

VIEWPOINT

Providing antiretroviral therapy to all who are HIV positive: the clinical, public health and programmatic benefits of *Treat All*

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In September 2015 the World Health Organization (WHO) recommended antiretroviral therapy (ART) be offered to all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count [1]. This recommendation was supported by more than two decades of research into the clinical and public health benefits of immediate ART [2].

WHO had previously assessed the benefits of *Treat All* in mid-2013 by reviewing the results of observational studies and mathematical models that suggested starting ART as soon as possible would reduce HIV-related morbidity, mortality and incidence. After deliberations lasting almost 2 days, the 2013 Guideline Development Group concluded that there were insufficient grounds to recommend a global policy of *Treat All*, and instead recommend that the threshold for starting ART be raised from ≤ 350 cells/mm³ to ≤ 500 cells/mm³ [3]. However, immediate, lifelong ART was recommended for HIV serodiscordant couples and HIV-positive pregnant women to prevent onward transmission [4] and, importantly in the case of pregnant women, to simplify service delivery as pioneered in Malawi [5]. Immediate ART was also recommended for all children under 5 years, again based on programmatic ease and efficiencies and to reduce early death by starting ART early among children, half of whom will die in the first 2 years following birth without treatment [6]. Finally, it was recommended to start ART in all individuals with TB or hepatitis B coinfections, given the established clinical benefits. Taken together, these recommendations meant that the majority of people living with HIV in high HIV-burden settings were already eligible for ART prior to *Treat All* becoming global policy.

The formulation of guideline recommendations at WHO follows a careful assessment of all available evidence across a number of domains. Clinical evidence of benefits and harms, appraised through systematic reviews and the GRADE framework, forms the basis for deliberation, but also consider values and preferences, feasibility, acceptability, resources and equity [7]. When the next WHO 2016 Guideline Development Group was convened in June 2016, the

START and TEMPRANO trials had both recently concluded and investigators from both trials made the main findings available to the Guideline Development Group ahead of publication [8,9]. In addition to the evidence of clinical benefit from these two randomized trials and 17 observational studies, a number of additional inputs were provided to support the decision to recommend *Treat All*, including: country experience in providing immediate ART for HIV serodiscordant couples, key populations, and pregnant women; cost effectiveness modeling, surveys of community values and preferences, and feasibility studies [10]. In considering the potential programmatic benefits of *Treat All*, particular value was placed on the potential reduce the substantial loss to care among pre-ART patients who had been diagnosed with HIV infection but were not yet eligible to start ART. A systematic review of retention in care prior to starting ART found that 41% of patients were lost to care in the step between testing HIV positive and being assessed for eligibility for treatment (by CD4 cell count or clinical stage), and 32% of patients were lost between determination of eligibility and starting ART [11]. Rapid initiation of ART, including starting ART on the same day that a positive HIV diagnosis is made, is now strongly by WHO as a way to reduce losses to care during this pre-ART period [12,13].

As of the end of 2017, 70% of low and middle-income countries had adopted the *Treat All* policy, demonstrating a high level of acceptability of this recommendation by policy makers (Figure 1) [14]. Despite fears expressed previously with respect to expanding ART eligibility, no major stock-outs of ART or other essential supplies have been reported to be associated with the implementation of *Treat All*. Clinical and implementation research continue to provide important insights into the effectiveness of treating all persons living with HIV. Data from the START trial have found that immediate ART led to improved quality of life [15], and the programmatic benefits of early and rapid ART initiation in terms of reducing pre-ART loss-to-care can be substantial [13,16,17].

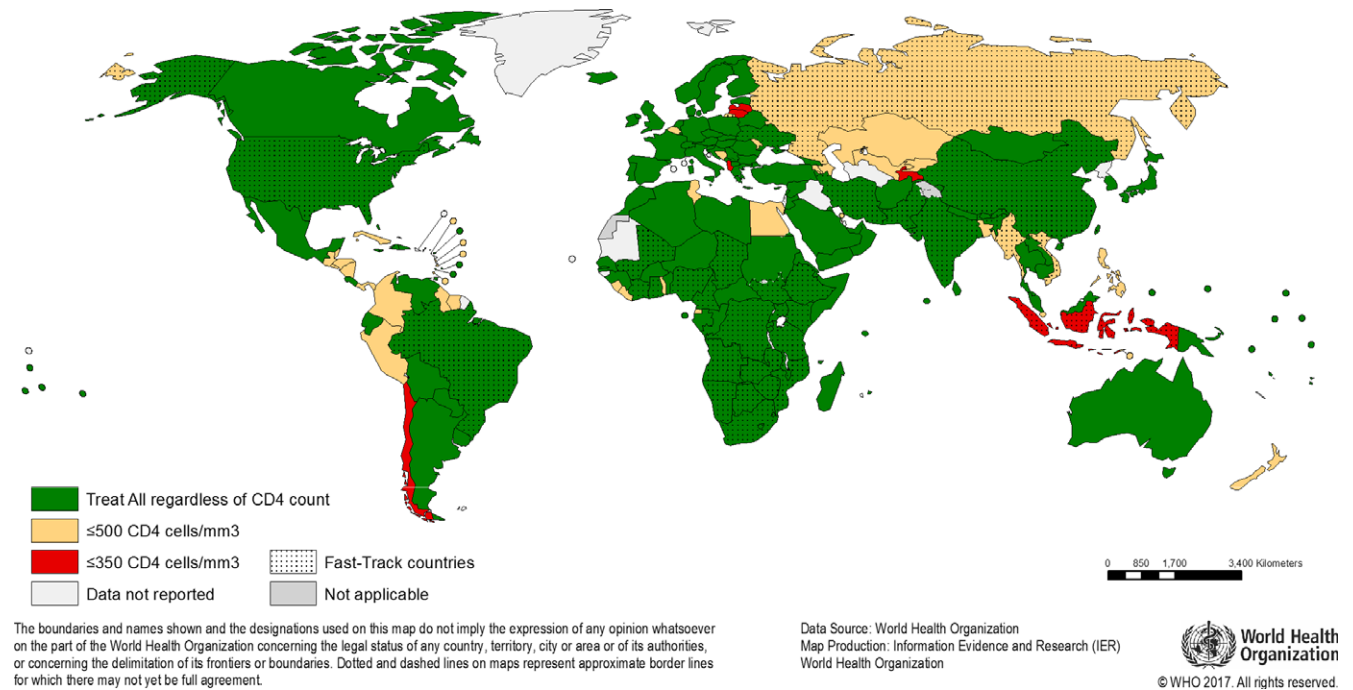


Figure 1. Uptake of WHO policy for Treat All ART initiation among adults and adolescents living with HIV (situation as of November 2017).

Notwithstanding these benefits, there are important programmatic challenges to achieving the full benefits of *Treat All*. The first randomized trial to assess the effect of immediate ART at the population level was unable to demonstrate a reduction in HIV incidence, a finding explained by the challenges faced in ensuring adequate linkage to care [18]. This finding is echoed by cohort data demonstrating that despite a progressive guideline evolution toward earlier initiation of ART in recent years, still approximately a third of people starting ART do so at a CD4 cell count <200 cells/mm³ [19].

WHO and country guidelines recommending *Treat All* are an important first step, but the clinical, public health and programmatic benefits will only be realized if progress is made in testing people earlier, ensuring effective linkage, and maximizing ARV adherence and retention in HIV care over the long term. These are the key challenges ahead in making progress towards the goal of achieving epidemic control in the next decade.

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NF Wrote the first draft of this Viewpoint. All authors contributed equally to the writing of this manuscript and approved the final version.

COMPETING INTEREST

None.

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