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INVITED COMMENTARY

Achieving Viral Suppression in 90% of People Living With Human Immunodeficiency Virus on Antiretroviral Therapy in Low- and Middle-Income Countries: Progress, Challenges, and Opportunities

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Although significant progress has been made, the latest data from low- and middle-income countries show substantial gaps in reaching the third "90%" (viral suppression) of the UNAIDS 90-90-90 goals, especially among vulnerable and key populations. This article discusses critical gaps and promising, evidence-based solutions. There is no simple and/or single approach to achieve the last 90%. This will require multifaceted, scalable strategies that engage people living with human immunodeficiency virus, motivate long-term treatment adherence, and are community-entrenched and -supported, cost-effective, and tailored to a wide range of global communities.

Keywords. human immunodeficiency virus (HIV); 90-90-90; antiretroviral therapy (ARV); viral suppression; low- and middle-income countries (LMICs).

There are currently nearly 11 million persons living with human immunodeficiency virus (HIV) who need to achieve the third "90" (viral suppression) UNAIDS target by 2020, not including the 3–5 million new infections expected between 2017 and 2020 [1, 2]. Of note, regional differences in viral suppression rates exist between low- and middle-income countries (LMICs) compared with high-income countries; for example, in sub-Saharan Africa, eastern and southern countries had better suppression rates (50%) than countries in the west/central region (25%) [3]. Herein and in Table 1, we discuss barriers and potential solutions to achieve the third "90" of the HIV care cascade in high-burden LMICs.

DIFFERENTIATED SERVICE DELIVERY MODELS TO ACHIEVE VIRAL SUPPRESSION

Differentiated service delivery (DSD) models simplify and decentralize HIV care by adapting services across the care cascade to the preferences and expectations of different subpopulations of persons living with HIV. Examples of DSD initiatives include shifting tasks to lower-cadre healthcare workers to mitigate human resource shortages and community-based antiretroviral therapy (ART) clubs (CACs), which provide adherence support and fast-track ART refills. In South Africa, CAC (vs community-based clinics) participation was associated with a 67% reduction in the risk of loss to follow-up (adjusted hazard ratio, 0.33; 95% confidence interval [CI], .27–.40) and breakthrough viremia (adjusted hazards ratio, 0.53; 95% CI, .51–.55) [4]. Also, DSD models have been shown to be cost-effective [5]. However, task shifting may face implementation barriers in selected LMICs (eg, Brazil, Argentina, Mexico, and Puerto Rico), where a physician needs to be present to sign-off on all prescriptions [6]. Such barriers lower care efficiency and should be reevaluated to improve patient outcomes.

SAME-DAY ANTIRETROVIRAL THERAPY INITIATION TO IMPROVE VIROLOGIC OUTCOMES

A systematic review and meta-analysis based on trial data from South Africa, Haiti, and Uganda showed that ART initiation on the same day as HIV diagnosis increased viral suppression (relative risk, 1.17; 95% CI, 1.07–1.27) and improved 12-month retention (relative risk, 1.11; 95% CI, .99–1.26) [7]. However, 1 year after ART initiation,

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Table 1. Achieving 90% Viral Suppression in Low- and Middle-Income Countries: Target Populations, Challenges, and Opportunities

Target HIV-Infected Population	Challenges	Priority Solutions
General	• Late HIV diagnosis and delayed initiation of ART	➢ Expanded and consistent access to HIV testing, including independent testing for adolescents[a] ➢ Peer psychosocial support for HIV testing and initiation of ART ➢ Same-day ART initiation[a]
Pregnant and breastfeeding women	• Poor ART adherence and retention in care, especially postpartum • Postpartum VL testing after stopping ART • Fear of HIV status disclosure • Postpartum depression • Lack of social and male partner support • Gender inequity	➢ Prioritization of VL testing in pregnant and breastfeeding women[a] ➢ Integrate HIV/PMTCT gender-based violence programming[a] ➢ Peer support for mental health, disclosure, ART adherence, and retention in care ➢ Improve male partner participation in HIV care for women
Children	• Missed opportunities for early infant diagnosis • Limited pediatric antiretroviral drug formulations • Limited caregiver competency • Poor virologic suppression	➢ Point-of-care virologic infant HIV diagnostic testing[a] ➢ Improved access to newer antiretroviral drugs in pediatric formulations[a] ➢ Family-centered, community-based care
Adolescents	• Missed opportunities for diagnosis • Linkage, adherence, viral suppression, and retention in care • Lack of disclosure to perinatally infected youth • Poor healthcare transitioning procedures	➢ Legally protected, independently accessible HIV testing[a] ➢ Individual and/or group peer support ➢ Comprehensive healthcare transition guidelines ➢ Adolescent-friendly services, including peer support ➢ Anticipatory HIV disclosure guidance for healthcare workers, parents/guardians, and youth ➢ Robust healthcare transition as part of differentiated care[a]
LGBT community	• Stigma • Criminalization and targets of violence in some countries	➢ Advocacy for human rights[a] ➢ Decentralized, community-based, differentiated service delivery models, including testing, access to ART, adherence counseling, VL monitoring ➢ Safe spaces for HIV care and treatment
Sex workers	• Stigma • Gender violence • Criminalization in some countries	➢ Advocacy for human rights[a] ➢ Adapted, integrated services, including gender-based violence prevention and outreach for testing and ART ➢ Safe spaces for HIV care and treatment ➢ Differentiated service delivery including testing, access to ART, adherence counseling, VL monitoring
People who inject drugs	• Stigma • Criminalization in some countries	➢ Advocacy for human rights[a] ➢ Integration and linkage of HIV and drug abuse treatment[a] ➢ Adapted services, including outreach for testing and ART ➢ Differentiated service delivery, including testing, access to ART, adherence counseling, VL monitoring, DAART ➢ Safe spaces for HIV care and treatment
Prisoners	• Stigma • Poorly resourced health services	➢ HIV testing with linkage to care and DAART during incarceration[a] ➢ Linkage to care with support upon release[a]

Abbreviations: ART, antiretroviral therapy; DAART, directly administered ART; HIV, human immunodeficiency virus; LGBT, lesbian, gay, bisexual, and transgender; PMTCT, prevention of mother-to-child HIV transmission; VL, viral load.

[a]Especially important.

retention in care and viral suppression were well below 90%. Nonetheless, these findings informed a recent World Health Organization (WHO) recommendation to scale up same-day ART initiation, especially for those at high mortality risk (CD4 count <200 cells/mm^3 or WHO clinical stage 3 or 4 disease); pregnant women (to reduce mother-to-child HIV transmission [MTCT]); and patients with acute HIV infection due to high sexual transmission risk. Due to potential life-threatening immune reconstitution inflammatory syndrome following rapid ART initiation, patients with tuberculosis and cryptococcal meningitis are excluded [8, 9].

REACHING VULNERABLE POPULATIONS

Pregnant and Postpartum Women

Viral suppression is critical for pregnant/breastfeeding women because sustained viremia reduces the impact of ART for prevention of MTCT (PMTCT) and maternal health, but there has been limited implementation of viral load (VL) monitoring [10]. Viral load measurement at 36 weeks gestation may be most predictive of viremia at delivery, identifying HIV-exposed infants who should receive enhanced antiretroviral prophylaxis [11, 12].

Disengagement from PMTCT services is unacceptably high, especially postpartum, with a sizable proportion of women (~30%) experiencing at least 1 episode of viral rebound in this period [13, 14]. Postpartum transfer from PMTCT services to general HIV care is an important but neglected step in the HIV care cascade for pregnant women; studies are evaluating whether continued ART provision via PMTCT programs during breastfeeding would improve maternal

retention and viral suppression [15]. Differentiated service delivery involving referral to lay counsellor-operated CACs resulted in improved retention outcomes among postpartum women [16]. Other studies show higher viral suppression rates among women who have disclosed their HIV status to male partners [17]. A structured PMTCT peer-support intervention in Nigeria was successful in improving retention (adjusted odds ratio = 5.9; 95% CI, 3.0–11.6) and viral suppression (adjusted odds ratio, 4.9; 95% CI, 2.6–9.2) among postpartum women [18]. Similarly, a South African study reported that mHealth and/or peer support for ART adherence were acceptable and feasible among pregnant women initiating life-long ART [19]. Finally, strategies to improve male partner involvement and to mitigate gender-based violence are important [20].

Children and Adolescents

Although there have been pediatric HIV treatment gains, only 50% of HIV-infected children received ART in 2015. Viral suppression among children and adolescents in LMICs remains far below that in high-income countries [21, 22]. Antiretroviral therapy adherence and viral suppression have been particularly challenging among adolescents and youth living with HIV [23].

A DSD designed to reduce patient-level barriers and maximize health system efficiency in rural Uganda and Kenya showed promise in improving retention and viral suppression among adults and children [24]. Community-based support for caregivers was associated with improved retention and viral suppression among children and adolescents in Zimbabwe [25], and an integrated, family-based model of care resulted in increased enrollment of children in care and initiating ART in Uganda [15, 26]. Transition from pediatric to adult HIV care is a particularly vulnerable time for loss-to-follow-up among youth; a variety of models to facilitate transition in LMICs have been developed, but outcomes data are limited [27].

KEY POPULATIONS: MEN WHO HAVE SEX WITH MEN, PEOPLE WHO INJECT DRUGS, FEMALE SEX WORKERS, AND TRANSGENDER INDIVIDUALS

In a prospective study among 793 HIV-tested men who have sex with men (MSM) and transgender individuals in Brazil, 131 (16.5%) were HIV-infected; 95 (72.5%) were linked to HIV care, 80 (61.1%) initiated ART, and only 50 (38.2%) were suppressed 1 year after diagnosis [28]. Among 1146 HIV-infected MSM in India, only 30% were aware of their HIV-positive status, 23% were linked to care, 16% had started ART, and 10% were virally suppressed [29]. Data collected among female sex workers in Johannesburg, South Africa, documented poor viral suppression, with 81% not receiving ART [30]. Also, injection drug use has been documented in 20 African countries [31]. In Kenya, predicted HIV prevalence 5 years after initiating injection drug use was nearly 20% in Nairobi and 17% in the coastal region; <5% in both regions were virally suppressed [32]. Decentralized care with unfettered access to DSD (eg, specific clinics for MSM, female sex workers, or people who inject drugs) could help infected persons achieve and sustain viral suppression. Furthermore, efforts targeting stigma, discrimination, and human rights violations, including protective and empowering legal environments, are urgently needed.

COMMUNITY-BASED COMBINATION HUMAN IMMUNODEFICIENCY VIRUS INTERVENTIONS

A Botswana combination prevention project documented that among 2609 individuals receiving ART with a VL measurement, 2517 (96.5%; 95% CI, 96.0–97.0) had a suppressed VL [33]. Community-based testing and ART initiation in rural Kenya and Uganda achieved 90% virologic suppression within 2 years of program implementation [34]. Recent population-based HIV impact assessments from Zimbabwe, Malawi, and Zambia reported viral suppression in 89% of persons living with HIV on ART in these countries; however, there were substantially lower viral suppression rates among men, adolescents and young adults, and children [35]. In the HPTN071/PopART TasP trial in Zambia, after two rounds of delivering the intervention, 90% of HIV+ women and about 80% of HIV+ men were estimated to know their HIV+ status. Of those known HIV+, an estimated 80% were on ART; but VL data is not yet available [36]. In the ANRS 12249 TasP trial in KwaZulu-Natal, South Africa, 68.8% of an estimated 3933 persons living with HIV were newly diagnosed, of whom 70.1% and 70.8% were initiated on ART and virally suppressed, respectively [37].

ROBUST FIRST-LINE ANTIRETROVIRAL THERAPY, PROACTIVE ADHERENCE MONITORING, AND POINT-OF-CARE VIRAL LOAD AND HUMAN IMMUNODEFICIENCY VIRUS DRUG-RESISTANCE TESTING

There is no gold standard to monitor ART adherence, but real-time adherence monitoring tools such as electronic drug monitoring and electronic pharmacy refill tracking systems can be useful to prompt evidence-based adherence interventions (eg, peer counseling and/or mHealth) among patients with documented poor adherence before breakthrough viremia and emergence of drug resistance [38]. Due to the relative low cost, electronic pharmacy refill tracking systems are likely to be cost-effective and scalable in LMICs. Increased VL monitoring access can serve as a metric for optimal ART adherence; in most LMICs, persons living with HIV with unsuppressed VLs resuppress following enhanced adherence counseling, indicating viremia was largely due to nonadherence [39].

A recent systematic review and meta-analysis found the annual increase in the odds of detecting pretreatment HIV drug resistance between 1996 and 2016 were 23% in southern Africa, 17% in western and central Africa, and 11% in Asia [40]. Access to affordable, point-of-care HIV VL assays and genotypic drug-resistance testing could facilitate better ART regimen choices. Assessments for 2 major nucleoside reverse transcriptase inhibitor–associated mutations (M184V and K65R) and 4 major non-nucleoside reverse transcriptase inhibitor–associated mutations (K103N, Y181C, G190A, and V106M) would be the most useful for point-of-care resistance testing in LMICs.

Increasing pre-ART HIV drug-resistance levels, combined with better tolerability, efficacy, and the high-resistance barrier of dolutegravir–based ART, support a recent WHO recommendation for integrase strand transfer inhibitor–based ART as the new preferred first-line ART in LMICs to provide improved viral suppression and limit resistance development. Dolutegravir -based ART as a first-line regimen was introduced in Brazil and Botswana in 2017, and several other LMICs are in the process of doing the same.

CONCLUSIONS

Although there has been progress toward achieving the third "90," many challenges remain, particularly for vulnerable and key populations. Even as successes and challenges toward "90-90-90 by 2020" are outlined, new fast-track "95-95-95 by 2030" targets have been established due to concerns that the original targets may not achieve epidemic control. Regardless of a specific target, efforts to scale up evidence-based strategies that are generalizable, cost-effective, community-based, and acceptable to persons living with HIV must be intensified.

Notes

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