

# Necessary but Not Sufficient: The Need for Innovative Strategies to Enhance Retention and Viral Suppression After Rapid Initiation of Antiretroviral Therapy

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(See the Major Article by Amstutz et al on pages 2608–14.)

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The massive scale-up of access to antiretroviral therapy (ART) over the past 15 years has been one of the greatest achievements in the history of public health. More than 23 million persons living with human immunodeficiency virus (PLWH) are now on treatment, and an estimated 13.6 million lives have been saved due to ART [1]. In the process, health systems have been strengthened in many of the world's poorest countries, and a variety of innovative strategies have been implemented to facilitate ART initiation and retention in care.

However, global reductions in new human immunodeficiency virus (HIV) infections and AIDS-related deaths are getting smaller year by year, and it is unlikely that the 90-90-90 targets of the Joint United Nations Programme on HIV/AIDS (UNAIDS), in which 90% of PLWH will know their HIV status, 90% of those who know their status will be on ART, and 90% of PLWH on ART will have viral suppression, will be achieved

by 2020 [1]. At the end of 2018, an estimated 79% of PLWH knew their HIV status, 78% were on ART, and 86% of those on ART had viral suppression. Of the estimated 37.9 million PLWH worldwide, 53% had suppressed viral loads, well short of the 90-90-90 target of 73% [1, 2]. Six countries (Botswana, Denmark, Eswatini, Namibia, the Netherlands, and the United Kingdom) have achieved all 3 of the 90-90-90 targets, but their level of development and healthcare is clearly not comparable to that of most low-income countries [1]. They not only have more resources, but fewer patients requiring ART. Botswana, Eswatini, and Namibia are high-HIV-burden countries, and they should be lauded for this exemplary achievement, but it is noteworthy that they are middle-income countries with populations of <3 million people.

To make headway toward ending HIV as a public health problem, it is critical to increase the number of individuals who know their HIV status, and to link them to effective treatment services. To achieve this, home-based HIV testing services have been widely implemented. However, rates of linkage to care are generally low after home-based testing, particularly if patients who are newly diagnosed with HIV are referred for facility-based care without further interventions to facilitate retention [3, 4]. In isolation, home-based testing efforts will not be sufficient to

overcome the barriers that many PLWH face in linking to care, and achieving timely initiation of ART.

The CASCADE study team realized these challenges early on, and they were the first to conduct a randomized trial to determine if the provision of home-based same-day ART could improve linkage to care and viral suppression. They initiated CASCADE in rural Lesotho during a door-to-door HIV testing campaign in 2016. Participants were randomized to usual care (n = 137) or same-day ART (n = 137). The primary outcomes (3-month linkage to care and 12-month viral suppression), which demonstrated the superiority of same-day ART initiation in this setting, were published last year [5]. In the same-day ART group, 94 (69%) linked to care within 3 months, 87 (64%) were retained in care, and 69 (50%) had 12-month viral suppression, in comparison with 59 (43%), 66 (48%), and 47 (34%), respectively, in the standard group.

In this issue of *Clinical Infectious Diseases*, Amstutz et al describe 24-month outcomes for the CASCADE study. Participants in both groups received facility-based HIV care for the second year of treatment, and those who were not in care at 12 months were contacted and encouraged to engage in care. First contact was made by phone and, if unsuccessful, was followed by physical

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tracing through village health workers, health facility staff, or the study nurse. About 10% of participants in each group who were retained at 12 months were lost to follow-up during the second year of treatment. This attrition was offset by 11 participants newly engaging in care in the same-day ART group and 21 newly engaging in care in the standard group. Due to higher rates of later engagement in care in the standard group, outcomes between the 2 groups had equalized by 24 months. In the same-day group, 88 (64%) participants were retained and 81 (59%) had viral suppression, compared to 81 (59%) and 74 (54%), respectively, in the standard group.

The findings of the CASCADE study offer many important insights to guide efforts toward realization of the 90-90-90 targets. First, the CASCADE intervention included a 30-day supply of ART after a counseling session, and a readiness assessment, which found that 98% of participants were ready to start same-day ART. This intervention is straightforward and scalable, and it offers an initial step toward improving retention in care after home-based testing. The services that were provided to the usual care group, which included an appointment in a health facility within the subsequent 28 days for ART initiation, multiple pre-ART visits, and failure to contact patients who do not present for care, can no longer be viewed as optimal care [6].

Second, even though outcomes had equalized by 24 months in the CASCADE trial, this does not argue against the implementation of same-day ART. The majority of participants in CASCADE had early-stage HIV disease and a CD4 count  $\geq 350$  cells/ $\mu\text{L}$ . Immediate ART would have decreased their risk of both serious AIDS-related and serious non-AIDS-related events [7]. Yet the usual care group had substantial delays in initiating ART. Viral suppression rates were significantly higher in the same-day ART group at 12 months, and one-quarter of participants in the usual care group who eventually engaged in care did not

initiate ART until the second year after enrollment. Same-day ART also serves as a public health intervention for U=U (undetectable=untransmittable) [8, 9]. The sooner PLWH are placed on effective ART, the more likely they will become virally suppressed, cutting the chain of transmission [10].

Third, the CASCADE intervention was helpful but not sufficient. Participants in the same-day ART group were instructed to visit the nearest health facility within 2–4 weeks to initiate facility-based care. However, only 69% had linked to facility-based care within 3 months after enrollment, and 64% were in care at 12 months. Linkage to care is the largest drop-off in the HIV care cascade, and the point where an additional intervention could yield major benefits. The CASCADE study team is now conducting the VIBRA (Village-Based Refill of ART) study, a cluster-randomized trial to evaluate the effectiveness of follow-up ART care provided by village health workers [11]. Participants in the intervention clusters are offered same-day ART initiation, followed by village-based ART visits and refills through village health workers, with scheduled health facility visits at 6 and 12 months after ART initiation. The intervention also includes monthly SMS (short message service) adherence reminders and individually tailored SMS messages according to viral load results. Strategies such as the VIBRA intervention, which aims to overcome barriers to linkage to care, are essential for the improvement of long-term outcomes.

Fourth, newer ART agents may offer opportunities for further progress toward the 90-90-90 targets. Lesotho is transitioning to a single-tablet regimen of dolutegravir–tenofovir disoproxil fumarate–lamivudine (TLD) as the preferred first-line ART regimen, due to the higher potency, superior efficacy, greater barrier to resistance, and improved tolerability of dolutegravir, compared with efavirenz-based regimens. Rates of viral suppression for the total CASCADE study

cohort increased from 76% at 12 months after enrollment, to 90% at 24 months after enrollment. Data are not provided on ART regimen, but it is likely that the transition to TLD explains at least part of this improvement. Furthermore, the high barrier to resistance of the TLD regimen makes it optimal for the CASCADE intervention, to minimize the risk of drug resistance in patients who stop ART after completing the 30-day supply provided on the day of HIV diagnosis. We also applaud the CASCADE team for using 100 copies/mL as the cutoff for viral suppression, even though the World Health Organization utilizes the higher 1000 copies/mL threshold. Persistent viremia between 200 and 1000 copies/mL is associated with a higher risk of emergence of resistance mutations [12].

When long-acting ART regimens become available, they may also offer new opportunities to improve treatment outcomes for some patients. Long-acting injectable cabotegravir–rilpivirine has been shown to be noninferior to oral therapy in phase 3 trials in maintenance therapy, and other long-acting regimens are also in development [13, 14]. It is significant that Amstutz et al found that rejection of contact with the health system and unwillingness to take ART were major reasons given by participants who had not engaged in care. A daily pill is a daily reminder of HIV status, and long-acting ART may benefit some patients with challenges in adhering to oral therapy.

In summary, the CASCADE study demonstrated that same-day ART initiation improved rates of retention and viral suppression at 12 months, but not 24 months. Additional interventions will be necessary to achieve long-term viral suppression after rapid ART initiation. We have the tools to end the AIDS epidemic, but we need to quicken our pace to move past the rhetoric and “Make AIDS History” [1].

#### **Note**

*Potential conflicts of interest.* The author: No reported conflicts of interest. The author has

submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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