Getting to 90-90-90: experiences from the MaxART early access to ART for all (EAAA) trial in Eswatini

Walsh, F.; Khan, S.; Barnighausen, T.; Hettema, A.; Lejeune, C.; Mazibuko, S.; ... ; Spiegelman, D.

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TREATMENT AS PREVENTION (SH VERMUND, SECTION EDITOR)

Getting to 90–90–90: Experiences from the MaxART Early Access to ART for All (EAAA) Trial in Eswatini

Fiona Walsh[1] · Shaukat Khan[2] · Till Bärnighausen[3,4,5] · Anita Hettema[6] · Charlotte Lejeune[7] · Sikhathele Mazibuko[8] · Charmaine Khudzie Mlambo[6] · Ria Reis[9,10,11] · Yvette Fleming[12] · Gavin Khumalo[13] · Mandisa Zwane[14] · Velephi Okello[15] · Donna Spiegelman[16,17]

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Abstract

Purpose of Review The MaxART Consortium—led by the Eswatini Ministry of Health—implemented multiple interventions between 2012 and 2017 to achieve UNAIDS 90–90–90 targets. We summarize key findings from community outreach strategies in support of the first 90 goal, and from the Early Access to ART for All (EAAA) trial on the implementation of a "Treat All" strategy to achieve the second and third 90 goals within a government-managed public health system.

Recent Findings The MaxART Consortium demonstrated that "Fast Track," a problem-solving approach, was effective at increasing testing coverage in the community. Compared with baseline data at 3 months prior to the start of the Fast Track, there was a 273% proportional increase in HIV tests conducted among adolescent males, adolescent females, and adult men, and 722% over baseline for adolescent males. The MaxART EAAA trial further showed that implementation of the Treat All policy was associated with significant two-fold shorter time from enrollment into care to ART initiation than under the standard CD4+ cell threshold-based treatment guidelines. Finally, through the MaxART trial, Eswatini was able to identify areas for further investment, including addressing the system-side barriers to routine viral load monitoring, and designing and implementing innovative community-based approaches to reach individuals who were not more routinely accessing HIV testing and counseling services.

Summary As low- and middle-income countries adopt the Treat All approach in their national HIV care and treatment guidelines, further implementation science research is needed to understand and address the system-level barriers to achieving the benefits of Treat All for HIV-infected individuals and those at risk.

Keywords Universal test and treat · HIV testing · Retention · Viral suppression · Sub-Saharan Africa · Eswatini

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✉ Donna Spiegelman
donna.spiegelman@yale.edu

Fiona Walsh
fjwalsh@gmail.com

Shaukat Khan
skhan@clintonhealthaccess.org

Till Bärnighausen
till.baernighausen@uni-heidelberg.de

Anita Hettema
ahettema@clintonhealthaccess.org

Charlotte Lejeune
clejeune@clintonhealthaccess.org

Sikhathele Mazibuko
smazibuko11@gmail.com

Charmaine Khudzie Mlambo
khudzie@gmail.com

Ria Reis
r.reis@uva.nl

Yvette Fleming
yvettefleming71@gmail.com

Gavin Khumalo
khumalogavin@gmail.com

Mandisa Zwane
mandisa@safaids.net

Velephi Okello
vjokello@gmail.com

Extended author information available on the last page of the article

Introduction

Over the past decade, randomized controlled trials and observational studies have demonstrated that starting individuals with human immunodeficiency virus (HIV) on antiretroviral therapy (ART) immediately upon diagnosis improves their health and reduces HIV transmission [1–4]. Extrapolating these results, mathematical modeling predicted that scaling up a "Treat All" approach (also known as "universal test and treat," "early access to ART," "immediate ART," or "test and start") held the potential to reduce HIV incidence rate to below epidemic levels in high-prevalence settings [5, 6]. To achieve these promising projections, however, 81% of HIV-positive individuals would need to be on treatment, and 73% of HIV-positive individuals virally suppressed. Strengthening the HIV care and treatment cascade is, therefore, central to the success of Treat All in ending the AIDS epidemic.

The 2014 Joint United Nations Programme on HIV/AIDS (UNAIDS)' announcement of the 90–90–90 targets served as a call to action in support of Treat All, urging policymakers and practitioners to diagnose 90% of all HIV-positive persons, to provide antiretroviral therapy (ART) to 90% of those diagnosed, and to achieve viral suppression for 90% of those on ART by 2020 [7]. Yet, between 2012 and 2014, few countries in sub-Saharan Africa, which represent 65% of new HIV infections globally, were on track to meet those targets [8–10]. Doubts were raised about the feasibility and impact of introducing a Treat All approach before most countries had met the 90–90–90 targets, which were set against previous CD4+ cell count threshold-defined guidelines [11••]. Specifically, there were concerns about the potential for poor retention as programs expanded and patient volumes increased, reducing the time and resources available to manage the additional demand on fragile health systems [12, 13]. These concerns were broadly supported by empirical evidence from ART programs in sub-Saharan Africa [14••, 15].

In Eswatini, HIV was first reported in 1986 and quickly escalated to epidemic proportions. By 2006, the country was facing one of the world's most severe HIV epidemics with an adult HIV prevalence of 26% among adults 15–49 [16]. With an annual adult HIV incidence of 1.36%, the numbers in need of ART and the costs to manage their care and treatment were expanding each year [17]. In response, the government scaled up its national HIV prevention and treatment programs, including rolling out a voluntary medical male circumcision program [18]. In 2011, further systems strengthening investments were made—including the introduction of nurse-initiated ART, roll-out of point-of-care CD4 testing, improvements to commodity and supply chain management, and expanded community mobilization and demand creation campaigns—to dramatically scale up HIV testing, improve access to ART, and reduce loss to follow-up for those on ART [19]. By 2014, the country had achieved its ambitious targets: more than 315,000 people were being tested annually for HIV, 91% of people in need of ART (at CD4 count of ≤ 350, the national treatment threshold at that time) were on treatment, and loss to follow-up for those on treatment was reduced from 22 to 9% [19].

Recognizing the promise of Treat All, Eswatini's government sought to better understand the requirements for successfully implementing this strategy nationally. While the clinical evidence was mounting, critical implementation questions about the feasibility of scaling this intervention through routine, public health sector health systems remained unanswered. How would starting HIV-positive patients on ART upon diagnosis impact their clinical outcomes? What would be the social and behavioral impacts of starting asymptomatic patients on a lifetime treatment immediately following their HIV diagnosis? Would Eswatini's health workforce be able to cope with the additional patient volumes? At this time, there was little evidence to inform the design and roll-out of a Treat All policy in the "real-world" setting of a public sector health system.

In 2014, the Eswatini Ministry of Health, alongside their partners in the MaxART Consortium—including the Clinton Health Access Initiative (CHAI), Aidsfonds, Eswatini National Network of People Living with HIV/AIDS (SWANNEPHA), the Southern African AIDS Information Dissemination Service (SAfAIDS), the South African Centre for Epidemiological Modelling and Analysis (SACEMA), and University of Amsterdam—launched a 3-year stepped-wedge randomized controlled trial, Early Access to ART for All (EAAA), in its public sector health system to assess the impact of providing early access to ART versus the then-current CD4 threshold-based care and treatment guidelines on retention and viral suppression [20]. The trial utilized a multidisciplinary, mixed-methods approach to assess the impact of Treat All on patient satisfaction and experiences of ART initiation, adherence, and retention; patient welfare; provider satisfaction; health care expenditures; and the affordability of this strategy when rolled out as a national policy in Eswatini.

In September 2015, 1 year after the start of the MaxART trial, the World Health Organization (WHO) endorsed Treat All in its global treatment guidelines, recommending that all people living with HIV should start ART irrespective of disease stage and at any CD4 cell count [21]. Between July and December 2016, seven sub-Saharan African countries adopted Treat All in their national HIV care and treatment guidelines: Burundi, Kenya, Malawi, Rwanda, Uganda, Zambia, and Eswatini [22••]. By mid-2018, 84% of low- and middle-income countries had adopted Treat All [23].

With UNAIDS' 2020 deadline on the horizon, Eswatini's initial experience implementing Treat All can offer valuable insights on the system challenges and potential solutions for achieving the 90–90–90 targets in this manner. Here, we review lessons learned by Eswatini through the MaxART trial experience.

The First 90: Knowledge of HIV Status

Meeting the goal of viral suppression among at least 73% of HIV-positive individuals on ART requires first identifying and diagnosing 90% of people living with HIV [24]. At the end of 2017, UNAIDS estimated that 75% of people living with HIV globally knew their HIV status, meaning that 5.7 million additional HIV-positive individuals needed to be offered a test, accept the test, and correctly diagnosed to achieve the first 90 [25]. Closing the testing gap has proven to be a significant limitation of the Treat All approach, particularly so when considering young adults and men who are less likely to access health services.

Historically, testing strategies have focused on facility-based testing by targeting pregnant women attending antenatal care clinics (ANC) and by patients voluntarily presenting themselves at testing centers, who are often further along in their disease progression. This strategy has resulted in higher coverage of testing in women, nearly 70% of all adults tested, primarily driven by testing uptake in ANC [26]. Widescale testing of pregnant women, coupled with the provision of ART to those testing positive, is likely largely responsible for the impressive gains made towards eliminating mother to child transmission by PMTCT programs. While the gains in identifying and treating HIV-positive adult women have been high, adolescents, young adults, and men—groups who have proven harder to reach via existing testing modalities—are being left behind.

Community Mobilization and Demand Creation for HIV Testing and Counseling

As of 2012, more than one in three HIV-positive infected adults in Eswatini were unaware of their status [27]. This public health gap was recognized as a priority and a critical part of the foundation that needed to be in place before a national Treat All policy could be successfully introduced. Between 2011 and 2017, Eswatini nearly tripled the number of HIV tests conducted each year, primarily by introducing and scaling up provider-initiated HIV testing services and through multiple community-level interventions. Community engagement has been shown to improve the effectiveness of demand creation for HIV testing and counseling, and Eswatini's strategy to increase its HIV testing uptake—especially among hard-to-reach populations including men and adolescents—was no exception [28]. Before the MaxART trial, Eswatini worked first to improve uptake for HIV testing and counseling (HTC) through several targeted community mobilization and systems strengthening initiatives, for example, demand-creating community dialogs, male-focused health days, and training for traditional community leaders.

One specific intervention that was particularly effective in increasing Eswatini's HIV testing coverage was "Fast Track," a problem-solving approach designed by General Electric that is used to address a well-defined challenge within a 90-day timeframe [29]. Eswatini applied this strategy to rapidly increase the historically low uptake of HTC among men and adolescents. As a first step, the local government and community leaders held two planning and scoping meetings to identify the composition of the intervention teams, set targets, and develop an action plan. Once the Fast Track strategy was launched, the team assessed progress towards their predefined targets at 30, 60, and 90 days. Over 3 months, 35 out of 55 country's constituencies were included in the Fast Track intervention, engaging 5,000 community members as team members. The Fast Track teams held 570 events, reaching 86,485 people through door-to-door campaigns. Compared with baseline data at 3 months prior to the start of the Fast Track, there was a 273% proportional increase in HIV tests conducted among adolescent males, adolescent females, and adult men, and 722% over baseline for male adolescents across all Fast Tracks (Fig. 1) [30]. The success of the Fast Track program underlines the importance and potential impact of engaging community leaders to assist with outreach to hard-to-reach populations in rural settings.

Optimizing HIV Testing and Counseling Services

Within Eswatini's health facilities, men and women experienced barriers related to complicated clinical processes, long waiting times in designated queues that compromised confidentiality, and low-quality counseling services. Health workers felt overburdened by the frequent changes in HIV treatment guidelines, increasing workloads, lack of incentives, and protocol constraints [31]. These findings informed the development of an upgraded HIV counseling toolkit, particularly for provider-initiated HTC in the public sector health facilities.

Increasing provider-initiated HTC (PIHTC), especially in outpatient departments, contributed substantially to overall increases in HTC. Between 2009 and 2013, HTC nearly doubled and the PIHTC contribution increased from 37 to 59% of total tests [32]. A representative sample survey of people living with HIV further supported the need for normalizing testing, as 81% of participants had not been tested for HIV prior to their positive test, only 39% through PIHTC, and over 50% sought testing because they were falling ill [33].

Eswatini has made significant progress towards decentralizing and optimizing its HIV testing services to reach those who do not know their status. According to the most recent data, 85% of the country's HIV-positive individuals are aware of their status, and the positivity rate dropped from 8 in 2012 to 5.5% in 2017 [34, 35]. As a result, to reach the first 90, the Ministry of Health has now introduced a targeted testing

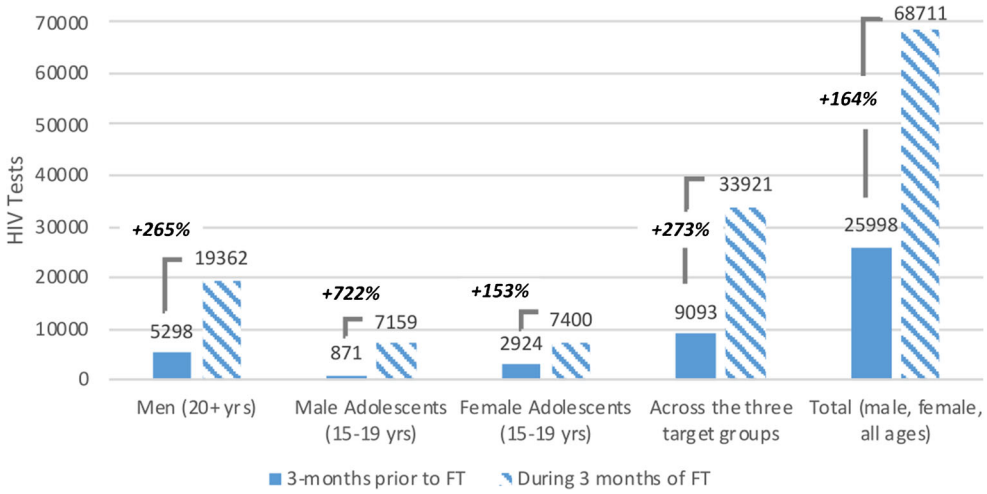

Fig. 1 Total HIV tests completed across 35 Fast Tracks over 3 months during Fast Track as compared with baseline of 3 months prior, and proportional increases over baseline

strategy through index testing, HIV self-testing, and a HIV testing service eligibility assessment, specifically targeting underserved populations (children, adolescents, men, and key populations).

The Second 90: Treatment Uptake

The loss to care between diagnosis and ART initiation has traditionally been the largest "leak" in the HIV care and treatment cascade. As of 2017, 41% of all people living with HIV globally—and 21% of those aware of their HIV status—were not receiving ART [25]. A concern about the Treat All policy was that more asymptomatic HIV-positive individuals would be, for the first time, eligible for ART and would rapidly increase the number of HIV-positive individuals enrolled in care and treatment, which shifts both the perceived and actual workload of health workers and ART-related attitudes and behaviors. Programs need to close these evidence gaps related to the attainment of the second 90 target.

Linkages to Care and Treatment

In Eswatini, as expected, the MaxART trial found that Treat All was associated with significant two-fold shorter time from enrollment into care to ART initiation than under the CD4 threshold-based treatment guidelines (standard of care) [36]. Under standard of care, only 16% (95% confidence interval (CI) 15–18) of clients initiated on ART on the same day as their test versus 61% (95% CI 59–63) under Treat All [36].

To gain a deeper understanding about the acceptability of earlier ART initiation, the MaxART trial included a social science component designed to examine why some newly diagnosed HIV-positive clients chose to delay initiating ART. While most clients responded positively to starting ART early, some needed more time to accept their diagnosis and the prospect of lifelong treatment before they were willing to initiate ART [37]. For individuals enrolled in pre-ART care under the previous threshold-based treatment guidelines, the Treat All policy was inconsistent with previous messages about not needing ART until specific criteria were met. Some clients weighed the benefits of treatment against its potential side effects (i.e., nausea, vomiting, skin darkening) when considering a lifetime of ART. In interviews with health workers, it was found that they were encouraging asymptomatic clients to initiate early to avoid the visible signs of illness and the subsequent stigma from their community. Health workers were generally found not to be communicating the preventive benefits of ART to clients during their initiation counseling [37].

The MaxART trial findings are consistent with those of another implementation study in the Shiselweni Region in Eswatini, led by Médecins Sans Frontières (MSF), that found that the cumulative 3-month ART initiation for patients offered ART under Treat All was greater than those offered ART under CD4 threshold-based guidelines, 91% versus 74% ($p < 0.001$) respectively [38]. A recent analysis in six African countries also showed rapid ART initiation under Treat All with 82% of patients starting ART within 30 days of enrollment [22••].

Retention

As countries have adopted Treat All, the ART population has rapidly expanded, raising concerns about the impact of loss to follow-up. Since most countries in sub-Saharan Africa have only adopted Treat All within the past few years, limited longitudinal data are available to assess the impact of Treat All on retention in "real-world" public sector health systems. The controlled setting of clinical trials may not be generalizable to the context of resource-limited health systems. Initially, practitioners were concerned that implementing Treat All would adversely impact the performance of public sector HIV treatment programs [20]. On the provider side, some

hypothesized that Treat All would alter the capacity or motivation of health workers to provide ART, while on the patient side, some were concerned that Treat All would have a negative effect on the patient experience at potentially overburdened health facilities, which, in turn, could affect ART retention and viral suppression [39].

In Eswatini, similar hesitations were initially expressed, but the MaxART trial found that the opposite was true. After the introduction of Treat All, self-reported adherence and disclosure levels remained high, and there was an observed improvement in patient interactions with the health system. Overall, there was a highly significant 60% (95% CI 15–220%) improvement in retention at the end of the study period under Treat All compared with standard of care [40]. At 12 months, retention among patients who initiated ART earlier was greater than those in the standard of care: 86% (95% CI 83–88%) and 80% (95% CI 77–83%), respectively. Patients' reasons for stopping ART were the result of a complex chain of events, but a recurring theme among respondents was that stopping ART was related to their relocation to another town or community that was far from the facility where they received their HIV care and treatment [41]. While longer follow-up is necessary to evaluate long-term impacts under Treat All, the MaxART trial found that there was neither a short-term beneficial effect of a Treat All approach on mortality nor any evidence of harm [42].

Similar results were reported by another public sector treatment program in rural South Africa, showing an 18% improvement in 12-month retention for patients who were immediately initiated on ART compared with those who started ART when their CD4 count fell below 350 cells/μl [14••]. Results from Eswatini and other low–middle-income countries suggested that offering patients ART immediately at diagnosis could improve retention in care, counter to the caution raised when Treat All was proposed. It will be important to continue examining retention over a longer period under Treat All to ensure these gains are sustained.

One key factor influencing retention is patient satisfaction with HIV care services. Dissatisfied patients are typically less likely than satisfied ones to return for follow-up visits. Treat All could influence patient satisfaction relative to a CD4 threshold-based eligibility approach, due to either longer wait times at facilities or the negative impact of ART side effects experienced by asymptomatic patients [14••, 43]. MaxART showed that Treat All policies did not affect patient satisfaction in Eswatini. The proportional odds ratios comparing EAAA to control were 0.91 (95% CI 0.66, 1.25) for overall patient satisfaction and 1.04 (95% CI 0.61, 1.78) for satisfaction with wait time, 0.90 (95% CI 0.62, 1.31) for satisfaction with involvement in treatment decisions, 0.86 (95% CI 0.61, 1.20) for satisfaction with consultation time, and 1.35 (95% CI 0.93, 1.96) for satisfaction with respectful treatment [44]. At the same time, observational data from MaxART showed that both overall patient satisfaction and for satisfaction subdomains declined over time in both the EAAA intervention and the standard-of-care arms, indicating that there are other mechanisms than this policy change that influenced patient satisfaction, such as increases in patient volume and decreasing patient satisfaction with increased time on ART [44].

The Third 90: Viral Suppression

At the individual level, viral load suppression may serve as a proxy for ART adherence and treatment effectiveness. In addition, community-average viral load may serve as a proxy for the risk of transmission and thus the effectiveness of a Treat All policy [45]. As such, to achieve the third 90 and the targets for Treat All, viral load (VL) monitoring was put forward by the WHO as the global standard of care in 2013, recommending it for all patients on ART for more than 6 months to support earlier detection of treatment failure due to resistance and differentiate treatment failure from potential adherence issues [46].

At the time of the 2013 WHO recommendation, however, the high cost and logistical challenges of implementing routine VL monitoring in national HIV care and treatment programs meant that most resource-limited countries were continuing to use CD4 for clinical monitoring. In sub-Saharan Africa, of the 11 million patients on ART, only five million had access to viral load testing in 2015 [47]. The laboratory capacity required to conduct VL monitoring varies significantly across sub-Saharan Africa: for example, in 2015, 91% of people living with HIV in South Africa had received one VL result, compared with only 19% in Malawi [48].

In Eswatini, MaxART found an improved viral suppression rate at 12 months post-ART initiation of 79% (95% CI 75–83) among the Treat All arm compared with 4% (95% CI 2–7) in the standard of care arm in the intent to treat analysis [40]. This analysis only includes those who had sufficient follow-up to satisfy ART initiation criterion, survived 6 months beyond initiation, and received at least one viral load measurement beyond this 6-month point; thus, this comparison is potentially biased. Analyses comparing viral suppression rates—even in randomized trials—need to be carefully thought through. Nevertheless, these results highlight significant gaps in Eswatini's health system's capacity to provide routine viral load monitoring: 80% of participants in the standard of care and 66% in the Treat All arm never received a viral load measurement between 180 days post-ART initiation and the end of their follow-up in the study. The health system challenges observed during the trial mirrored the broader logistical issues faced by the country as it worked towards rolling out routine viral load monitoring.

Before the WHO's guideline change in 2013, Eswatini's Ministry of Health—in partnership with MSF—had already

started piloting routine VL monitoring with enhanced adherence counseling for patients with detectable VL in a region of the country supported by MSF [49]. The country had VL testing capacity in its National Reference Laboratory, but it had historically only been used for "targeted monitoring" for patients with suspected treatment failure. This study found that routine VL monitoring was feasible in Eswatini's high-prevalence setting but that it required strong programmatic and clinical supervision to ensure timely receipt of test results and linkage of test results to patient records. Only 52% of eligible patients in this study received a VL test over the 12-month study period.

In the MaxART trial, multiple challenges in the implementation of routine viral load at the facility level were identified, such as the unavailability of daily sample transport to the national referral laboratory and the timing of sample pickup in the morning, leaving patients who arrived in the afternoon unable to have a viral load test taken. Lack of sample transport was further compounded by the fact that the facilities in the study did not have access to centrifuges or refrigerators. Since dried blood spot (DBS) testing for routine monitoring load was not available, these infrastructure issues challenged the processing of plasma preparation for the viral load tests. Sample transport is not a unique challenge in HIV care, and as countries continue to decentralize services, expanding access to point-of-care viral load testing would improve the timeliness of viral load monitoring.

Recognizing these implementation challenges at the study sites, a "Know Your Viral Load" campaign was introduced to create demand from patients, focused on highlighting the importance of VL monitoring. The campaign aimed to empower patients to proactively request VL testing during their follow-up visits with health workers, thus informing patients and reminding clinical staff about this new test available to support HIV care and treatment. Reminder stickers were placed in appointment booklets, noting the expected month for a repeat viral load test, the last test date, and the last viral load test results. During the follow-up period, the median time to first VL from ART initiation was significantly lower in the group who received the "Know Your Viral Load" campaign (intervention) than the control: 208 days (95% CI 203–212) compared with 257 days (95% CI 248–266), respectively. After adjusting for sex, age, and CD4 at ART initiation, the hazard ratio for time to receiving a first VL monitoring test was nearly 3-fold higher in the intervention group than in standard of care (95% CI 1.62–5.27, $p < 0.0001$). These results informed Ministry of Health's nationwide roll-out of new patient booklets, which now include the reminder stickers.

Today, access to viral load monitoring in Eswatini has improved significantly as the country works to make HIV care and treatment services more patient-centered. In 2018, the country had performed 177,156 viral load tests, close to 15,000 tests per month; 55% of people living with HIV on ART had a viral load test in 2018 [50]. There have also been significant investments to decentralize and strengthen the country's laboratory services. There are now four laboratories performing viral load monitoring across the country. Centrifuges and refrigerators were bought for all mini-laboratories across the country to facilitate the preparation of the viral load plasma samples. Recognizing the delays with the sample transport system, the country is now using DBS for children under the age of 15; DBS is also used for monitoring viral loads among adolescents on ART who attend treatment support "Teen Clubs," which happen on Saturdays when the laboratories are closed.

As countries increase access to ART under a Treat All approach, these results from the MaxART trial demonstrate the importance of empowering patients to be active participants in their care as countries work to expand access to high-quality, well-resourced routine VL monitoring. Achieving the 90–90–90 targets requires not only a scale-up of laboratory equipment but also investments in training and messaging to inform patients and health workers about the benefits and importance of regular VL measurements.

While much global effort has been made to increase the uptake and coverage of routine VL monitoring for patients on ART, access to VL monitoring is still limited. Scale-up of VL testing has been challenging due to insufficiently trained laboratory personnel, high cost of establishing and operating centralized laboratories, and challenges with sample transport and result delivery, all of which lead to long turnaround times [51]. Point-of-Care (POC) VL technologies can address some of these gaps by allowing tests to be conducted directly in the health facilities. This way, results can be made available in less than 2 h. Potential advantages of POC include reduced patient loss to follow-up between elevated VL and clinical action, such as enhanced adherence counseling or switching to second-line treatment regimens. POC may also lead to improved targeted testing, such as in pregnant and breastfeeding women, for faster identification and management of treatment failure. Additionally, POC VL could enable faster identification of stable patients who could benefit from decentralized service delivery, further reducing the burden on the client and the health system.

Conclusion

In this review, we have shown that it is possible to maintain and advance progress towards achieving the 90–90–90 targets in high-prevalence countries, such as Eswatini, that have adopted the Treat All policy. These gains have been possible due to Eswatini's early and deep commitment to strengthening and expanding HIV testing and counseling services, expanding ART access, and building up laboratory capacity. Additionally, through the MaxART trial, the country

identified areas where it needed to invest further to accommodate the additional patient volumes and clinical monitoring requirements under the Treat All policy, by addressing the system-side barriers to routine viral load monitoring and designing and implementing innovative community-based approaches to reach individuals who were not accessing routine HIV testing and counseling services. Today, Eswatini is continuing to work towards making its interventions even more patient-centered and -targeted, including examining how to best engage communities and traditional leaders to support the national decentralization efforts further.

As countries that were early adopters of a Treat All policy accrue further follow-up data, there will be further valuable lessons to be learned about the impact of Treat All on the HIV care cascade when moving from a CD4 threshold-based guideline to one where every HIV-positive person is started on ART regardless of CD4 cell count. To plan properly for transitioning to a Treat All policy, countries need to anticipate the operational and programmatic implications. Countries will need to close their HIV testing gaps to achieve the full benefits of a Treat All policy, including working closely with communities to find and engage hard-to-reach populations, and ensure that system-side barriers to HIV care and treatment, such as access to routine viral load monitoring, are removed. Continued investment in reaching the 90–90–90 goals will support the successful implementation of Treat All.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Affiliations

Fiona Walsh[1] · Shaukat Khan[2] · Till Bärnighausen[3,4,5] · Anita Hettema[6] · Charlotte Lejeune[7] · Sikhathele Mazibuko[8] · Charmaine Khudzie Mlambo[6] · Ria Reis[9,10,11] · Yvette Fleming[12] · Gavin Khumalo[13] · Mandisa Zwane[14] · Velephi Okello[15] · Donna Spiegelman[16,17]

1 Mesurado Cooperative, Cambridge, MA, USA
2 Clinton Health Access Initiative (CHAI), 333 Dorchester Avenue, Boston, MA, USA
3 Heidelberg Institute of Global Health, University of Heidelberg, 130.3 INF, 69120 Heidelberg, Germany
4 Department of Global Health and Population, Harvard T.H Chan School of Public Health, Boston, MA, USA
5 Africa Health Research Institute, KwaZulu-Natal, South Africa
6 Clinton Health Access Initiative (CHAI), Tsekwane St, Mbabane, Eswatini
7 Clinton Health Access Initiative (CHAI), Dakar, Senegal
8 Eswatini National ART Program (SNAP), Ministry of Health, Mbabane, Eswatini
9 Leiden University Medical Center, Leiden University, Leiden, Netherlands
10 Amsterdam Institute for Social Science, University of Amsterdam, 1012 WX Amsterdam, Netherlands
11 Children's Institute, University of Cape Town, Cape Town, South Africa
12 aidsfonds, Condensatorweg 54, 1014 AX Amsterdam, Netherlands
13 Eswatini National Network of People Living with HIV (SWANNEPHA), P. O. Box 4161, Mbabane, Eswatini
14 SAfAIDS, Lamvelase Building, Nkoseluhlaza Street, Manzini, Eswatini
15 Directorate Office, Ministry of Health, Mbabane, Eswatini
16 Department of Biostatistics, Center on Methods for Implementation and Prevention Science, Yale School of Public Health, 60 College Street, New Haven, CT 06510, USA
17 Departments of Epidemiology, Biostatistics, Nutrition and Global Health, Harvard T.H Chan School of Public Health, Boston, MA, USA