

New WHO Guidelines: Implications on Therapeutics and Monitoring of HIV Infections

Shweta Naik¹ and BR.Das^{2*}

¹Research scientist, SRL Limited, Goregaon, Mumbai-400062, India

²President-Research & Innovation, Mentor-Molecular Pathology and Clinical Research Services, SRL Limited, Goregaon, Mumbai-400062, India

Abstract

The new WHO guidelines in 2015 on initiation of early antiretroviral therapy (ART) and on pre-exposure prophylaxis for HIV mark the next stage in the fight to curb the epidemic of HIV-AIDS. With ART for all, the number of people eligible for ART rises significantly. Implementation of these guidelines in the high burden, low income countries are the stepping stone to achieving the UNAIDS target of eliminating the HIV-AIDS epidemic by 2030. Scaling up of programmatic capacities globally to diagnose, treat and monitor therapy for HIV-AIDS is the need of the hour. Drug resistance may arise as a further challenge to the efficacy of therapy with the expected upsurge in ART coverage.

Keywords: WHO guidelines 2015; ART; Drug resistance

List of Abbreviations: HAART: Highly Active Antiretroviral Treatment; WHO: World Health Organization; NAE: Non-AIDS-defining Event; PrEP: Pre-Exposure Prophylaxis; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside RT Inhibitor; LMICs: Low- and Middle-Income Countries

Introduction

An estimated 37 million people are living with HIV infection according to the UNAIDS report in 2014 [1]. Many of these live in developing countries, with sub-Saharan Africa bearing the maximal burden of 25.8 million infected cases [1]. Advances in therapy, monitoring the clinical response and global programs have transformed the impact of HIV-AIDS. What was considered as a certain death sentence in 1980's is now considered as a chronic manageable disease [2]. In 1996, highly active antiretroviral treatment (HAART) was shown to suppress the viral replication significantly and improve survival. Programs such as "3 by 5" initiative by the World Health Organization (WHO), President's Emergency Plan for AIDS Relief (PEPFAR) and UNAIDS ensured the reduction in cost and increased access to antiretrovirals in the developing countries with around 16 million people receiving ART in 2015 as per UNAIDS [3,4]. Enhanced emphasis on prevention of transmission of HIV has reduced the rate of new infections by 35% in adults and 58% in children and mortality has reduced by 42% since 2004 [4].

With an ambitious aim to end the AIDS epidemic by 2030, UNAIDS has launched the 90-90-90 strategy in 2014; by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART and 90% of all people receiving ART will have viral suppression [5]. The new set of guidelines from WHO in 2015 are a stepping stone to achieve this target [6].

Evolution of Guidelines

WHO guidelines regarding initiation of ART have been progressively revised over the years. In 2003, WHO recommended initiating ART at a CD₄ count below 200 cells/mm³. This threshold has since been increased to 350 cells/mm³ in 2010 and to 500 cells/mm³ in 2013 [5].

While the effect of ART in decreasing morbidity, mortality and HIV transmission was evident [7], the timings of starting ART remained a matter of debate. The WHO guidelines are corroborated

by new studies that evidence advantages of early initiation of ART and aim at addressing this debate. The HIV Prevention Trials Network (HPTN052) trial on HIV-1-serodiscordant couples in 2014 noted that early initiation of antiretroviral treatment delayed the time to AIDS events and reduced transmission rate by 96% [8]. Strategic Timing of Antiretroviral Therapy (START) in 2015 compared immediate treatment of HIV diagnosis with treatment started with CD₄ count of 350 cells/mm³. It demonstrated 72% relative reduction in serious AIDS-related events with early therapy, concluding that immediate initiation of ART in patients with HIV infection regardless of CD₄ count is beneficial [9]. The TEMPRANO ANRS 12136 trial in 2015 also showed that early initiation of ART reduced the risk of severe HIV-related illness by 44% than with deferred initiation of ART [10]. These broad based studies with global relevance are growing evidence of the clinical benefits of earlier treatment initiation. In December 2015, WHO issued new guidelines based on studies reporting clinical, immunological and virological outcomes and HIV transmission [6] (Figure 1).

The new guidelines strongly recommend that for all adults, ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD₄ count [6]. With implementation of these new guidelines, further decline in incidence is expected. The advantages of early initiation of ART are manifold. Initiation of ART at the point of HIV diagnosis without waiting for CD₄ count to fall has been documented to decrease HIV related illness and AIDS related death [7,8]. Secondly, studies in serodiscordant couples have proven that HIV transmission reduces significantly with early initiation of ART and low viral loads [8-13]. Another advantage is that with tuberculosis being one of the major opportunistic infections in patients with HIV, the early initiation of ART has shown to reduce the incidence of TB infection up to 67% in such patients, which is of great importance in developing countries [14,15]. With untreated HIV infections, several non-AIDS-defining events (NAEs) such as cardiovascular, renal, hepatic and

***Corresponding author:** BR. Das, President-Research and Innovation, Mentor-Molecular Pathology and Clinical Research Services, SRL Limited, Goregaon, Mumbai-400062, India; Tel: + 022-6780 1314; E-mail: brdas@srl.in

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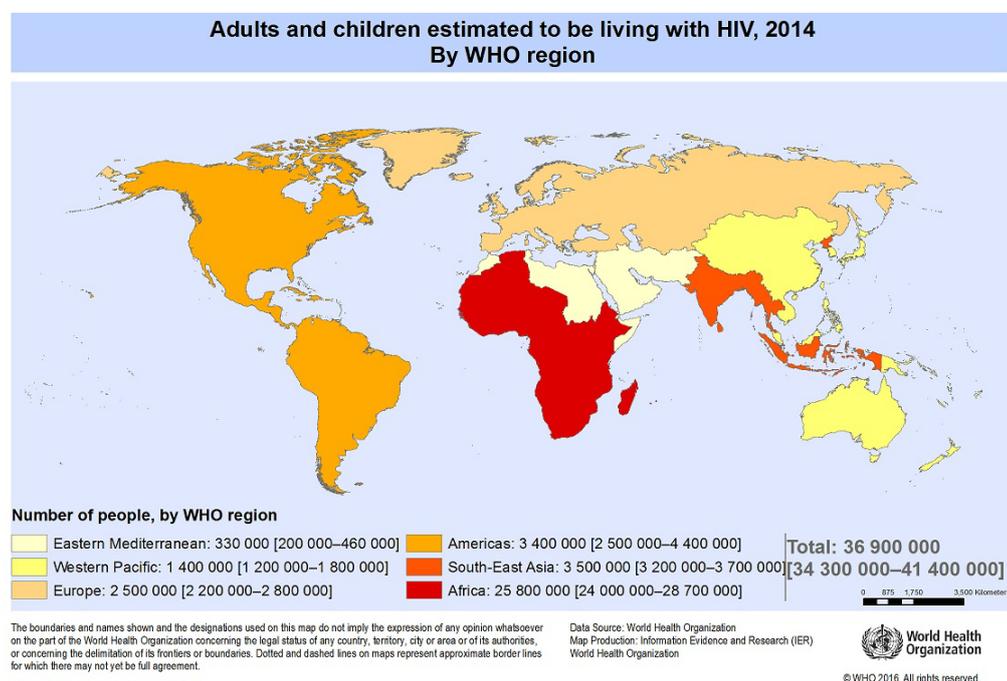


Figure 1: Global prevalence of HIV (sourced from WHO 2016).

neurocognitive disorders are gaining importance as a prominent cause of mortality [16]. The Cohort of the AIDS Research Network (CoRIS) has noted the protective effect of early ART in the occurrence of NAEs [17]. Further, cost effectiveness models have shown the cost of early initiation of ART was offset by the prevention of common, expensive-to-treat opportunistic diseases and premature death [18,19].

For pregnant and breastfeeding women and children under 1 year of age living with HIV, the early initiation of ART regardless of WHO clinical stage and at any CD₄ count is strongly recommended in the new guidelines [6]. For children and young adolescents (1-19 yrs), the guidelines give a conditional recommendation for immediate initiation of ART as there is paucity of evidence of the advantages provided by early ART in this age group [6]. However, drawbacks of early initiation of ART in this age group may include short term side effects which may lead to sub-optimal adherence to treatment and subsequent emergence of drug resistance with long term therapy [20-22].

New recommendations are also made for the use of oral pre-exposure prophylaxis (PrEP) containing tenofovir as an additional prevention choice for people at substantial risk of HIV infection [6]. This guideline enables PrEP to be offered to a wider range of population rather than limiting it to specific high risk populations. Multiple studies have proven PrEP with high adherence to be effective to block acquisition of HIV [23,24].

Implementation Considerations

A wide range of operational considerations need to be addressed before implementation of the recommendations in the new guidelines [6]. Only 16 million people (40%) are currently receiving ART out of the estimated 37 million people living with HIV worldwide [4]. The new guidelines halt the ambiguity over when to start treatment but bring the number of people eligible for ART to 37 million. The new set

of guidelines imply a manifold increase in the target population to be administered ART (Figure 2).

With a bulk of the target population residing in developing countries, maintaining supply chains of ART drugs is a crucial challenge as even currently many programs face frequent non availability of stocks [3]. As adherence to ART is essential for effective viral suppression and with earlier initiation of ART, sub-optimal adherence may emerge as a challenge in the effectiveness of therapy. With longer treatment durations, retention in care may also prove to be a factor in enabling effective viral suppression (Figure 3).

Studies indicate that 10-30% of patients on first line ART develop virological failure due to resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs) or non-nucleoside RT inhibitor (NNRTI) [25]. With increase in ART coverage, the incidence of transmitted drug resistance is also on the rise [25,26]. Recently, tenofovir resistance has been noted to be as high as 50% in sub-Saharan Africa in patients with virological failure [27]. As greater number of people with HIV will receive ART, the problem of drug resistance is expected to increase. Unlike upper-income countries where HIV-1 genotypic resistance testing is used to ensure efficacy of treatment in patients with virological failure, in the high burden low- and middle-income countries (LMICs), the limited resources and capacity hamper the efforts to achieve individual management of such cases. This will require further laboratory strengthening so as to enable the early diagnosis of virological failure and starting the appropriate second line regimen in a timely manner [3].

A major barrier to early initiation of ART is lack of diagnosis, as 17 million people are estimated to be unaware that they are infected by HIV [4,28]. This leads to presentation to medical care in later stages of HIV due to which the advantages of early initiation of ART will not be achieved in a substantial number of patients. Adverse effects related

The Fast-Track

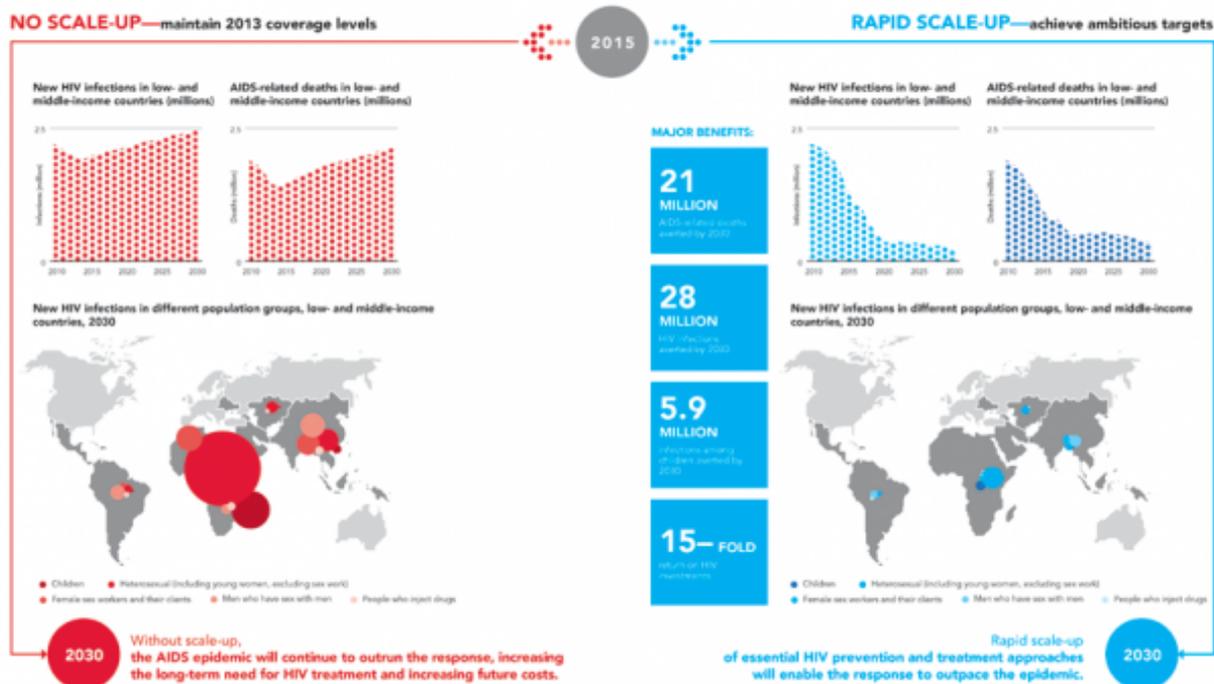


Figure 2: Scenarios of ARV eligibility (sourced from UNAIDS, 2014).

SCENARIOS OF ANTIRETROVIRAL TREATMENT ELIGIBILITY: WHO VISION

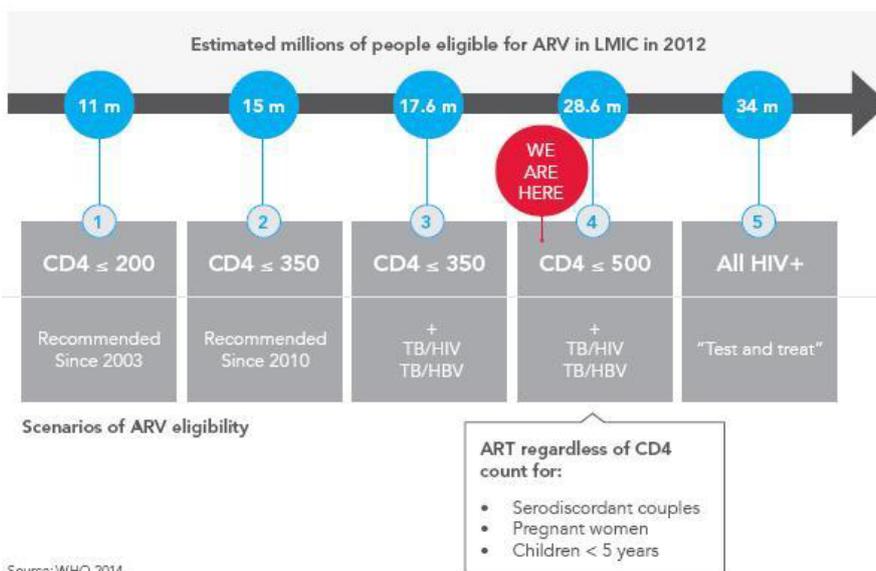


Figure 3: Impact of rapid scale up of ART (sourced from UNAIDS, 2014).

to long term ART will also have to be monitored as the duration of therapy will increase substantially [3]. For use of PrEP, HIV testing and renal function monitoring requires to be done on a regular basis [6].

Algorithms for laboratory monitoring will also undergo a sea change. With ART being started irrespective of CD₄ counts, viral load monitoring is now recommended by WHO as the preferred monitoring approach [6]. Viral load monitoring using plasma specimens is the gold standard [29]. Routine viral load monitoring is to be conducted at 6 months after initiation of therapy and repeated every 12 months thereafter. CD₄ retains importance for assessing baseline risk for disease progression. However, reliable access to routine viral load remains limited in the developing countries as yet. New cost effective point-of-care technologies for viral load estimation need to be developed, which will be of immense help in monitoring therapy. WHO recommends use of dried blood spot specimens for viral load testing to improve coverage and reach especially in remote and rural areas where access to testing plasma viral load is not available [29].

Continued research in area of therapeutics for HIV has evolved and nascent technologies such as gene editing [30] and antibodies [31] show promise. Until these are proven to be effective, ART remains the mainstay for treatment for HIV-AIDS.

Conclusion

Clinical benefits coupled with a striking effect on transmission risk by early initiation of ART provide substantial individual and population benefits over delayed ART. Though operational considerations will require mobilization of additional resources, adherence to the new guidelines will ensure that the most effective therapy is available to combat and end the HIV epidemic.

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