs in a given individual?

Current Status and Short-term Needs

The recent WHO report that provides an update on the 3 by 5 program should provide food for thought to policy makers regarding the financial implications of providing treatment under the program:

The estimate of approximately 1 million people now on treatment falls short of the milestone of 1.6 million set in the WHO/UNAIDS "3 by 5" strategy for June 2005. Current data and trends indicate that providing ART to 3 million people by the end of 2005 will be unlikely. However, there is reason to be hopeful that growth rates will continue to increase in the remainder of 2005 and beyond. Although less than what is needed, an estimated US$27 billion are available or have been pledged for HIV/AIDS globally from all sources for the three-year period 20052007. UNAIDS estimates that at least an additional US$18 billion above what is currently pledged is needed for global HIV/AIDS efforts over the next three years, including treatment, care and prevention. Donors should continue to increase their financial commitments, and work with countries to develop long-term funding arrangements that assure sustained and predictable support.[7]

Like several countries, including India, the WHO is also resource-constrained. Under these circumstances, will second-line agents be a realistic option, even though each one of the 5 million-plus patients in India (plus those in the rest of the developing world) would become candidates for these, sooner or later (sooner, rather than later, if we initiate treatment early)?

Summary and Conclusion

We must look for alternative mechanisms that can identify individuals at greater risk of developing an OI. At a bare minimum, we must reconsider the 200 cells/mcL CD4+ cell count cutoff for initiating ART among those who are asymptomatic.

Authors and Disclosures

Ajay Wanchu, MD, DM, has disclosed no relevant financial relationships.

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