Research priorities for achieving universal HIV treatment in Africa

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Research priorities for achieving universal HIV treatment in Africa

Nearly all countries in sub-Saharan Africa (SSA) have adopted national policies for universal HIV treatment, regardless of CD4 cell count or clinical stage. Evidence to date from SSA suggests that, once linked to care, timely antiretroviral therapy (ART) initiation with retention and viral suppression is the norm. However, ART initiation in SSA usually occurs late in the course of infection, driving up mortality and new infection rates. With 10.3 million people untreated and a projected 1.2 million new infections per year in SSA, the universal treatment era presents strategic opportunities for health systems to substantially reduce AIDS-related mortality and HIV incidence. This special issue of the *Journal of Virus Eradication*, with contributing authors from the African regions of the IeDEA consortium and the World Health Organization (WHO), contains an editorial and eight articles focused on issues critical to ensuring the success and impact of universal treatment implementation in SSA.

Denis Nash
Marcel Yotebieng
Annette H Sohn

Supplement Editors
Aims and objectives
The aim of this journal is to provide a specialist, open access forum and fast-track pathway to publish work in the rapidly developing field of virus eradication, particularly of HIV, HBV and HCV. The Journal has been set up especially for these and other viruses, including herpes and flu, in a context of new therapeutic strategies, as well as societal eradication of viral infections with preventive interventions.

Scope
The Journal not only publishes original research, but also provides an opportunity for opinions, reviews, case studies and comments on the published literature. It focuses on evidence-based medicine as the major thrust in the successful management of HIV and AIDS, HBV and HCV as well as includes relevant work for other viral infections. The Journal encompasses virological, immunological, epidemiological, modelling, pharmacological, pre-clinical and *in vitro*, as well as clinical, data including but not limited to drugs, immunotherapy and gene therapy. It will be an important source of information on the development of vaccine programmes and preventative measures aimed at virus eradication.

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Treating all people living with HIV in sub-Saharan Africa: a new era calling for new approaches

Denis Nash1,2,*, Marcel Yotebieng3 and Annette H Sohn4

1 Institute for Implementation Science in Population Health, City University of New York, NY, USA
2 School of Public Health, City University of New York, NY, USA
3 College of Public Health, Division of Epidemiology, Ohio State University, Columbus, OH, USA
4 TREAT Asia, amfAR – Foundation for AIDS Research, Bangkok, Thailand

Abstract

Nearly all countries in sub-Saharan Africa (SSA) have adopted national policies to treat all persons with HIV, regardless of CD4 cell count or clinical stage (‘treat all’). With 10.3 million people untreated and a projected 1.2 million new infections per year in SSA, the current and anticipated unmet need for HIV treatment in SSA is substantial. Evidence to date from SSA suggests that, once linked to care, timely ART initiation with retention and viral suppression is the norm. However, ART initiation in SSA usually occurs late in the course of infection, driving high mortality and incidence rates. The ‘treat all’ era presents strategic opportunities for health systems to substantially reduce AIDS-related mortality and HIV incidence. This special issue of the Journal of Virus Eradication contains eight articles focused on issues critical to ensuring the success and impact of ‘treat all’ implementation in SSA.

Keywords: HIV, ‘treat all’, sub-Saharan Africa, HIV treatment guidelines

Introduction

The HIV pandemic has been among the major public health threats of our time. Since its beginning, an estimated 78 million people around the world have become infected with HIV, and 35 million have died of AIDS-related illnesses, driving major losses of life expectancy. Highly effective treatment for HIV, available in resource-rich settings since 1995, took another 10 years to reach those areas of the world hardest hit by HIV, such as sub-Saharan Africa (SSA), home to 25.7 million people or 70% of those living with HIV today [1]. The scale of the global public health response to the HIV pandemic is unprecedented. Through the combined efforts of people living with HIV, national public health programmes, global donors and a broad community of stakeholders, the number of people on antiretroviral therapy (ART) rose rapidly across SSA, going from about 100,000 in 2004 to 15.4 million by the end of 2017 [1,2]. This incredible accomplishment is saving millions of lives each year.

Scale-up and treatment guideline expansion have increased ART coverage in SSA, but substantial unmet needs persist

The early public health response to the HIV epidemic, including in SSA, began as an emergency response, with treatment initially recommended only for those with very advanced immunodeficiency and HIV disease, who were deemed at highest risk for death. Beginning in 2010 and then again in 2013, expansions in HIV treatment guidelines by WHO and national programmes in the region extended HIV treatment eligibility to individuals with less advanced disease.

Expansion of HIV treatment guidelines led to substantial gains in ART coverage for people in SSA, and concomitant improvements in life expectancy and reduced mortality. Nonetheless, we are confronted with sobering statistics regarding the current state of SSAs regional HIV epidemics (Figure 1) – there are still an estimated 660,000 AIDS-related deaths per annum among SSAs

Current evidence on the impact of ART guideline expansion and ‘treat all’ implementation

In late 2015, the WHO further expanded their HIV treatment guidelines to include all persons with HIV, regardless of CD4 cell count or clinical stage [3]. The ‘treat all’ guideline expansion heralds a new era in the response to the HIV epidemic in some of the hardest-hit areas of the world. Recent data from WHO suggest that, in less than 3 years, there has been nearly universal adoption of the WHO 2015 HIV treatment guidelines as national policy in SSA countries (Figure 3 [4]). ‘Treat all’ in SSA means that 10.3 million people living with HIV, and all people who subsequently acquire HIV infection, will be treated alongside the 15.4 million people in the region who are already receiving lifelong HIV treatment. The scale is enormous, and there will be numerous opportunities to learn what implementation models work best. ‘Treat all’ as national policy opens up new opportunities to reduce both AIDS-related mortality and new HIV infections.

First, ‘treat all’ has the potential to reduce AIDS-related mortality by improving both timely ART initiation and retention in HIV care, which have been found to occur with prior guideline expansions [5,6]. One recent randomised controlled trial (RCT) used a stepped wedge design to assess the impact of ‘treat all’ on timely ART initiation and retention in 14 real-world service delivery sites, among 3405 people enrolling in HIV care in eSwatini, from...
Figure 1. HIV care continuum and number of people with untreated HIV in sub-Saharan Africa, 2017. Adapted from UNAIDS 2018 estimates [1,17].

Figure 2. Trends in HIV incidence and deaths in sub-Saharan Africa, 1990–2017. (a) Eastern and southern Africa; (b) western and central Africa. Source: UNAIDS 2018 estimates [1,17].

Figure 3. Uptake of WHO policy for ‘treat all’ ART initiation among adults and adolescents living with HIV (situation as of mid-2018). Map provided by courtesy of WHO (Global AIDS Monitoring [UNAIDS/WHO/UNICEF] and WHO HIV country intelligence tool, 2018).
2014 to 2017 [7]. Six months after enrolling in HIV care, patients enrolling under the intervention condition were seven times more likely to be retained in care with viral suppression than those enrolling under the standard-of-care condition (i.e. the national guidelines in place at the time). At 12 months after enrolment, retention remained 60% higher in the ‘treat all’ compared to the control group.

Second, ‘treat all’ has the potential to help drive down new HIV infections through treatment as prevention (TasP). To date, evidence of the impact of ‘treat all’ on HIV incidence in SSA has been mixed, and the reasons for this are not yet clear. There have been two large-scale randomised studies conducted to examine the impact of ‘treat all’. The first, known as the Ya Tse study (the Botswana Community Prevention Project), was conducted in Botswana from 2013 to 2018, and randomised 30 communities to a ‘treat all’ condition or the standard of care under the national guidelines (which included ‘treat all’ from June 2016) [8]. The viral suppression rate was higher in the intervention communities than in the control communities. HIV incidence in the intervention communities was 30% lower than that of the control communities (incidence ratio 0.70, 95% CI: 0.50–0.99). A second Africa-based cluster RCT, the SEARCH study, was conducted among 186,354 adults (with and without HIV) in 32 communities of approximately 10,000 people each in Uganda and Kenya from 2013 to 2016. SEARCH compared the standard of care to a community-based strategy to increase HIV testing alongside other disease screenings (e.g. for diabetes and hypertension), followed by immediate linkage and treatment for persons with an HIV diagnosis [9]. Among those with newly diagnosed HIV, 60% in the intervention communities and 17% in the control communities started ART within 6 months following their diagnosis, which reached 80% versus 40% at 24 months following diagnosis. Moreover, by 36 months, 79% of those living with HIV in intervention communities, compared to 68% in control communities, had achieved viral suppression. However, the rate of new HIV infections did not differ between study arms (0.8% per year). Early findings of both trials around retention and viral suppression under ‘treat all’ conditions are also encouraging.

The way forward: ‘treat all’ implementation in SSA, with a focus on earlier diagnosis and linkage, can bend the curves of AIDS-related deaths and new HIV infections

To help ensure the success of ‘treat all’ on reducing both HIV mortality and incidence, it is essential to identify and scale up strategies capable of getting people with HIV in SSA diagnosed and initiated on treatment at much higher than current CD4 cell counts. The large numbers of both deaths and new infections in SSA are driven by distressingly low median CD4 cell counts at care enrolment and ART initiation [10–14], which were still below 300 cells/mm³ in 2015 [10]. To put these CD4 cell counts into perspective, the median CD4 cell count at ART initiation in the treatment arm of the HPTN 052 trial, which drove a >90% reduction in onward transmission among serodiscordant partners, was 445 cells/mm³ [15]. The median CD4 cell count in the treatment arm of the INSIGHT START trial, which demonstrated a reduction in mortality at higher CD4 counts, was 650 cells/mm³ [16].

Another reason why HIV treatment has not had a sustained substantial public health impact on HIV incidence could be suboptimal HIV care outcomes among adolescents and young adults, who tend to be more sexually active than older persons. Historically, in these groups, there has been delayed treatment uptake and poor retention under CD4 cell count-based treatment guidelines. Treatment guideline expansions have resulted in increases in timely ART initiation among younger persons [6]. Targeted efforts to improve outcomes among adolescents and young adults as part of ‘treat all’ implementation are critical and could result in substantial impact on HIV incidence [17]. Strategies to more effectively reach adolescents must be highly scalable, since demographic trends anticipate a massive rise in the number of adolescents in SSA in the coming decade, and by extension, the potential number of adolescents with HIV [18].

A special issue on ‘treat all’ in SSA

To support the goal of identifying knowledge gaps that need to be addressed in order to best inform, guide and increase the impact of ‘treat all’ implementation in SSA, the African regions of iedEa convened a ‘Treat All’ Consensus Statement Working Group (TACSGW) and the All-Africa iedEa Meeting in Kigali, Rwanda (November 2017) to identify research priorities with the potential to inform and guide ‘treat all’ implementation in SSA [19]. The Working Group summarised relevant literature from SSA in key areas, and the dissemination of this information is the motivation for this special issue of the Journal of Viral Eradication, which is themed around identifying research priorities to inform ‘treat all’ implementation in SSA. The articles are led by investigators from the African regions of iedEa, as well as other stakeholders and collaborators.

The first article in this issue by Ford and colleagues [20] from the WHO, summarises the ways in which observational data in general, and data from iedEa specifically, have supported the work of WHO in developing treatment guidelines and monitoring their implementation. After more than a decade of ad hoc collaboration between iedEa and WHO, the partnership was formalised in 2014. Zaniewski et al. [21] describe the genesis and structure of the collaboration and its outcomes.

It is difficult to treat all persons with HIV in SSA without examining how poor mental health and substance use may serve as barriers to timely HIV diagnosis, and initiation and adherence to lifelong treatment. These important issues have long been neglected in the region, and represent new areas for implementation research. Parcesepe et al. [22] along with Lancaster and colleagues [23] provide overviews of mental health and substance use research, respectively, among those living with HIV in SSA, and interventions or strategies to address comorbid mental illness and substance use among individuals living with HIV. They also highlight research gaps relevant to ‘treat all’ implementation, including the need for implementation science research to evaluate promising models of integrated mental health and substance use screening and treatment within HIV care delivery systems.

SSA is home to 85% of children living with HIV. Lifelong ART has been the policy for infants since 2010, expanding to children under 5 years, and pregnant and breastfeeding women (Option B+) in 2013. Although ART coverage among pregnant and breastfeeding women has surpassed 90% in some Southern and Eastern African countries, the rate of mother-to-child transmission (MTCT) in the region remains higher than expected, suggesting serious gaps along the prevention of MTCT cascade. For children living with HIV, ART coverage still lags substantially behind that of adults. Abuogu and colleagues [24] provide a review of the progress, gaps, and research needs to achieve the 90–90–90 targets and optimise ART outcomes for pregnant and postpartum women. Enane et al. [25] highlight the complex challenges in optimising the ART cascade for children and adolescents, ranging from underdiagnosis to lower rates of ART initiation and viral suppression compared to adults.
Policy development and resource allocation greatly benefit from the ability to forecast the potential impact of different implementation scenarios using mathematical models. Kimmel et al. [26] examine how mathematical models have informed scale-up and implementation of ‘treat all’ in Southern Africa and highlight the need for local, pragmatic policy assessments with realistic assumptions. Related to this, a scoping review by de Waal and colleagues [27] describes gaps in current knowledge related to HIV drug resistance in SSA, and how to address current and future resistance challenges by combining real-world data from IeDEA and mathematical modelling.

‘Treat all’ sets the stage for moving beyond the status quo approaches to ART scale-up Evidence and experience from SSA to date suggests that if people can be linked to HIV care, most will get onto treatment rapidly and be retained in care [5–7]. However, without better strategies for earlier testing and linkage, those living with HIV may remain undiagnosed and out of care until they develop symptoms, driving up mortality and ongoing transmission. With national policies expanded to ‘treat all’ across SSA, the stage is set for a new era in the response to the region’s epidemic that must identify, implement and scale test-and-treat strategies, and accelerate diagnosis and treatment initiation, at higher CD4 cell counts. Importantly, with diminishing resources for HIV service provision [28], this cannot be achieved simply by using the same approaches that national programmes have used in the past. Populations and sub-populations that have not been reached are likely to have greater individual, health system, and cultural barriers to HIV testing and treatment. Achieving success and impact sooner rather than later in SSA’s ‘treat all’ era will require identification and deployment of contextually appropriate, locally informed strategies that can be more effective and efficient at achieving earlier diagnosis and linkage than the status quo.

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The contribution of observational studies in supporting the WHO ‘treat all’ recommendation for HIV/AIDS

Nathan Ford1*, Martina Penazzato1, Marco Vitoria1, Meg Doherty1, Mary-Ann Davies2, Elizabeth Zaniewski3, Olga Tymejczyk4,5, Matthias Egger3 and Denis Nash4,5

1 Department of HIV and Global Hepatitis Programme, WHO, Geneva, Switzerland
2 Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, South Africa
3 Institute of Social and Preventive Medicine, University of Bern, Switzerland
4 Institute for Implementation Science in Population Health, City University of New York, NY, USA
5 Graduate School of Public Health and Health Policy, City University of New York, NY, USA

Abstract

In 2015, the World Health Organization (WHO) recommended that all people living with HIV (PLWH) should start antiretroviral therapy (ART) irrespective of clinical or immune status. This recommendation followed almost 20 years of research into the clinical and population-level benefits and risks of starting ART early compared with deferring treatment.

This article summarises the ways in which observational data support the work of WHO, including the support provided by the International epidemiology Databases to Evaluate AIDS (IeDEA), taking the example of ‘treat all’.

Introduction

In 2015, the World Health Organization (WHO) recommended that all people living with HIV (PLWH) should start antiretroviral therapy (ART) irrespective of clinical or immune status [1]. This recommendation followed almost 20 years of research into the clinical and population-level benefits and risks of starting ART early compared with deferring treatment [2].

The WHO ‘treat all’ recommendation was supported by evidence from randomised trials showing significant clinical benefits and a reduced risk of HIV transmission following immediate ART initiation [3-5]. The randomised trials confirmed an association that was reported by prior observational studies [6-9]; however, observational data alone were insufficient for the WHO guidelines panel to make a ‘treat all’ recommendation when this question was first assessed in 2013. Nevertheless, the observational evidence helped to strengthen the rationale for this recommendation. Observational studies have also provided important additional evidence supporting the feasibility of implementing the ‘treat all’ approach, and these studies continue to generate insights into the challenges and benefits of a treat-all policy across different settings and populations.

This article summarises the ways in which observational data support the work of WHO, including the support provided by the International epidemiology Databases to Evaluate AIDS (IeDEA) [10], taking the example of ‘treat all’ (see Table 1).

Role of observational data in WHO guidelines

The development of high-quality guidelines relies on a systematic review of the evidence and an appraisal of the certainty of the evidence. Guideline development processes have widely adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [16], which, following a long-standing approach to ranking evidence [17], rates randomised trials as generally providing high-quality evidence for questions of intervention effect, and observational studies as providing low-quality evidence (in certain exceptional situations observational studies can be considered to provide evidence of high quality [18]).

WHO adopted the GRADE approach in 2008, following public criticism that many WHO guidelines at the time relied too heavily or exclusively on expert opinion [19]. In contrast to clinical practice guidelines, WHO guidelines aim to make recommendations from a public health perspective, and are thus primarily intended for ministries of health and programme managers in low- and middle-income settings, rather than individual clinicians. As such, the formulation of WHO recommendations relies not only on information about comparative effectiveness and harms, but also considerations about the feasibility, acceptability and resource requirements for implementing a given intervention or set of interventions as well as complex interventions. While randomised trials remain the gold standard study design for assessing efficacy and safety of clinical interventions, observational studies are often a better way – and in some cases the only way – to assess intervention effectiveness in routine settings.

WHO also has a responsibility to evaluate the uptake and impact of the recommendations it makes, and these evaluations rely on observational research from implementation in routine programmes. Lessons from these studies serve to highlight challenges in implementation, which in turn can inform priorities for future guidance (Figure 1).

From treating the sickest to ‘treat all’: formulating recommendations

WHO first considered making a recommendation to start ART in all people living with HIV irrespective of clinical or immune status in 2013. At the time, there were no available data from randomised trials with respect to clinical benefit, and guideline deliberations were primarily informed by observational data and mathematical modelling. The 2013 WHO Guideline Development Group concluded that there was insufficient evidence to recommend ‘treat all’, and WHO instead recommended that the CD4 cell count threshold for stating ART be raised from ≤350 cells/mm3 to ≤500 cells/mm3 [20].

Randomised controlled trial evidence was available demonstrating the benefit of providing immediate treatment in the context of serodiscordant partnerships to reduce HIV transmission [5], and this recommendation was included in the WHO 2013 guidelines.
For pregnant women with HIV, a recommendation was made in favour of starting ART irrespective of CD4 cell count (PMTCT Option B+) [21]. This recommendation, aimed at increasing ART uptake among pregnant women, was based on a recognition of the need to simplify ART provision during pregnancy and breastfeeding, and to avoid delays in starting ART in pregnant women in settings where CD4 cell count testing was not available or where waiting for results could result in missed opportunities to prevent vertical transmission. Evidence supporting the benefits of this approach came from observational studies that provided outcomes from programmes implementing Option B+; these studies all found that uptake of ART was more timely, and that women experienced health benefits in terms of immunological and clinical parameters [22–24].

Similarly, ART initiation for all children aged under 5 years was recommended to address the low treatment coverage in children; however, at the time, this recommendation was made in the absence of randomised controlled trial evidence of clinical benefit, and primarily on the basis of observed rapid immunological decline in the absence of ART as well as causal modelling analysis of observational data from Southern Africa [13].

While several observational studies also suggested a clinical benefit to providing lifelong ART as soon as possible following an HIV diagnosis [9,25], the WHO recommendation was only made 2 years later, once data from the START and TEMPRANO randomised trials became available [3,4]. However, these trials did not include children, and the ‘treat all’ recommendation across all age groups, including children, was supported by observational data (17 cohort studies) and mathematical modelling [26,27] (Table 1).

The WHO recommendation to treat all people living with HIV also raised questions regarding how quickly ART should be initiated following confirmation of HIV diagnosis. Removing the need to have the results of clinical or laboratory assessments on hand prior to starting ART opens up the possibility to start ART on the same day that an HIV diagnosis is confirmed. In 2017, WHO recommended that ART should be offered within 7 days following the same day that an Hiv diagnosis is confirmed. in 2017, WHO recommended that ART should be offered within 7 days following the same day that an Hiv diagnosis is confirmed. in 2017, WHO recommended that ART should be offered within 7 days following the same day that an Hiv diagnosis is confirmed.

**Benefits and challenges of ‘treat all’: assessing implementation**

The clinical benefits of ‘treat all’ are no longer disputed, and this recommendation has been adopted by almost all countries worldwide [30]. Questions remain, however, regarding the feasibility of implementation and the extent to which the benefits seen in clinical trials will be realised in routine programme settings [31].

Drawing on both iDea data and information retrospectively gathered on the nature and timing of country-specific ART guideline expansion, a recently published analysis from the iDea-WHO Collaboration [32] found that ART guideline expansion supporting earlier ART initiation is associated with increased and more timely uptake of ART [33]. This analysis further showed that these improvements did not come at the expense of crowding out sicker patients. This analysis has recently been updated to include settings that have implemented ‘treat all’ and concluded that the greatest improvements in timeliness of ART initiation under successive guideline expansions that included expansion to ‘treat all’ occurred in low-income countries, likely to be due to the simplification of initiation decisions, i.e. opening the possibility to initiate treatment while waiting for baseline CD4 cell count test results. Young people aged 15–25 years also benefited from more timely ART initiation under ‘treat all’, as CD4 cell count-based guidelines disadvantaged this group of patients, who were likely to have been recently infected and therefore more likely to have higher CD4 cell counts.

Experience of implementing ‘treat all’ for pregnant and breastfeeding women (Option B+) has found that, while the approach is feasible across a variety of settings, there is a need to ensure
adequate retention in care and medication adherence, particularly during the first year following ART initiation [34]. This may also be a concern for anyone starting ART at higher CD4 cell counts, although the evidence so far is mixed [35,36].

Implementation of recommendations for rapid ART initiation has also been informed by observational data. While the results of several randomised trials all favoured rapid ART initiation, in particular by reducing the risk of loss to follow-up before ART initiation, some observational studies reported increased losses to follow-up after ART initiation. This suggests that different approaches to adherence counselling after starting ART may be needed when ART is started rapidly, as people are still coming to terms with their diagnosis. A recent study by the iDeA collaboration in Rwanda suggested that patients enrolling in care at sites conducting fewer ART readiness counselling sessions initiated ART more rapidly and had better retention 6 months post initiation [37].

**Identifying gaps in policy and practice**

Observational cohorts provide valuable insights into the programmatic impact of ART scale-up and, in doing so, can reveal gaps in the response that are a priority for future intervention research and policy guidance.

Several studies from the iDeA collaboration have highlighted the fact that men with HIV have worse outcomes compared to women with HIV [38,39], and this has contributed to a recognition of the need to identify models of care to improve uptake and outcomes for men [40].

The enduring burden of advanced HIV disease is another challenge that has been highlighted through observational research. Successive studies by the iDeA collaboration have shown that, despite major progress in ART scale-up, an important proportion of patients continues to present late for care, with advanced HIV disease [14,41,42]. This work directly contributed to the development of WHO guidance on the management of advanced HIV disease in 2017 [28], and continues to drive discussions about how to best promote earlier diagnosis and linkage to care globally.

Rapid introduction of new antiretrovirals for which limited experience has been gathered outside the setting of randomised clinical trials requires increasing attention to longer-term monitoring of treatment outcomes and toxicity profiles across populations. As countries strengthen their pharmacovigilance systems to enable active monitoring and high-quality surveillance, cohort collaborations such as iDeA can play a critical role in addressing this important evidence gap.

Future research will improve our understanding of the challenges faced in implementing the ‘treat all’ policy, in particular whether there are differences in adherence, retention, viral suppression and viral resistance among people starting ART without having developed clinical disease, and the possible need for differential adherence support for different patient populations. Indeed, observational research has the advantage of capturing the experience and patient outcomes that occur outside the controlled environments of research protocols and are critical for policies and guidelines, including large populations of persons who are not typically recruited into, or represented, in randomised trials, but are none the less differentially impacted by the HIV epidemic, such as children, pregnant women, persons with TB, persons with mental health and substance use disorders, and marginalised populations. Observational cohorts, such as iDeA, also have the advantage of scale and the ability to examine implementation and health outcomes in a variety of diverse settings and care delivery contexts.

**Conclusions**

Evidence from observational cohorts has made a central contribution to the development of WHO guidelines, and will continue to do so. Observational data can be especially critical for groups of people who have not been enrolled in randomised trials in addressing a given implementation question, for example, pregnant women and children. Randomised trials are also not generally well suited for assessing rare harms (owing to limited sample sizes and rigorous exclusion criteria), which often only become apparent when a drug is being rolled out. In addition, observational studies provide valuable insights into the feasibility and implementation challenges associated with a given intervention or set of interventions. Finally, increasing attention is being paid to the need to evaluate the uptake and impact of WHO guidelines on critical health outcomes in countries (Figure 1). Observational studies are well suited to evaluating the impact of policy change in routine practice.

The continued contribution of observational data to shaping the response to HIV depends on continued investment in data systems by national programmes and international donors. It has been recommended that 5–10% of all HIV programme budgets be directed towards data collection and use [43]. Sustained investment in the generation and analysis of observational data will make an important contribution to programme performance, as well as helping to inform the global response.

Approaches to data interpretation are being continuously updated to improve the reliability of evidence from observational research. Collaboration between cohorts across different countries can enhance the comparability of findings and their generalisability (provided all findings point in the same direction) or point towards important sources of heterogeneity (if they do not). Advances in statistical software have increased the usage of tools such as multiple imputation to analyse incomplete datasets. Increased use of design and analytical approaches, such as regression discontinuity, difference-in-difference, g-estimation and propensity score methods, have helped achieve more analytical rigour for assessing causal associations and impact, provided the most critical confounders have been directly or indirectly controlled.

The iDeA–WHO partnership [32] is an example of an effective collaboration that can provide valuable insights into whether WHO guidelines are making a difference to outcomes for people living with HIV, and guide how future iDeA analyses can have more policy relevance. The potential to expand this collaboration to cover other disease areas should be explored.

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Conflicts of interest

The authors declare no conflicts of interests.

References

IeDEA–WHO Research-Policy Collaboration: contributing real-world evidence to HIV progress reporting and guideline development

Elizabeth Zaniewski1*, Olga Tymejczyk2,3, Azar Kariminia4, Sophie Desmonde5, Valériane Leroy5, Nathan Ford6, Annette H Sohn7, Denis Nash2,3, Marcel Yotebieng8, Morna Cornell9, Keri N Althoff10, Peter F Rebeiro11 and Matthias Egger1,9

1 Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland
2 Institute for Implementation Science in Population Health, City University of New York, NY, USA
3 Kirby Institute, University of New South Wales, Sydney, NSW, Australia
4 Inserm U1027, Université de Toulouse, Toulouse, France
5 World Health Organization, Geneva, Switzerland
6 Division of Epidemiology, Ohio State University, College of Public Health, Columbus, OH 43210 USA
7 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
8 Vanderbilt University School of Medicine, Nashville, TN, USA

Abstract

Partnerships between researchers and policymakers can improve uptake and integration of scientific evidence. This article describes the research-policy partnership between the International epidemiology Databases to Evaluate AIDS (IeDEA) (www.iedea.org) and the World Health Organization (WHO), which was established in 2014. IeDEA is an international research consortium, which analyses data on almost 2 million people living with HIV under care in routine settings in 46 countries in Asia-Pacific, the Caribbean, Central and South America, North America and sub-Saharan Africa. Five multiregional analyses were identified to inform the WHO on progress towards the second and third 90s of the 90-90-90 targets in adults and children: (i) trends in CD4 cell counts at the start of antiretroviral therapy (ART); (ii) delays from enrolment in HIV care to ART initiation; (iii) the impact of ART guideline changes; (iv) retention in care, mortality and loss to follow-up; and (v) viral suppression within the first 3 years after initiating ART. Results from these analyses were contributed to the 2015 and 2016 WHO global HIV progress reports, will contribute to the 2018 report, and were published in academic journals. The partnership has been mutually beneficial: discussion of WHO policy agendas led to more policy-framed, relevant and timely IeDEA research, and the collaboration provided the WHO with timely access to the latest data from IeDEA, as it was shared prior to peer-review publication.

Keywords: research-policy partnerships, HIV, cohort data, observational data, World Health Organization

Background

Over the past decade, the World Health Organization (WHO) has published a series of global HIV progress reports, documenting the successes and challenges of the massive antiretroviral therapy (ART) scale-up in resource-limited settings that resulted in nearly 21 million people receiving ART by mid-2017 [1–5]. National governments, international donor agencies, and implementing agencies use these reports to assess progress and reorient priorities. The WHO also supports ART scale-up through a series of ART regimens to promoting service delivery models to assist people living with HIV, healthcare workers and country-level policymakers, in making informed decisions about healthcare interventions [6–9].

WHO progress reporting and evidence-based guidelines aim to translate and incorporate the best available research evidence into well-informed guidelines and recommendations [6,7,10]. However, production and dissemination of scientific evidence does not necessarily lead to its integration into policy [11,12]. Partnerships between researchers and policymakers can facilitate and improve uptake and integration of scientific evidence [12–16]. Communication between stakeholders allows researchers to be aware of policy-related evidence gaps and upcoming policy priorities, leading to more pertinent and opportune policy-relevant research [10,14,17]. Such research-policy partnerships can also provide the opportunity for critical information to be communicated rapidly and prior to completion of the often lengthy peer-review and publication process.

This article summarises the process, output and challenges of a research-policy partnership between the International epidemiology Databases to Evaluate AIDS (IeDEA) and the WHO that aims to formalise and facilitate uptake and integration of IeDEA scientific evidence into WHO ART progress reporting and HIV health policy development.

The International epidemiology Databases to Evaluate AIDS (IeDEA)

IeDEA (www.iedea.org) is an international research consortium of HIV cohorts funded by the National Institutes of Health (NIH) since 2006 [18–20]. IeDEA pools existing clinical and epidemiological data on people living with HIV under care in routine settings as a cost-effective way of generating large data sets to address high priority and evolving research questions in HIV/AIDS treatment and care. The seven regions included in IeDEA are: Asia-Pacific; the Caribbean, Central and South America (CCASA); North America; and four regions in Africa (Figure 1). Across these regions, IeDEA has individual-level data on over 1.7 million patients from over 480 clinic and research centres in 46 countries, in both high- and low-HIV burden settings.

*Corresponding author: Elizabeth Zaniewski, Institute of Social and Preventive Medicine, University of Bern, Mittelstrasse 43, CH-3012 Bern, Switzerland
Email: elizabeth.zaniecki@ispm.unibe.ch
leDEA collects routine data from both urban and rural settings, in primary through tertiary care facilities, and from small private clinics to large programmes run by national health systems. Patient information, clinic visit history, laboratory measurements, medications and clinical outcomes are some of the data collected by leDEA regional cohorts. Regional cohorts do not collect data through a single standardised protocol, so leDEA implements a prospective data exchange standard (www.leDEADES.org) for a selection of existing data – based on the HIV Cohorts Data Exchange Protocol (www.hicdep.org) – to facilitate sharing and merging of data across leDEA regions. A series of site assessment surveys obtain up-to-date information on facility policies and procedures and the clinical and support services provided to HIV patients enrolled at leDEA clinics [21–26]. leDEA is also a network of epidemiologists, clinicians, statisticians and data management specialists, who participate in topic-specific working groups to foster collaboration between regional cohorts, facilitate data harmonisation and dissemination, and advance the international HIV scientific research agenda.

The leDEA-WHO collaboration
The leDEA-WHO collaboration was launched at the end of 2014, after more than a decade of ad hoc work between leDEA and the WHO. The WHO was seeking to formally collaborate with leDEA so that up-to-date leDEA data and analyses could contribute in a predictable and sustainable way to WHO annual global HIV progress reporting and guideline development. The WHO wanted to rapidly assess implementation of new HIV policy recommendations, and identify and characterise gaps in the response, which randomised control trials and observational studies based on outdated data cannot address. The leDEA Southern Africa region was awarded an NIH grant supplement to fund a part-time project manager to initiate, plan and develop a formal collaboration between the leDEA consortium and the WHO.

At that time, UNAIDS had just released ambitious 90-90-90 fast-track targets: 90% of all people living with HIV know their status, 90% of those diagnosed with HIV are on sustained ART, and 90% of all people receiving ART are virally suppressed by 2020 [27]. These fast-track targets aimed to improve the HIV cascade of care with the goal of ending the AIDS epidemic as a public health threat by 2030 [27]. In the following year, the WHO released the ‘treat all’ guideline update, recommending immediate ART for all people living with HIV, eliminating prerequisites for initiating treatment [28].

The collaboration commenced with a face-to-face meeting at the WHO headquarters in Geneva, Switzerland in November 2014, where four members of the WHO Department of HIV/AIDS and four investigators of the leDEA Southern Africa team based in Bern, Switzerland, discussed potential collaborative work. Four video conference calls were subsequently held in early February 2015 to discuss analyses that the leDEA consortium could undertake to support the WHO 2015 global HIV progress report. Each call had between 10 and 12 participants from the seven leDEA regions, the NIH-funding institutions and the WHO. Later that month, during the leDEA Scientific Symposium at the Conference on Retroviruses and Opportunistic infections (CROI), attended by more than 20 leDEA investigators representing every leDEA region, the leDEA consortium agreed to undertake this collaboration with the WHO, and identified five core multiregional cascade analyses and the teams that would undertake them. These cascade analyses aimed to inform the WHO on progress towards the 90-90-90 targets, guideline implementation and trends in the epidemic, using routinely collected leDEA programme data (Table 1).

leDEA-WHO analyses
Cohorts cannot provide information on the number of people living with HIV or the number who know their status in their settings, so the collaboration is unable to assess the first 90 (percentage knowing their status). The leDEA collaboration can, however, examine how quickly patients are started on ART after linkage to care and enrolment at their clinics, and how many of those who start ART have stopped treatment (the second 90 target), while those cohorts that collect routine viral load data can also assess the third 90 target. With more than 15 years of
Table 1. Analysis of data from ieDeA to inform progress on 90-90-90 targets

<table>
<thead>
<tr>
<th>90-90-90 target</th>
<th>Analyses performed</th>
<th>Data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First 90:</strong> 90% of all people living with HIV know their status</td>
<td>No data available in ieDeA</td>
<td>None</td>
</tr>
<tr>
<td><strong>Second 90:</strong> 90% of people diagnosed with HIV are on sustained ART</td>
<td>Analyses of CD4 cell counts at the start of ART [29–31]</td>
<td>All seven ieDeA regions, ART-CC, COHERE, NiSDI, PHACS and IMPACT</td>
</tr>
<tr>
<td></td>
<td>Analysis of delays from enrolment in HIV care to ART initiation and the influence and impact of ART guideline changes among adults and children [32,33]</td>
<td>All seven ieDeA regions</td>
</tr>
<tr>
<td></td>
<td>Analysis of retention in care, mortality and loss to follow-up among HIV-infected children and adults on ART [34]</td>
<td>All seven ieDeA regions</td>
</tr>
<tr>
<td><strong>Third 90:</strong> 90% of all people receiving ART are virally suppressed</td>
<td>Analysis of routine viral load data to assess viral suppression among adults and children within the first 3 years after initiating ART [35]</td>
<td>All seven ieDeA regions</td>
</tr>
</tbody>
</table>


longitudinal data and accompanying facility information, ieDeA can monitor and examine temporal trends in patient care uptake and outcomes, and the impact of HIV guideline changes.

Progress towards the second 90 target was evaluated by two multiregional ieDeA-WHO analyses that focused on the pre-ART care cascade, and assessed delays from linkage to and enrolment in HIV care to ART initiation and the influence and impact of ART guideline changes among adults and children, separately [32,33]. The ieDeA West Africa data centre undertook the multiregional analysis that focused on children, and the ieDeA Central Africa data centre performed the multiregional analysis on adults. These analyses were undertaken in 2015, 2016 and 2017. The ieDeA Central Africa team additionally collaborated with the WHO to collect historical data on country-level ART guideline expansions by searching the internet for national ART policies and contacting ieDeA and WHO in-country experts.

A third ieDeA-WHO analysis described retention in care, mortality and loss to follow-up among children and adults living with HIV on ART, and compared outcomes under different ART eligibility guidelines to examine whether people who start ART remain on ART [34]. This multiregional analysis was performed at the ieDeA Southern Africa data centre in 2015, 2016 and 2017. A fourth ieDeA-WHO analysis assessed outcomes in younger (10–14 years of age) and older (15–19 years of age) adolescents to provide insights into long-term retention for the mixed population of perinatally and behaviourally infected youth. The ieDeA Asia-Pacific data centre undertook this analysis in 2016. The last core multiregional analysis of the collaboration used ieDeA routine viral load data to assess viral suppression (<1000 copies/mL) among adults and children within the first 3 years after initiating ART [35]. This multiregional analysis was undertaken in 2015 and 2017 by the ieDeA Asia-Pacific data centre. Additionally, one analysis took advantage of South Africa’s National Population Register, with nearly complete enumeration of deaths and extensive long-term follow-up data of patients on ART, to assess advances in life expectancy over time [36]. The ieDeA Southern Africa data centre performed this analysis in 2015 using data from South African cohorts.

Since the ieDeA-WHO collaboration began, ieDeA has produced 12 multiregional analyses and one region-specific analysis – an average of four analyses per year using newly reported ieDeA data. The WHO received a summary report for each analysis within 6 months from data collection. Over the years, these analyses have supported three WHO global progress reports. Several analyses have also supported the development of WHO guidelines; these are summarised in a separate article in this supplement [37].

Project organisation and management

More than 65 ieDeA regional investigators across the seven ieDeA regions, 10 representatives of the NIH funding institutions, and nine WHO staff members have been involved with this collaboration since its inception. The collaboration project manager liaised between the ieDeA network and the WHO, and provided updates on work and progress in monthly ieDeA working group conference calls and by email. ieDeA held project debriefs to discuss and evaluate the process and work of the collaboration following publication of the annual WHO progress reports.

ieDeA multiregional data are only available after review and approval of a concept proposal by the ieDeA Executive Committee. This committee is composed of principal investigators from the seven ieDeA regions and representatives of the NIH funding institutions, including the National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver Institute on Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health and the National Institute on Drug Abuse. For each iteration of the above analyses, ieDeA, in consultation with the WHO, drafted new concept proposals that were reviewed by the ieDeA Strategic Data Working Group (WG) prior to submission to the Executive Committee. The Strategic Data WG holds monthly conference calls to promote and guide ieDeA multiregional research conducted in collaboration with external partners, and consists of representatives from each ieDeA region and programme staff from the NIH and the WHO. Following Executive Committee approval, the concept proposal teams worked with the ieDeA Data Harmonization WG, comprised of ieDeA regional data managers and analysts, to clarify data elements and organise data transfer.

To help navigate, streamline and facilitate ieDeA procedures, a timeline was drafted, outlining deliverables and deadlines to ensure research occurred in a timely manner and aligned with the timeline for the development of annual WHO Progress Reports. ieDeA also undertook efforts to synchronise and increase the frequency of data collection to ensure that the most up-to-date data were available for these purposes.
Reports and publications

The results from the iDeA-WHO collaboration analyses were presented in two WHO reports and several academic publications. The *Global health sector response to HIV, 2000–2015: focus on innovations in Africa* was published in November 2015 [3]. The report relied on evidence produced by the iDeA-WHO collaboration to highlight gaps between HIV diagnosis and treatment initiation. Evidence on over 800,000 adults from 10 African countries enrolled in iDeA clinics from 2004 to 2014 showed that over 22% of adults were lost to follow-up before initiating ART. Despite this shortfall, iDeA data indicated a steady shift towards earlier enrolment in HIV care as illustrated in a graph showing increasing median CD4 cell count at enrolment in HIV care across iDeA programmes from 2004 to 2014. The report stressed the importance of retention in care and the need to retain more people on ART. It highlighted another collaboration analysis that found only 45% of adults on ART in iDeA achieved viral suppression after 3 years, increasing to over 92% when excluding deaths to follow-up and deaths. A graph showing the declining proportion of people on ART retained in care during the first 5 years, and across iDeA regions, provided further evidence of high attrition (Figure 2).

The 2016 WHO global HIV progress report *Prevent HIV, test and treat all – WHO support for country impact*, published in November 2016, focused on the latest WHO recommendation to initiate all people living with HIV on ART regardless of CD4 cell count or clinical stage [4]. This report highlighted key gaps in achieving the ‘treat all’ recommendation, including linkage from testing to treatment, citing the iDeA-WHO collaboration’s latest findings on delays from enrolment in HIV care to ART initiation in adults. Despite these challenges, the report found people have been starting ART earlier and at higher CD4 cell counts, as illustrated in a figure showing increasing median CD4 cell count at ART initiation in iDeA clinics up to 2015 (Figure 3). This report also highlighted another collaboration analysis as evidence that a high level of viral suppression can be achieved, even in resource-limited settings.

At present, the collaboration is undertaking four multiregional cascade analysis updates to assess the impact of recent guideline change and progress towards the 90-90-90 targets across all age groups, to support the 2018 WHO global progress report that is currently under development for release at the end of 2018.

Beyond supporting WHO, these analyses have also generated 14 abstracts presented at international research conferences, including the International Workshop on HIV and Hepatitis Observational Databases (IWHOD), CROI, the International AIDS Society conferences, and Australian HIV and AIDS conferences. Several collaborative analyses have also been published in peer-reviewed journals including AIDS, *Journal of Acquired Immune Deficiency Syndromes*, *Journal of the International AIDS Society* and *PLoS Medicine* [32–36].

**Discussion**

Over the past 4 years, iDeA has produced 13 analyses based on iDeA multiregional cohort data to support WHO HIV guideline development and ART progress reporting. Evidence from iDeA contributed to the 2015 and 2016 WHO global HIV progress reports and two WHO HIV guideline updates. Research evidence from these analyses also informed audiences outside of the WHO. Fourteen oral abstract presentations and posters were presented at international HIV conferences and workshops. The five core analyses and the one regional analysis have also resulted in five peer-reviewed publications [32–36].

The iDeA-WHO collaboration is an example of a research-policy partnership overcoming barriers that often hinder the rapid uptake and integration of research evidence into policy development [12,14,16,38]. Increased interaction and regular communication strengthened links between iDeA and WHO, as each became more aware of how iDeA could be a resource to WHO and vice versa. Opportunities for discussion of upcoming WHO policy agendas led to more policy-framed, relevant and timely iDeA research. The science has also been strengthened through this opportunity for the WHO and iDeA research teams to communicate on the strengths and weaknesses of reporting indicators. The collaboration also provided the WHO with more timely access to the latest iDeA scientific evidence, as it was shared with them prior to peer-review publication. Efforts to synchronise and accelerate data extraction in iDeA resulted in more timely and up-to-date data that benefited the collaboration work as well as

![Figure 2. iDeA evidence included in WHO Global Health Sector Response to HIV, 2000–2015: Focus on Innovations in Africa, published November 2015 [3]. Retention rates of people on ART in the first 5 years after initiating ART between 2009 and 2014 in iDeA.](image-url)
other multiregional research. The collaboration timelines ensured iDEA procedures were navigated efficiently, allowing analyses to be completed annually. This research-policy partnership provided a unique opportunity for the WHO to monitor current implementation progress of their action-oriented guidelines and for iDEA to produce more innovative policy-relevant observational research evidence.

Although iDEA successfully produced and shared multiregional analyses with WHO, combining large volumes of data from such a wide range of settings on tight timelines can present a number of challenges. Issues of missing data on key variables, and varying definitions and data collection protocols, led to a duplication of time-consuming data cleaning efforts undertaken simultaneously by research teams. Inconsistent data distribution and a large variability in the volume of data across regions, due to the uneven burden of disease and temporal trends, limited the ability to provide region-specific and age-specific stratified estimates, complicating the interpretation of findings. Service delivery models, clinical protocols, standards of care, monitoring schedules and efforts in place to trace patients lost to follow-up also vary widely. The tight timeline dictated by the WHO publication schedule increased and concentrated the workload of iDEA regional data managers responsible for preparing and transferring data for up to five separate research proposals requesting varying data elements and eligibility criteria within the same timeframe, and alongside other regional and multiregional data requests, each year. However, engagement with WHO also highlighted areas where iDEA and its data workflows could be improved or made more efficient.

Data and structural challenges experienced in this collaboration with WHO propelled iDEA to develop and implement improvements to expand and increase data collection and analytic capacity. The Strategic Data WG was established in the second year of the collaboration to facilitate regular dialogue between the iDEA network and the WHO through monthly teleconference calls. Data harmonisation improvements were undertaken to ensure iDEA data standards were up-to-date and met current multiregional research needs. The iDEA data exchange standard (www.iDEADES.org) was translated from paper format to an online research electronic data capture (REDCap) database to simplify, coordinate and accelerate updates across multiple platforms, and enable faster and better data exchange and collaborative research [39]. In response to the growing number and frequency of multiregional concept proposals, iDEA developed an online review hub to simplify, streamline and expedite the concept proposal review and approval process for multiregional research.

Limitations of the data have led iDEA researchers to develop methods and approaches to improve the reliability of findings. For example, loss to follow-up can be substantial in ART programmes with unknown outcomes for patients lost. Analyses of programme-level outcomes that are based on patients retained in care may be biased in this situation [40]. iDEA researchers developed novel approaches and tools to correct estimates of programme-level mortality for loss to follow-up, taking into account the results of tracing of patients who were lost to follow-up [29,41–44]. For instance, a study in an iDEA site in Malawi found that among patients lost to follow-up, and found to be alive on tracing, a majority (56%) were still taking ART, sourced from another clinic [45]. Figure 4 shows the results from a recent attempt to adjust ART programme-level outcomes for unrecorded deaths and transfers among patients lost to follow-up [34]. In South Africa, iDEA investigators took advantage of the nearly complete recording of deaths and linked birth, laboratory and death registries to improve mortality outcome information among patients lost to follow-up [46]. Some iDEA regions have now implemented standardised tracing efforts to bring patients back to care and to ascertain outcomes of patients lost to follow-up. In the analysis of global trends in CD4 cell count at the start of ART, multiple imputation was used to deal with missing CD4 cell counts at the start of ART [47]. In the same analysis [47], estimates for World Bank country income groups were weighted by the number of patients starting ART in a given country and year (as reported by UNAIDS [48]), so that countries with many patients were appropriately represented.

Now 12 years old, the iDEA consortium is uniquely positioned to provide operational and clinical research that is highly relevant to WHO policy development and progress reporting. With close to two million patients from nearly 500 sites in 46 countries, including both high- and low-HIV burden settings and across a range of contexts, iDEA can assess outcomes at both the

Figure 3. iDEA evidence included in the WHO Progress Report 2016 [4]: Prevent HIV, Test and Treat all – WHO support for country impact. Median CD4 cell count at ART initiation among adults by iDEA regions over time.
Figure 4. iaDEA evidence from the iaDEA-wHO collaboration: Cumulative incidence of antiretroviral therapy outcomes among adults. Panel A: outcomes recorded in clinic databases. Panel B: outcomes adjusted for unrecorded deaths and transfers among patients lost to follow-up. Reproduced from Haas et al. [34].

Conclusion

The research-policy collaborative partnership between iaDEA and wHO allows for a better understanding of current policy priorities and data and research limitations, leading to more well-timed and policy-relevant research. Regular communication provides a pathway to facilitate and expedite exchange of crucial knowledge and scientific evidence prior to peer-reviewed publication. Such partnerships that promote dialogue between stakeholders should be encouraged, to facilitate and improve uptake and integration of research evidence, to provide timely and reliable insights into progress and challenges in the global response to HIV, and to support the development of health policy.

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References


Mental health and HIV: research priorities related to the implementation and scale up of ‘treat all’ in sub-Saharan Africa

Angela M Parcesepe1,2,*, Charlotte Bernard1,4, Robert Agler3, Jeremy Ross9, Marcel Yotebieng7, Judith Bass6, Edith Kwobah8, Adeola Adedeji10, Joseph Goulet11,12 and Keri N Althoff3

1Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
2Institute for Implementation Science in Population Health, City University of New York, NY, USA
3Bordeaux Population Health Research Center, University of Bordeaux, INSERM, Bordeaux, France
4INSERM, ISPED, Bordeaux Population Health Research Center, Bordeaux, France
5Department of Psychology, Ohio State University, Columbus, OH, USA
6TREAT Asia, amFAR - The Foundation for AIDS Research, Bangkok, Thailand
7College of Public Health, Division of Epidemiology, Ohio State University, Columbus, OH, USA
8Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
9Department of Mental Health, Moi Teaching and Referral Hospital and Moi University, Eldoret, Kenya
10Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
11Yale School of Medicine, Department of Emergency Medicine, New Haven, CT, USA
12VA Connecticut Healthcare System, West Haven, CT, USA
13Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Abstract

World Health Organization (WHO) guidelines call for antiretroviral therapy (ART) for all people living with HIV (PLWH) regardless of CD4 cell count, a policy often referred to as ‘treat all’. This article seeks to: (1) provide an overview of mental health research among PLWH in sub-Saharan Africa (SSA) and interventions or strategies to address comorbid mental illness among those living with HIV; and (2) describe key mental health-related recommendations to inform the successful implementation and scale up of ‘treat all’ policies in SSA. An initial set of mental health-related research recommendations was developed by a working group comprising investigators affiliated with the International epidemiology Databases to Evaluate AIDS (iDeA) consortium. Recommendations were shared with those who attended the All-Africa iDeA Meeting in Kigali, Rwanda in November 2017 and refined following the meeting. Recommendations reflect a need for epidemiological research to examine the prevalence, incidence, and impact of mental health multimorbidities on HIV treatment outcomes, intervention research to examine the extent to which improving the mental health of people living with HIV enhances HIV treatment outcomes, and implementation science research to evaluate promising models of integrated mental health and HIV care. Key research recommendations can advance understanding and treatment of mental illness among those living with HIV in sub-Saharan Africa and beyond.

Keywords: mental health, HIV, Africa, treat all

The World Health Organization (WHO) guidelines call for antiretroviral therapy (ART) for all people living with HIV (PLWH) regardless of their CD4 T cell count, a policy often referred to as ‘treat all’. ‘Treat all’ strategies, increasingly common in low-resource settings, are motivated by evidence that treating HIV as soon as possible after infection can improve patient outcomes and reduce transmission [2,3]. Large-scale success of the implementation and scale-up of ‘treat all’ requires understanding and addressing known barriers to achieving optimal HIV treatment outcomes. Insufficient attention has been paid to identifying and addressing the mental health needs of PLWH, particularly in sub-Saharan Africa (SSA), a region that accounts for more than 70% of the global burden of HIV [4]. Because mental health disorders are common among PLWH, often underdiagnosed and undertreated in low-resource settings, and associated with suboptimal HIV treatment outcomes, addressing the mental health needs of those living with HIV should be a critical component of successful implementation, scale-up, and achievement of ‘treat all’ priorities in SSA and beyond [5–11]. This article seeks to: (1) provide an overview of research regarding the mental health of PLWH in SSA and interventions and strategies to address comorbid mental illness among PLWH and (2) describe key mental health-related research priorities to inform the successful implementation and scale up of ‘treat all’ policies in SSA and other low-resource settings. Because substance use disorders are the focus of a separate paper in this supplement [12], such disorders are not addressed in this article.

Mental health disorders among PLWH

Mental health disorders (e.g. depression, post-traumatic stress disorder [PTSD]) are among the most prevalent comorbidities in PLWH globally and more common among PLWH than the general population [5,13,14]. It has been estimated that approximately half of PLWH meet criteria for one or more mental health disorder [5]. High rates of mental health disorders have been documented among PLWH residing in low- and middle-income countries (LMICs), including SSA [14]. Research suggests that these are associated with delayed HIV diagnosis [15], and with suboptimal HIV treatment outcomes, including late ART initiation, poor ART adherence, lack of viral suppression, and increased AIDS-related mortality across LMICs [15,16].

It is important to note that most studies focused on the mental health of PLWH in SSA and globally do not distinguish between pre-existing mental health disorders among PLWH and mental health disorders with an onset subsequent to HIV infection or its diagnosis. Two studies from South Africa have revealed that an important proportion of HIV test seekers experience mental health symptoms prior to their diagnosis. In the first, 55% of individuals surveyed displayed depressive symptoms prior to HIV testing and individuals with depressive symptoms prior to HIV
diagnosis were less likely to receive CD4 cell count testing after diagnosis [17]. In the second, the prevalence of major depressive disorder, generalised anxiety disorder and PTSD among HIV test seekers was 14%, 5% and 5%, respectively [18]. Additional longitudinal research is needed to better understand the course and severity of mental health disorders among PLWH in relation to HIV infection, diagnosis, and treatment.

Depression
Depression is the most prevalent mental health disorder among PLWH globally and in SSA [5,19,20]. Estimates of depressive symptoms among PLWH on ART in SSA have varied between 14% and 32%, with substantial variability within and between measurement scales [21]. A meta-analysis of studies conducted in Western countries found the prevalence of major depressive disorder to be nearly two-fold higher among PLWH compared to those who did not have HIV [22].

Little is known about the relationship between depression and delayed HIV diagnosis in SSA. However, depression has been associated with suboptimal HIV treatment outcomes in SSA, including late ART initiation and poor adherence, lack of viral suppression, more rapid decline in CD4 cell count, faster progression to AIDS and increased AIDS-related mortality [8,9,23]. Similar to other mental health disorders, depression remains underdiagnosed and undertreated throughout SSA, compromising timely ART initiation and treatment adherence at individual and population levels, and attainment of ‘treat all’ objectives [10,11,23].

Anxiety disorders
Estimates of the prevalence of anxiety-related symptoms or anxiety disorders among PLWH in SSA have varied between 9% and 34% [5,24] compared to 3–7% among general populations throughout SSA [25].

Among PLWH in South Africa, anxiety was significantly associated with delayed engagement in HIV care following diagnosis, but not significantly associated with ART adherence [11,24]. Little is known about the relationship between anxiety symptoms or diagnoses and viral suppression or HIV disease progression in SSA. In high-income settings, anxiety symptoms have been associated with poor adherence to ART, higher viral load and lower CD4 cell count [26,27].

Post-traumatic stress disorder
Exposure to traumatic events in childhood and adulthood, including child physical and sexual abuse, intimate partner violence, sexual assault, and war is also prevalent among PLWH and associated with mental health disorders and suboptimal HIV treatment outcomes [28]. Estimates of PTSD among PLWH in SSA are limited and vary widely. Studies conducted with PLWH in South Africa estimated PTSD prevalence at 5–20% [29,30] compared to approximately 2% among the general population [31,32].

Little is known about the relationship between PTSD and ART initiation, care engagement, or HIV disease progression globally and throughout SSA [5]. Findings regarding the relationship between PTSD and ART adherence remain equivocal [33,34].

Bipolar disorder and psychotic disorders
Estimates of the prevalence of bipolar disorder and psychotic disorders such as schizophrenia among PLWH in SSA are largely lacking. However, one study of PLWH in South Africa estimated a prevalence of bipolar disorder of 6% while a study with PLWH in Nigeria found a prevalence of psychotic disorders of 6% [35,36]. Estimates of bipolar disorder among the general population in SSA are largely unavailable. However, estimates of bipolar disorder among the general population across 11 countries in the Americas, Europe and Asia range from 0.4% to 2% [37]. Little is known about the relationship between bipolar disorder or psychotic disorders and HIV treatment outcomes in SSA. One study with PLWH in Uganda found that serious mental illness at ART initiation was associated with worse retention in HIV care [38]. While limited, research in high-income settings has found bipolar disorder to be associated with poor ART adherence [39,40].

Psychiatric multimorbidity
Among individuals with mental health disorders, psychiatric multimorbidity (i.e. having more than one concurrent mental health or substance use disorder) is common and associated with greater symptom severity and worse health outcomes. Among PLWH in the US with a past-year mental health disorder, half met criteria for multiple mental health diagnoses [41]. Co-occurring mood and anxiety disorders and co-occurring mood and substance use disorders were particularly common. In the US, psychiatric multimorbidity has been associated with greater HIV symptomology and worse quality of life [42]. Among veterans living with HIV in the US, multimorbidity (co-occurring substance use disorder, psychiatric disorder, and medical disease) was associated with having a detectable viral load [43]. Research into the prevalence and impact of psychiatric multimorbidity among PLWH in SSA and other low-resource settings is particularly limited.

Mediators and moderators of the relationship between mental health disorders and HIV treatment outcomes
Several factors have been found to mediate or moderate the relationship between mental health and HIV treatment outcomes among PLWH in SSA including ART adherence, HIV care self-efficacy and motivation, among others. Research with PLWH in Uganda found that cognitive and affective (e.g. depressed mood and loss of interest in activities that are normally pleasurable), but not somatic symptoms of depression (e.g. fatigue, difficulty sleeping) were associated with ART adherence [44]. Furthermore, depression alleviation was associated with improved ART adherence and HIV clinic attendance among this population [44]. HIV care self-efficacy and adherence motivation have been found to mediate the relationship between depression and ART adherence among PLWH in SSA [44]. In high-income settings, integrated interventions that address depression and ART adherence have been effective at improving both depression and ART adherence [45].

Priority populations
UNAIDS has identified ambitious treatment goals of having 90% of PLWH know their HIV status, 90% of those diagnosed with HIV receiving ART, and 90% of those on ART virally suppressed by 2020 [46]. The identification and treatment of mental health disorders may be of particular importance in the successful attainment of 90–90–90 goals among specific priority or underserved populations, including children and adolescents living with HIV, pregnant and postpartum women living with HIV, and additional key populations living with HIV, including men who have sex with men, sex workers and transgender individuals.

Children and adolescents living with HIV
Adolescence represents a period of particular vulnerability among PLWH. Among the general population, most mental health disorders first emerge during adolescence and are associated with
poor physical and mental health in adolescence and into adulthood [47]. In addition, adolescents living with HIV are often in transition to adult care and may be particularly vulnerable to disruptions and disengagement from HIV care. While limited, research indicates that many adolescents living with HIV experience mental health disorders and may have higher prevalence of mental health disorders than adolescents without HIV [48,49]. Studies of children and adolescents living with HIV in SSA have estimated the prevalence of depression to be 18–25% [50–52]. A study of children and adolescents living with HIV in Kenya found that the prevalence of anxiety disorders to be 32% [50]. Comparative research examining the mental health of children and adolescents with and without HIV in SSA is rare. However, a study of children and adolescents in Rwanda found that HIV-affected children (i.e. children who are living with HIV, living with a caregiver who has HIV, or had a caregiver who died from HIV) had a significantly higher likelihood of depression, anxiety, and conduct disorder compared to HIV-unaffected children and adolescents [53]. However, there was no significant difference in the likelihood of mental health problems between children who were living with HIV and those who did not have HIV [53].

Similar to adults living with HIV, symptoms of depression and anxiety among adolescents living with HIV have been associated with worse HIV treatment outcomes, including poor ART adherence and lack of viral suppression, and greater HIV sexual risk behaviour [49]. However, most research on the relationship between adolescent mental health and HIV treatment outcomes has been conducted in high-income countries [54]. More research is needed to understand the prevalence and impact of mental health disorders among adolescents living with HIV in SSA and how to effectively identify and address these disorders in this population.

Pregnant and postpartum women living with HIV

Pregnancy and the postpartum period represent periods of vulnerability among women living with HIV during which mental health disorders are common. Mental health disorders are more common among pregnant women living with HIV compared to pregnant women in the general population [55]. In non-African settings, perinatal depression (i.e. depression occurring during pregnancy or the postpartum period) has been associated with non-adherence to ART [56]. Few studies have examined the effects of perinatal depression on HIV treatment outcomes among women in SSA. Among women newly diagnosed with HIV in the Democratic Republic of Congo, antenatal depression (i.e. depression occurring during pregnancy) was not associated with engagement in HIV care [57]. Factors associated with perinatal depression among women living with HIV in SSA remain poorly understood. Identifying and addressing mental health disorders among women during pregnancy and the postpartum period has the potential to improve HIV outcomes among women living with HIV, reduce vertical transmission of HIV, and foster attainment of ‘treat all’ objectives among mothers and children. Data on other mental health disorders among women living with HIV in SSA during pregnancy and the postpartum period are largely unavailable. One study found that pregnant women living with HIV in South Africa had significantly higher levels of anxiety compared to pregnant women without HIV [58]. Additional research on mental disorders beyond depression among women living with HIV during pregnancy and the postpartum period is warranted.

Additional key populations living with HIV

Little is known about the mental health of additional key populations living with HIV in SSA, including sex workers, men who have sex with men and transgender individuals. Research from outside SSA indicates that mental health symptoms and disorders are common among these key populations and more common among young key populations than older key population peers [59–62]. Research with key populations in high-income countries suggests that mental health symptoms are associated with increased risk of HIV acquisition and suboptimal HIV treatment outcomes [59,60]. Little is known about the extent to which poor mental health influences HIV treatment outcomes among key populations living with HIV in SSA.

Systems interventions and strategies to address co-morbid mental illness among PLWH

Despite the prevalence of mental health disorders among PLWH in SSA and associations with suboptimal HIV outcomes, many HIV providers neither screen nor treat patients for mental health disorders, contributing to underdiagnosis of mental health disorders and a substantial mental health treatment gap among PLWH [63,64]. Numerous factors contribute to challenges identifying and treating PLWH with mental health disorders in SSA including: a substantial mental health workforce shortage, especially in rural areas; limited time available in HIV and primary care settings; limited mental health training of HIV and primary care clinicians; few validated and culturally appropriate screening and diagnostic tools for mental health disorders; limited availability of psychiatric medications; competing priorities; and poor integration of mental health services into HIV care [5,23,65].

Integrating mental health care into HIV care has been identified as a promising strategy for improving the mental health and HIV treatment outcomes of PLWH in SSA and may facilitate attainment of ‘treat all’ objectives [63]. More research is needed into the feasibility, acceptability and effectiveness of models of integrated mental health and HIV care throughout SSA. The scale up and implementation of ‘treat all’ objectives adds challenges to already overburdened health systems (e.g. increased workload) in SSA that must be better understood [66]. The Mental Health Gap Action Programme (mhGAP), published in 2008 and updated in 2015, provides evidence-based guidelines for diagnosis and management of priority mental health conditions in non-specialised health settings and presents a promising model for integration of mental health care into HIV care in SSA [67]. Integration of the mhGAP into primary care in Nigeria was associated with increased identification, treatment, and referral for mental health disorders [68]. To the authors’ knowledge, the feasibility, acceptability or effectiveness of integrating mhGAP specifically into HIV care settings in SSA has not yet been evaluated. The Programme for Improving Mental Health Care (PRIME) is a multi-country initiative evaluating the implementation and scale up of mental health services in primary and maternal health care settings in Ethiopia, India, Nepal, South Africa and Uganda [69]. Results from this work are forthcoming and will contribute to the knowledge base regarding the implementation and scale up of evidence-based mental health care in non-specialty settings in LMICs.

Task-shifting and task-sharing have emerged as promising strategies to increase access to evidence-based mental health care in SSA. Evidence suggests that mental health screening, evaluation and pharmacological interventions can be effectively implemented by non-specialists in SSA when appropriate training, supervision and mentorship are available [70,71]. Evidence also indicates that psychological interventions can be effectively delivered in non-specialty settings and by lay health workers in SSA. Randomised trials of the Friendship Bench intervention in Zimbabwe in which trained, supervised lay health workers delivered individual problem-solving therapy in primary care, found that the intervention was
associated with significant improvement in symptoms of depression and other common mental health disorders [72,73]. While integration of this intervention into HIV care has not yet been evaluated, previous trials were conducted among a population with high HIV prevalence [74,75]. Although this intervention has been shown to improve depressive symptoms, the extent to which this intervention impacts HIV treatment outcomes remains unknown.

Individual- and group-level interventions to improve outcomes among PLWH with mental health disorders

Evidence-based, individual- and group-level mental health interventions offer promising strategies to manage mental health disorders among PLWH and improve health and HIV treatment outcomes. Their implementation and scale up in SSA may begin to address the mental health treatment gap among PLWH.

Depression

Pharmacological interventions have been implemented by non-specialists in SSA. A pilot trial of a measurement-based care (MBC) approach to antidepressant medication management trained non-specialists to screen and monitor depression symptoms in an HIV treatment setting in Cameroon. This study found that the intervention was associated with improvements in depression symptoms and HIV treatment outcomes [71,76]. A cluster randomised trial in Uganda compared two task-shifting models of pharmacological depression care: a structured protocol model and a model focused on clinical acumen [70]. The two models performed similarly in the prescription of antidepressants to clinically depressed participants. However, those who screened positive for depressive symptoms were significantly more likely to receive a diagnostic evaluation in the structured protocol arm as compared to the clinical acumen arm [70].

Group interpersonal psychotherapy (IPT-G), recommended by the WHO, has been successfully adapted for delivery in LMICs and has demonstrated effectiveness at reducing depression [77,78]. The effectiveness of IPT-G should be evaluated with PLWH in SSA. A group support psychotherapy intervention for depression among PLWH in Uganda has also been associated with lower mean depression scores; changes in HIV treatment outcomes were not reported [79]. Cognitive behavioural interventions have also demonstrated effectiveness in LMICs [80]. Research in the US found that integrating evidence-based treatment for depression and evidence-based adherence counselling improved adherence and depression among PLWH [45]. Similar research is needed with PLWH in SSA.

Anxiety disorders

Although selective serotonin reuptake inhibitors (SSRIs) are a common and effective treatment for anxiety disorders in middle- and high-income countries, access to SSRIs and health professionals trained to prescribe SSRIs are limited in SSA. One US-based study reported 66% of medications prescribed for anxiety among PLWH were benzodiazepines [81]. Benzodiazepines should be used cautiously due to their potential for abuse. To our knowledge, there are no published studies of pharmacological, psychotherapeutic or behavioural interventions for anxiety disorders among PLWH in SSA.

Post-traumatic stress disorder

Little is known regarding the effectiveness of interventions for PTSD among PLWH in LMICs. A review of psychological interventions for PTSD among PLWH in resource-poor settings identified seven such studies, six of which used cognitive behavioural therapy and none of which was conducted in SSA [82].

Children and adolescents living with HIV

Few evidence-based mental health interventions have been studied with children or adolescents living with HIV in SSA. One intervention that shows promise is the VUKA family-based programme, which has been implemented with pre-adolescents living with HIV and their caregivers in South Africa [83]. A pilot found that the intervention was associated with improved mental health and ART adherence [83].

Pregnant and postpartum women living with HIV

Similarly, few evidence-based mental health interventions have been studied with pregnant or postpartum women living with HIV in SSA. A randomised controlled trial (RCT) of a group counselling intervention which used a problem-solving therapy approach was associated with a marginally significant reduction in depression compared to standard of care (i.e. pre- and post-test voluntary counselling and testing for HIV and information on how to access prevention of vertical transmission of HIV services) among pregnant women living with HIV in Tanzania [84].

Additional key populations living with HIV

The effectiveness of mental health interventions with additional key populations living with HIV in SSA remains largely unknown. However, an RCT of a cognitive behaviour therapy intervention for ART adherence and depression was conducted with PLWH who had depression and were in treatment for injection drug use in the US [85]. The intervention was significantly associated with improvements in depression, ART adherence, and CD4 cell count post treatment. Similar research is needed with key populations living with HIV in SSA.

Key research priorities to improve the mental health and HIV treatment outcomes of PLWH with mental health disorders in SSA

Numerous research gaps exist in our understanding of how to effectively identify and manage mental health needs and optimise HIV treatment outcomes of PLWH in SSA. The authors recommend the following mental health-related research priorities to inform effective and efficient scale up and implementation of ‘treat all’ in SSA and beyond.

- Research is needed to advance understanding of the prevalence and incidence of mental health multimorbidities among PLWH and their impact on HIV treatment outcomes. Greater understanding of the prevalence of mental health symptoms and disorders among PLWH in SSA compared to people without HIV is also needed. Longitudinal studies that examine the onset and trajectory of mental health symptoms and disorders in relation to HIV infection, diagnosis and treatment are needed in SSA.
- Factors, such as ART adherence, that mediate or moderate the relationship between mental health and HIV treatment outcomes should be evaluated as potential intervention targets to improve mental health and HIV treatment outcomes among PLWH with mental health disorders. Additional mediators and moderators of the relationship between mental health and HIV treatment outcomes should be identified and evaluated as potential intervention targets.
- Research is needed to understand the prevalence, incidence, impact and treatment of mental health disorders among children and adolescents living with HIV in SSA. Such research should include the examination of whether, and in what ways,
the burden and impact of mental health disorders among children and adolescents living with HIV varies between children and adolescents who acquired HIV perinatally or behaviourally. In addition, research is needed to understand the burden and impact of mental health disorders among children and adolescents living with HIV compared to both HIV-affected (but not infected) children and adolescents in SSA as well as HIV-uninfected and uninfected children and adolescents in SSA.

- Research to examine the prevalence of and factors associated with mental health disorders during pregnancy and the postpartum period among women living with HIV is needed. Interventions to optimise mental health and HIV treatment outcomes among this population should be developed, implemented and evaluated. Such research should examine mental health disorders beyond perinatal depression, including perinatal anxiety disorders.

- Research to examine the prevalence of and factors associated with mental health disorders among key populations living with HIV is needed. Research that examines the extent to which mental health disorders influence HIV treatment outcomes among key populations living with HIV in SSA is needed. Interventions to optimise mental health and HIV treatment outcomes among sex workers, men who have sex with men, transgender individuals and other key populations should be developed, implemented and evaluated. The effectiveness of mental health interventions with such key populations living with HIV in SSA warrants investigation.

- The effectiveness of promising strategies to address psychiatric multimorbidity, such as a common elements treatment approach, a transdiagnostic intervention developed to treat mood and/or anxiety disorders in low-resource settings, needs to be evaluated among PLWH at critical points throughout HIV treatment.

- Intervention research is needed to understand the extent to which improving the mental health of PLWH improves HIV treatment outcomes. Research has consistently found that mental health disorders are associated with suboptimal HIV treatment outcomes. However, less is known about whether improvement in one’s mental health is associated with subsequent improvement in HIV treatment outcomes. Research is needed that examines the relationship between improvements in symptoms and severity of mental health disorders among PLWH and improvements in HIV treatment outcomes including uptake in HIV care, adherence to ART, immunological response and sustained viral suppression. Research that examines mechanisms through which changes in mental health are associated with changes in HIV treatment outcomes is also warranted. Such research should incorporate longer-term follow-up when possible to examine intervention sustainability and long-term effectiveness.

- Promising models of integrated mental health and HIV care should be implemented and evaluated. Although screening and treatment for mental health conditions are limited in many healthcare settings in SSA and globally [86], the integration of mental health care into HIV testing and care settings must be a priority. The International AIDS Society supports integrated healthcare systems as an important element of not only strengthening the HIV response, but also advancing global health [87]. There is a critical need for research to identify effective and efficient strategies to integrate mental health interventions into HIV service delivery programmes in the context of ‘treat all’ implementation. Implementation research is needed to more fully understand multilevel (e.g., patient-, provider-, and systems-level) barriers and facilitators to integrating mental health care into HIV care in the context of ‘treat all’ and to develop and evaluate strategies to address identified barriers. To address barriers to ART adherence and reach the 90-90-90 objectives, screening and treatment of mental health disorders is necessary at HIV diagnosis and throughout the patients’ life. Screening and treatment protocols for mental health disorders that can be integrated into HIV treatment and implemented by non-specialists need to be developed, implemented and evaluated. Strategies to effectively supervise non-specialists delivering mental health interventions with PLWH and to strengthen health systems to effectively integrate mental health care into HIV are also needed.

Conclusion

Key mental health-related recommendations have been identified to advance understanding and treatment of mental health disorders among PLWH and attainment of ‘treat all’ objectives in SSA and beyond. Key recommendations include a call for epidemiological research to examine the prevalence and impact of mental health multimorbidities on HIV treatment outcomes, intervention research to examine the extent to which improving the mental health of people living with HIV improves HIV treatment outcomes, and implementation research to evaluate promising models of integrated mental health and HIV care.

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Adult site investigators and study teams:

PS Ly* and V Khol, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; FJ Zhang* ‡, HX Zhao and N Han, Beijing Ditan Hospital, Capital Medical University, Beijing, China; MP Lee*, PCK Li, W Lam and YT Chan, Queen Elizabeth Hospital, Hong Kong, China; N Kumarasamy*, S Saghayam and C Ezhilaras, Chennai Antiviral Research and Treatment Clinical Research Site (CART CRS), YRGCARE Medical Centre, VHS, Chennai, India; S Pujari*, K Joshi, S Gaikwad and A Chitalikar, Institute of Infectious Diseases, Pune, India; TP Merati*, DN Wirawan and F Yuliana, Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia; E Yunihastuti*, D Imran and A Widhani, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia; J Tanuma*, S Oka and T Nishijima, National Center for Global Health and Medicine, Tokyo, Japan; JY Choi*, Na S and JM Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University, Seoul, South Korea; BLH Sim*, YM Cani, and R David, Hospital Sungai Buloh, Sungai Buloh, Malaysia; A Kamarulzaman*, SF Syed Omar, S Ponpammalavanar and I Azwa, University Malaya Medical Centre, Kuala Lumpur, Malaysia; R Ditanggo*, E Uy and R Bantique, Research Institute for Tropical Medicine, Manila, Philippines; WW Wong* †, WW Ku and PC Wu, Taipei Veterans General Hospital, Taipei, Taiwan; DTK Khoo, AN Pham, and LT Nguyen, National Hospital of Pediatrics, Hanoi, Vietnam; ON Le, Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam; AH Sohn*, JL Ross, and C Sethaputra, TREAT Asia/amfAR – The Foundation for AIDs Research, Bangkok, Thailand; MG Law* and A Kariminia, The Kirby Institute, UNSW Australia, Sydney, Australia; (‡) Steering Committee members; † Current Steering Committee Chair; ‡ co-Chair.

Central Africa (CA-IeDEA)

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Site investigators and cohorts:

Nimbona Pélagie, ANSS, Burundi; Patrick Gateretse, Jeanine Munezero, Valentin Nitereka, Théodore Nyongobgo, Christelle Twizere, Centre National de Référence en Matière de VIH/SIDA, Burundi; Hélène Bukuru, Thierry Nahimana, CHUK, Burundi; Jérémie Biziaquesenyuka, Risa allé Scalistique Manyundo, HPRC, Burundi; Tabeyang Mbuy, Kenge Thompson Njie, Edmond Tchassem, Kien-Atsu Ts, Bamenda Hospital, Cameroon; Rogers Aje, Mark Benwi, Anastase Dzudie, Akideh Mbuy, Mr Roland Nkamagi, Victorine Nkome, CRENC & Douala General Hospital, Cameroon; Djenanou Amadou, Eric Ngassam, Eric Walter Pefura Yone, Jomot Hospital, Cameroon; Alice Ndelle Ewango, Norbert Fuengwa, Chris Moki, Denis Nseme Nfonowe, Limbe Regional Hospital, Cameroon; Catherine Akele, Faustin Kitetele, Patricia Lelo, Martine Tabala, Kalambelembem Pediatric Hospital, Democratic Republic of Congo; Emile Wemakoy Oktolonda, Landry Wenzi, Paediatric site investigators and cohorts:

PS Ly*, and V Khol, National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia; J Tucker, New Hope for Cambodian Children, Phnom Penh, Cambodia; N Kumarasamy*, and E Chandrasekar, YRGCARE Medical Centre, CART CRS, Chennai, India; DK Wati*, D Vedawari, and IB Ramajaya, Sanglah Hospital, Udayana University, Bali, Indonesia; N Kumar* and D Muktair, Cipto Mangunkusumo – Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia; SM Fong*, M Lim, and F Daut, Hospital Likas, Kota Kinabalu, Malaysia; NK Nik Yusoff* ‡, and P Mohamad, Hospital Raja Perempuan Zainab II, Kelantan, Malaysia; TJ Mohamed* and MR Dravis, Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; R Nallusamy*, and KC Chan, Penang Hospital, Penang, Malaysia; T Sudjaritruk*, V Sirisantha, and L Auripibul, Department of Pediatrics, Faculty of Medicine, and Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; R Hansudwechakul*, P Ounchanum, S Denjanta, and A Krongphono, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; P Jornud, PHPT-IRD UMI 174 (Institut de recherche pour le développement and Chiang Mai University), Chiang Mai, Thailand; T Puthanakkit*, S Anugulruengkit, W Jantarabenjakul and R Nadasarn, Department of Pediatrics, Faculty of Medicine and Research Unit in Pediatric and Infectious Diseases, Chulalongkorn University, Bangkok, Thailand; K Cheokephaibulkit*, K Lapphra, W Phongsamart, and S Srirahorechani, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; KH Truong*, QT Du, and CH Nguyen, Children’s Hospital, Ho Chi Minh City, Vietnam; VC Do*, TM Ha, and VT An Children’s Hospital 2, Ho Chi Minh City, Vietnam; LV Nguyen*, DTK Khu, AN Phan, and LT Nguyen, National Hospital of Pediatrics, Hanoi, Vietnam; ON Le, Worldwide Orphans Foundation, Ho Chi Minh City, Vietnam; AH Sohn*, JL Ross, and C Sethaputra, TREAT Asia/amfAR – The Foundation for AIDs Research, Bangkok, Thailand; MG Law* and A Kariminia, The Kirby Institute, UNSW Australia, Sydney, Australia; (‡) Steering Committee members; † Current Steering Committee Chair; ‡ co-Chair.
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Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico: Juan Sierra Madero, Brenda Crabtree Ramirez, Paco Belauzaran, Yanink Caro Vega.

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Site investigators and cohorts

Diero L, Ayasa S, Sang E, MOI University, AMPATH Plus, Eldoret, Kenya; Bukusi E, Charles Karue Kibaara, Elisheba Mutegi, KEMRI (Kenya Medical Research Institute), Kisumu, Kenya; John Ssali, Mathew Ssemakadde, Masaka Regional Referral Hospital, Masaka, Uganda; Mwebesa Bosco Dwana, Michael Kanyesigye, Mbarara University Of Science and Technology (MUST), Mbarara, Uganda; Barbara Castelnuovo; John Michael Matovu, Infectious Diseases Institute (IDI), Mulago, Uganda; Fred Nalugoda, Francis X. Wasswa, Rakai Health Sciences Program, Kalsigo, Uganda; G.R. Somi, Joseph Nondi,

NACP (National AIDS Control Program) Dar es Salaam, Tanzania; Rita Elias Lyamuya, Francis Mayanga, Morogoro Regional Hospital, Morogoro, Tanzania; Kapella Ngonyani, Jerome Lwali, Tumbi Regional Hospital, Pwani, Tanzania; Mark Urassa, Denna Michael, Richard Machemba, National Institute for Medical Research (NIMR), Kissesa HDSS, Mwanza, Tanzania; Kara Woods-Kaloustian, Constantian Yiannoutsos, Rachel Vreeman, Beverly Musick, Indiana University School of Medicine, Indiana University, Indianapolis, IN, USA; Batya Elul, Columbia University, New York City, NY, USA; Jennifer Syvertsen, Ohio University, Columbus, OH, USA; Rami Kantor, Brown University/Miriam Hospital, Providence, RI, USA; Jeffrey Martin, Megan Wenger, Craig Cohen, Jayne Kulzer, University of California, San Francisco, CA, USA; Paula Brattstein, University of Toronto, Toronto, Canada.

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Site investigators and cohorts:

Constance A. Benson and Ronald J. Bosch, AIDS Clinical Trials Group Longitudinal Linked Randomized Trials; Gregory D. Kirk, AIDS Link to the IntraVenous Experience; Stephen Boswell, Kenneth H. Mayer and Chris Grasso, Fenway Health HIV Cohort; Robert S. Hogg.

P. Richard Harrigan, Julio SG Montaner, Angela Cescon and Karyn Gabler; HAART Observational Medical Evaluation and Research; Kate Buchacz and John T. Brooks, HIV Outpatient Study; Kelly A. Gebo and Richard D. Moore, HIV Research Network; Richard D. Moore, Johns Hopkins HIV Clinical Cohort; Benigno Rodriguez, John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western; Benigno Rodriguez, Reserve University; Michael A. Horberg, Kaiser Permanente Mid-Atlantic States; Michael J. Silverberg; Kaiser Permanente Northern California; Jennifer E. Thorne, Longitudinal Study of Ocular Complications of AIDS; Charles Rabkin, Multicenter Hemophilia Cohort Study–II; Lisa J. Jacobson and Gypsysamber D’Souza, Multicenter AIDS Cohort Study; Marina B. Klein, Montreal Chest Institute Immunodeficiency Service Cohort; Sean B. Rourke, Anita R. Rachlis, Jason Globerman and Madison Kopansky-Giles, Ontario HIV Treatment Network Cohort Study; Robert F. Hunter-Mellado and Angel M. Mayor, Retrovirus Research Center, Bayamon Puerto Rico; M. John Gill, Southern Alberta Clinic Cohort; Steven G. Deeks and Jeffrey N. Martin, Study of the Consequences of the Protease Inhibitor Era; Pagnna Patel and John T. Brooks, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; Michael S. Saag, Michael J. Mugavero and James Willig, University of Alabama at Birmingham 1917 Clinic Cohort; Joseph J. Eron and Sonia Napravnik, University of North Carolina at Chapel Hill HIV Clinic Cohort; Mari M. Kitahata, Heidi M. Crane and Daniel R. Drozd, University of Washington HIV Cohort; Timothy R. Sterling, David Haas, Peter Rebeiro, Megan Turner, Sally Bebawy and Ben Rogers, Vanderbilt Comprehensive Care Clinic HIV Cohort; Amy C. Justice, Robert Dubrow and David Fielin, Veterans Aging Cohort Study; Stephen J. Gange and Kathryn Anastos, Women’s Interagency HIV Study

Study administration:

Richard D. Moore, Michael S. Saag, Stephen J. Gange, Mari M. Kitahata, Keri N. Althoff, Rosemary G. McKaig and Aimee M. Freeman, Executive Committee; Richard D. Moore, Aimee M. Freeman and Carol Lent, Administrative Core; Mari M. Kitahata, Stephen E. Van Rompaeay, Heidi M. Crane, Daniel R. Drozd, Liz Morton, Justin Reynolds and William B. Lober, Data Management Core; Stephen J. Gange, Keri N. Althoff, Alison G. Abraham, Bryan Lau, Jinbing Zhang, Jerry Jing, Sharada Modur, Cheirse Wong, Brenna Hogan, Fidel Desir and Bin Liu and Bin YouHealth, Family Medicine, University of Cape Town, South Africa, Epidemiology and Biostatistics Core

IeDEA Southern Africa

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Site investigators and cohorts:

Gary Maartens, Aid for AIDS, South Africa; Michael Vinikoor, Centre for Infectious Disease Research in Zambia (CIDRZ), Zambia; Monique van Lettow, Dignitas, Malawi; Robin Wood, Cugulethu ART Programme, South Africa; Nosisa Sipambo, Harriet Shezi Clinic, South Africa; Frank Tanser, Africa Centre for Health & Population Studies (Hlabisa), South Africa; Andrew Boule, Khayelitsha ART Programme, South Africa; Geoffrey Fatti, Kheth’Impilo, South Africa; Sam Phiri, Lighthouse Clinic, Malawi; Cleophas Chimbetete, Newlands Clinic, Zimbabwe; Karl Technau, Rahima Moosa Mother and Child Hospital, South Africa; Brian Eley, Red Cross Children’s Hospital, South Africa; Josephine Muhairwe, SolidarMed Lesotho; Anna Jores, SolidarMed Mozambique; Cordelia Kunzekwenyika, SolidarMed Zimbabwe, Matthew P Fox, Themba Lethu Clinic, South Africa; Hans Prozesky, Tygerberg Academic Hospital, South Africa.

Data centres:

Nina Anderegg, Marie Baliff, Lina Bartels, Julia Bohlius, Frédérique Chammartin, Benedikt Christ, Cam Ha Dao Ostinelli, Matthias Egger, Lukas Fenner, Per von Grae, Andreas Haas, Taghavi Katayoun, Elane Rohner, Lilian Smith, Adrian Spöri, Gilles Wandelier, Elizabeth Zaniekowsk, Kathrin Zürcher, Institute of Social and Preventive Medicine, University of Bern, Switzerland; Andrew Boule, Morna Cornell, Mary-Ann Davies, Victoria Iyun, Leigh Johnson, Mmamapudi Kubjane, Nicola Maxwell, Thabakwane Nembonandza, Patience Nyakato, Ernest Mokotoane, Gem Patten, Michael Schomaker, Priscilla Tsondai, Renee de Waal, School of Public Health and Family Medicine, University of Cape Town, South Africa.

West Africa

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Site investigators and cohorts:

Adult cohorts: Marcel Djimon Zannou, CNHU, Cotonou, Benin; Armel Poda, CHU Souro Sanou, Bobo Dioulasso, Burkina Faso; Fred Senior Safro and Komfo Anokye Teaching Hospital, Kumasi, Ghana; Eugene Messou, ACONDA CePrEf, Abidjan, Cote d’Ivoire; Henri Chenal, CIRBA, Abidjan, Cote d’Ivoire; Kla Albert Minga, CNTS, Abidjan, Cote d’Ivoire; Emmanuel Bissagnene, & Aristophane Chammartin, Benedikt Christ, Cam Ha Dao Ostinelli, Matthias Egger, Lukas Fenner, Per von Grae, Andreas Haas, Taghavi Katayoun, Elane Rohner, Lilian Smith, Adrian Spöri, Gilles Wandelier, Elizabeth Zaniekowsk, Kathrin Zürcher, Institute of Social and Preventive Medicine, University of Bern, Switzerland; Andrew Boule, Morna Cornell, Mary-Ann Davies, Victoria Iyun, Leigh Johnson, Mmamapudi Kubjane, Nicola Maxwell, Thabakwane Nembonandza, Patience Nyakato, Ernest Mokotoane, Gem Patten, Michael Schomaker, Priscilla Tsondai, Renee de Waal, School of Public Health and Family Medicine, University of Cape Town, South Africa.

Paediatric cohorts: Sikiratou Adouni Koumakpai-Adeothy, CNHU, Cotonou, Benin; Lorna Awo Renner, Korle Bu Hospital, Accra, Ghana; Sylvie Marie N’Gbeche, ACONDA CePReF, Abidjan, Cote d’Ivoire; Henri Chenal, CIRBA, Abidjan, Cote d’Ivoire; Madeleine Amorissani Folquet, CHU de Cocody, Abidjan, Cote d’Ivoire; Francois Tanoh Eboua, CHU de Yopougon, Abidjan, Cote d’Ivoire;
Fatoumata Dicko Traore, Hopital Gabriel Toure, Bamako, Mali; Elom Takassi, CHU Sylvanus Olympio, Lomé, Togo

Coordinating and data centres:
Substance use and universal access to HIV testing and treatment in sub-Saharan Africa: implications and research priorities

Kathryn E Lancaster1*, Angela Hetrick1, Antoine Jaquet2,3, Adelbola Adedimeji4, Lukoye Atwoli5,6, Donn J Colby7, Angela Mayor8, Angela Parcensepe9 and Jennifer Syvertsen10

1 Division of Epidemiology, College of Public Health, Ohio State University, Columbus, OH, USA
2 University of Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, Bordeaux, France
3 Inserm, ISPED, Bordeaux Population Health Research Center, UMR, Bordeaux, France
4 Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA
5 Department of Mental Health, Moi University School of Medicine, Eldoret, Kenya
6 Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, Republic of South Africa
7 SEARCH, Thai Red Cross AIDS Research Center, Bangkok, Thailand
8 Retrovirus Research Center, Universidad Central del Caribe School of Medicine, Bayamón, Puerto Rico
9 Department of Maternal and Child Health, University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC, USA
10 Department of Anthropology, University of California, Riverside, CA, USA

Abstract

As universal testing and treatment for HIV, or ‘treat all’, expands across sub-Saharan Africa (SSA), substance use will likely have a negative impact on the success of scale-up efforts for antiretroviral treatment (ART). Overwhelming evidence highlights the negative impact of substance use on HIV care and treatment outcomes. Yet, as many countries in SSA expand ART, evidence of the extent of substance use, and its impact in the region, is more limited. Stigma, and the psychoactive effects of substance use, are barriers to seeking HIV treatment and adhering to ART regimens for persons with heavy alcohol use or substance use. As a result, we identified several implementation and operations research priorities and metrics for monitoring the impact of substance use and Treat All. Identifying barriers and facilitators to the integration of the prevention and treatment of substance use with HIV care, and assessing effects on HIV outcomes, through longitudinal studies are priorities that will determine the limits of substance use on ‘treat all’ in SSA. Future research must use existing infrastructure, including large networks of HIV clinics, to enhance our understanding of the implementation and service delivery of substance use screening, referral and treatment. These networks will also inform robust and standardised substance use estimates and interventions within the ‘treat all’ era in SSA.

Keywords: injection drug use, non-injection drug use, alcohol, antiretroviral treatment, Africa

Introduction

Substance use among people living with HIV (PLWH) is a major public health challenge globally and within sub-Saharan Africa (SSA) [1-4]. While alcohol is the most commonly used substance, injection drug use and non-injection drug use are growing [5]. An estimated 500,000 to 3 million persons reported injecting drugs in SSA and nearly one-fifth are estimated to be living with HIV [3,4]. Non-injection drug use in Africa ranges widely across substances; in 2014 an estimated 1.6 million persons used opiates, 2.8 million persons used cocaine, and 5.5 million persons used amphetamines and prescription stimulants [5]. In 2010, approximately 30%, or 314 million persons, consumed alcohol in Africa, and among those, 92 million were heavy episodic drinkers [6]. As Africa becomes more integrated within drug trafficking routes, injection and non-injection drug use are expected to expand [1].

The intertwining relationships between substance use and HIV are complex in many ways, with each simultaneously hindering optimal physical and mental health, well-being and quality of life. PLWH who use substances, and are not engaged in substance use treatment, may be less likely to achieve optimal engagement into HIV care and treatment when compared to non-substance-using PLWH [7-9]. In parallel, those who are engaged in substance use treatment are likely not offered HIV testing and do not receive HIV risk-reduction counselling [10-12].

In 2015, the World Health Organization expanded their global recommendations on the use of antiretroviral drugs for treating and preventing HIV infection by implementing a universal test and treatment strategy also known as ‘treat all’ [13]. The ‘treat all’ policy encompasses initiating antiretroviral treatment (ART) as soon as possible after a diagnosis of HIV infection, to both maximise the benefits for individual health and minimise the potential for forward transmission [14,15]. The elimination of ART eligibility criteria for PLWH is anticipated to have tremendous effects on achieving universal access to HIV treatment [16]. Globally, adoption of the ‘treat all’ policy has been high, and by 2017, nearly all countries within SSA had implemented some form of immediate ART initiation [17]. The International Epidemiology Databases to Evaluate AIDS (iDeA) consortium, funded by the US National Institutes of Health, is unique, and to our knowledge, the largest network of HIV clinics in SSA to monitor the implementation of ‘treat all’.

‘Treat all’ implementation is the critical first step toward universal testing and treatment, improved clinical outcomes for patients, and the prevention of new infections. However, to achieve the full benefits, all PLWH must be fully engaged in HIV care and treatment, including those engaging in substance use [18,19]. If left unaddressed, substance use could hinder potential advances of the ‘treat all’ policy in SSA. In this viewpoint, we characterise the current literature on substance use, including injection drug use, non-injection drug use, alcohol use and their potential impact on ‘treat all’ implementation in SSA. We conclude by identifying several knowledge gaps and providing examples of research priorities for the rollout of ‘treat all’ in the region.

Alcohol use

Alcohol continues to be the most predominantly used substance within SSA (Figure 1a) [6,20]. SSA has the highest prevalence of both HIV and heavy episodic drinking in the world [6,21]. In
(a) Total alcohol per capita consumption (15+ years). This is based on UK guidelines where no more than 14 units of alcohol (140 mL of pure alcohol) per week is recommended

Key

- Per capita alcohol use less than the UK’s recommended alcohol guidelines
- Per capita alcohol use over the UK’s recommended alcohol guidelines
- No information available
- Country outside sub-Saharan African region

(b) Injection drug use.

Key

- Evidence of injection drug use, no estimate
- >0.00–0.25%
- ≥0.25–1.00%
- ≥1.00%
- No evidence of injection drug use
- Country outside sub-Saharan African region

(c) Non-injection drug use

Key

- Evidence of cocaine use
- Evidence of non-injection heroin use
- Evidence of methamphetamine use
- No evidence of non-injection drug use
- Country outside sub-Saharan African region

Figure 1. All panels were created using ArcGIS Desktop (Release 10, Environmental Systems Research Institute, Redlands, CA, USA). Evidence of substance use, including: (a) Total annual alcohol per capita consumption of those 15 years or older in litres of pure alcohol as stated in each country’s profile in the WHO’s 2014 Global Status Report on Alcohol and Health was used [6,20]. In an effort to discern low and high rates of alcohol use in each country, the United Kingdom’s alcohol guidelines were used to differentiate levels of alcohol use. The UK guidelines recommend no more than 14 units of alcohol (140 mL of pure alcohol) per week or 7.28 L of pure alcohol per year; (b) Injection drug use—prevalence data were pulled from a systematic review by Degenhardt et al [42]; and (c) non-injection drug use within sub-Saharan Africa. A combination of search techniques was implemented to find evidence of non-injection drug use of cocaine [43-55], heroin [4,43,52,56-69] and methamphetamine [5,53,55,70-72] within each country in SSA. The United Nations Office on Drugs and Crime Statistics Online Tool was used to determine prevalence of amphetamine and cocaine use by country. If no data were available, then PubMed and Google Scholar search functions were used with each country’s name and ‘cocaïne’, ‘heroin’, ‘methamphetamine’, or ‘amphetamine’ to find studies that documented non-injection use from the year 2000 to the present. All non-injection drug use sources were combined to create Figure 1c.
many SSA countries, over half of key populations, such as female sex workers (FSW) and men who have sex with men (MSM), supplement sexual encounters with frequent heavy alcohol use, which may ultimately lead to alcohol use disorders [22–24]. The association between heavy alcohol use and HIV acquisition and transmission has been well documented [25]. Alcohol use can directly affect cognitive ability and judgement [26,27], which can lead to high-risk sexual behaviours, including unprotected, multiple sexual partners, and coercive sex [28–35]. Heavy alcohol use is also biologically linked with increased genital viral shedding, increasing the potential for HIV transmission [36,37]. In addition to HIV risk, heavy alcohol use among PLWH directly leads to sub-optimal ART adherence, decreasing the likelihood for plasma viral suppression, the ultimate goal for ART [23,27,36,38,39]. Often, due to concerns of potential interactions, ART medication is missed when drinking [40], which can lead to ART resistance [41]. These outcomes lead to higher mortality and morbidity rates, particularly among key populations, and are barriers to achieving the second and third 90-90-90 targets proposed by UNAIDS (by 2020, 90% of all people living with HIV will know their HIV status, 90% of those will be in care, and 90% of those will be virally suppressed).

Injection drug use

Injection drug use is now documented in many countries in SSA, with prevalence estimates ranging from 0% to 2.3% in the general adult population (Figure 1b) [42]. The number of persons who inject drugs (PWID) is growing, particularly within Kenya, Tanzania, Nigeria, Mauritius and South Africa [4,8,73]. The emergence of injection drug use provides an additional route for HIV transmission. Serial use and sharing of drug injection equipment, preparing drugs for injection, and collectively using shared drug preparations, create risks for acquiring and transmitting HIV [74]. Additionally, blood sharing practices, known as ‘flashing’, can directly increase transmission potential as a person injects a syringe full of blood drawn back immediately after initial injection to another person as a way of sharing drugs [75,76]. Injection drug use, particularly of heroin, is commonly associated with poor ART adherence [7]. However, involvement in substance use treatment, such as methadone substitution therapy, significantly improves HIV clinical outcomes, including ART adherence and viral suppression [9,77,78]. Aside from the negative impact of injection drug use on HIV treatment outcomes, this ‘hard-to-reach’ population is less likely to be aware of their HIV infection and entered/retained into care. PWID face persistent social barriers to HIV testing and linkage to care, including stigma and punitive legal systems [79,80]. It then will represent a major challenge in achieving the first 90 of the 90-90-90 targets proposed by UNAIDS [81]. Therefore, the integration or linkage of harm-reduction services with HIV care programmes might constitute a central element to achieve universal access to treatment. Evidence-based interventions that have been documented to prevent HIV transmission and improve HIV treatment outcomes are largely unavailable within SSA [8,82]. In 2009, only three African countries included harm reduction services, including syringe exchange and/or methadone substitution programmes, as part of their national plans [82]. However, since 2013, availability of these harm reduction services has expanded, particularly within East Africa [83–88].

Non-injection drug use

Non-injection substance use is emerging and is a major concern for several SSA countries (Figure 1c) [4,5,43–72]. Specifically, smoking or ingesting heroin, methamphetamine and amphetamine-type stimulants has been increasing [4,8,89]. Although injection drug use has received much attention for its direct link to HIV transmission, heroin is also commonly smoked, particularly in developing markets. Several countries within Africa have become major international transport corridors for heroin and cocaine trafficking [1,2,4]. As a result, cocaine use throughout West Africa and heroin consumption throughout East Africa have been documented [4,76,90]. South Africa is also experiencing a severe methamphetamine epidemic, the majority of which is with non-injection routes, particularly among key populations at risk for HIV, including sex workers and men who have sex with men [89,91]. Similar to other substances, non-injection substance use can lead to delays in HIV diagnosis, poor linkage to care and treatment, as well as sub-optimal ART adherence for viral suppression [8,70,92]. Without adequate surveillance, the impact of these emerging non-injection drug use epidemics on HIV acquisition, transmission and treatment within the context of high HIV prevalence is unknown [8]. Furthermore, harm-reduction strategies are often tailored for injection drug use to improve HIV treatment outcomes and need to include strategies for sexual and non-injection drug-related risk reduction [70].

Research priorities

The growing substance use epidemic has the strong potential to aggravate the HIV epidemic in SSA. For a successful rollout of ‘treat all’ in SSA, several knowledge gaps in understanding and addressing substance use require attention and resources. To address these gaps, we have identified a set of research priorities, including four implementation and operations priorities that address and reliable point-of-care drug use screening and treatment/referral.

Table 1. Research priorities for ‘treat all’ policy in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Implementation and operations</th>
<th>Metrics for monitoring impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop, adapt and evaluate valid and reliable screening methods for substance use, including injection and non-injection drug use</td>
<td>Estimate and characterise availability of evidence-based substance use disorder prevention and treatment services</td>
</tr>
<tr>
<td>Integration of low-cost and reliable point-of-care testing for alcohol use among patients receiving HIV care</td>
<td>Assess substance use effects, including time-varying changes in patterns of injection and non-injection substance use, on HIV outcomes (e.g., ART adherence, HIV viral suppression and sustained HIV viral suppression) through longitudinal studies</td>
</tr>
<tr>
<td>Develop, implement and evaluate screening and treatment/referral protocols for substance use disorders that can be integrated into HIV treatment and implemented by non-specialists</td>
<td>Evaluate substance use effects, including time-varying changes in patterns of injection and non-injection substance use, on co-occurring infections and non-communicable diseases through longitudinal studies</td>
</tr>
<tr>
<td>Identify barriers and facilitators to the integration of the prevention and treatment of substance use disorders with HIV care</td>
<td></td>
</tr>
</tbody>
</table>

Review
Implementation and operations

Screening

Substance use screening tools that are culturally appropriate and reliable must be prioritised. Within several areas of SSA, screening for substance use is either non-existent or severely limited [93]. Substance use screening can include biomarkers and self-report behavioural surveys, particularly within treatment settings. Biological tests for biomarkers of substance use, such as urinalysis, hair testing and saliva tests, can often be rapid and accurate for detecting recent substance use. However, these tests require proper training, specialised laboratories and adequate resources, which may be challenging in overburdened HIV clinical settings. Self-report screening tools are likely more feasible to implement within the current HIV care settings [94]. Several tools have been developed and validated within the United States, yet few have been evaluated with regard to their sensitivity and specificity for measuring substance use, misuse and disorders in other cultures [95]. For example, studies within Kenya have used generic questions to identify types of substances used as well as a pattern of use, while others have adapted the WHO Model Core Questionnaire among students and prison populations for the same purpose [96-99]. Cultural adaptations and validation of standardised screening tools must be undertaken to integrate local nomenclature for the various substances used in the region [100]. Common modifications have included the addition of contextual items such as factors associated with introduction to substance use and its continued use, as well as potential complications of use. Additionally, contextualisation will often require the inclusion of local names for various substances, information that would otherwise be missed without cultural context. Epidemiological studies require this ongoing ethnographic work to monitor the on-the-ground, and often rapidly changing, drug markets [101].

As alcohol use remains highly prevalent in SSA, strategies are needed to integrate low-cost and reliable point-of-care testing for alcohol use among patients receiving HIV care. As an example, the assessment of excessive alcohol use presents various challenges in the SSA context. An accurate measure of alcohol intake in a given setting requires a minimum knowledge of types of locally brewed alcoholic beverages regularly consumed as well as conversions into standard alcohol drinks. Reproducibility of alcohol intake measures across various settings and populations is also an issue to enable reliable comparisons. To this end, the diffusion and promotion of a common tool to assess alcohol use, such as the Alcohol Use Disorder Identification Test (AUDIT), or its short version, AUDIT-C, constitutes a key step in the documentation of alcohol use in SSA [102]. Besides these technical considerations, relying on self-report to diagnose excessive alcohol use is subject to desirability bias. This is particularly sensitive in a context of access to care for chronic and lifelong conditions, such as HIV infection. Indeed, recent research using alcohol biomarkers, such as phosphatidylethanol, has found significant rates of underreported alcohol intake among HIV-infected persons [103,104]. Other factors, such as religion, ethnicity and employment, might also significantly affect self-reported alcohol use. Previous prevalence estimates on alcohol use from SSA, based on self-report, showed a particularly low level of alcohol use in predominantly Muslim countries [105,106]. Whether or not these assessments reflect the true consumption of alcohol in these countries remains to be confirmed. The use of inexpensive and reliable point-of-care testing to complement self-report measurements of alcohol intake might provide more reliability in alcohol-use estimates [107].

Treatment

Written guidelines and protocols for substance use disorder treatment and referrals must be developed and implemented by non-specialists within HIV clinics. For example, the World Health Organization’s Mental Health Gap Action Programme (mhGAP) provides guidance for the integration of substance use care [108]. Until integration can be achieved, timely referral strategies can be employed to address treatment gaps in settings where referral services exist [109]. Referral strategies for those in need of substance use disorder treatment can be successful through collaboration between the patient, service providers and related treatment organisations. However, it is critical to note that throughout much of SSA, referral services are nonexistent or inaccessible, highlighting the need for development of new and innovated models for substance use care and support [110].

To facilitate an understanding of the barriers and facilitators to integrating substance use disorder and HIV treatments, we advocate for an implementation science framework approach for generating critical and actionable evidence. In HIV care settings in SSA, a complex set of patient, community, provider, organisational and systemic factors must come together to create integrated substance-use treatment among PLWH. At the patient and community levels, the challenges include the inability to engage and retain HIV-positive substance users in care due to varying levels of motivation, loss to follow-up, stigma associated with substance use (including from service providers), lack of social support, and co-morbid conditions including psychiatric and mental health disorders, as well as complex socioeconomic and contextual factors that inhibit access to and retention in care [109,111-114]. Provider and organisational level barriers include lack of knowledgeable and skilled providers, personnel shortages, inadequate diagnostic tools and poor treatment infrastructure, all within an environment that continues to prioritise HIV care over conditions that increases the risk of transmission. Systemic challenges are related to the absence of coherent and comprehensive substance abuse policies and programmes that support an integrated care model [3,115,116]. To further address the barriers to treatment among vulnerable drug-using populations, including MSM and FSW, non-HIV sector approaches that use dedicated substance abuse services and more community-based outreach models should be considered [109].

Metrics for monitoring impact

The focus of implementation science research must enhance our understanding of what resources are needed, how to most efficiently address multiple barriers to integrating substance use treatment and HIV prevention programmes, and how to develop and implement optimal interventions to maximise the benefits of ART in the ‘treat all’ era. This should include highlighting optimal models of care delivery, efficiency, and effects of interventions and policy innovations on HIV treatment [117]. More specifically, implementation science research should be designed to assess context-specific barriers at individual, community, health provider and structural levels to facilitate increased access to HIV prevention and treatment for substance use among PLWH. It is also necessary to identify the cost-effective approaches to facilitate the integration of substance use and HIV treatment because of the potential to dramatically improve the success of ‘treat all’ in SSA [117,118].

Multiple metrics will be necessary for monitoring the impact of substance use within the ‘treat all’ era. Robust estimates of substance use and characterisation of substance use treatment services are lacking, particularly at the country level, within SSA [119,120].
Although substance use and harm-reduction services are expanding across SSA, a number of structural barriers remain, including a lack of trained providers and an absence of policy for expansion [83-86,120]. Population estimates and identification of evidence-based substance use disorder prevention and treatment services will provide essential data for informing future programme development and research.

Longitudinal studies are needed on the time-varying changes in patterns of substance use, as well as the effect of substance use, on HIV outcomes and co-infections. Substance use is not widely captured in HIV clinical settings, particularly within SSA. This lack of regularity and standardisation in assessing substance use within clinical cohorts leads to a reliance on small convenience samples for characterising substance use among PLWH [121,122]. While these studies enhance our understanding of the impact of substance use on HIV outcomes and co-infections, the estimates are susceptible to bias, limiting the potential for guiding HIV treatment policies [123-126].

Conclusion

As the rollout of ART expands in SSA, substance use will remain an ongoing challenge for achieving universal testing and treatment. Evidence from other settings overwhelmingly emphasises the negative impact of substance use on HIV care and treatment outcomes. Within SSA, the evidence is limited for understanding and addressing substance use and HIV. Participating clinics within leDEA can serve as a representative sample of HIV treatment sites and provide critical insights on the implementation and operational management of service delivery for substance use screening, referral and treatment. Furthermore, this platform has successfully collected core information on ART exposure and has strong potential to contribute to more robust and standardised estimations of substance use among PLWH, especially in the context of ‘treat all’.

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Declaration of interests

The authors declare no competing interests.

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Note: Sources marked with ** indicate countrywide prevalence data used in Figure 1. All other sources are smaller studies within SSA countries.


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Achieving UNAIDS 90-90-90 targets for pregnant and postpartum women in sub-Saharan Africa: progress, gaps and research needs

Lisa L Abuogi1*, John M Humphrey2, Christian Mpody3, Marcel Yotebieng3, Pamela M Murnane4, Kate Clouse5, Lindah Otieno6, Craig R Cohen2 and Kara Wools-Kaloustian2

1Department of Pediatrics, University of Colorado, Denver, Aurora, CO, USA
2Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA
3Center for AIDS Prevention Studies, University of California San Francisco, San Francisco, CA, USA
4Division of Epidemiology, Ohio State University, Columbus, OH, USA
5Vanderbilt Institute for Global Health, Vanderbilt University, Nashville, TN, USA
6Center for Microbial Research, Research Care and Training Program, Kenya Medical Research Institute, Nairobi, Kenya
7Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Francisco, CA, USA

Abstract

The implementation of the 2013 World Health Organization Option B+ recommendations for HIV treatment during pregnancy has helped drive significant progress in achieving universal treatment for pregnant and postpartum women in sub-Saharan Africa (SSA). Yet, critical research and implementation gaps exist in achieving the UNAIDS 90-90-90 targets. To help guide researchers, programmers and policymakers in prioritising these areas, we undertook a comprehensive review of the progress, gaps and research needs to achieve the 90-90-90 targets for this population in the Option B+ era, including early infant HIV diagnosis (EID) for HIV-exposed infants. Salient areas where progress has been achieved or where gaps remain include: (1) knowledge of HIV status is higher among people with HIV in southern and eastern Africa compared to western and central Africa (81% versus 48%, UNAIDS); (2) access to antiretroviral therapy (ART) for pregnant women has doubled in 22 of 42 SSA countries, but only six have achieved the second 90, and nearly a quarter of pregnant women initiating ART become lost to follow-up; (3) viral suppression data for this population are sparse (estimates range from 30% to 98% peripartum), with only half of women maintaining suppression through 12 months postpartum; and (4) EID rates range from 15% to 62%, with only three of 21 high-burden SSA countries testing >50% HIV-exposed infants within the first 2 months of life. We have identified and outlined promising innovations and research designed to address these gaps and improve the health of pregnant and postpartum women living with HIV and their infants.

Keywords: prevention of mother-to-child transmission, prevention of vertical transmission, HIV, pregnancy, postpartum, sub-Saharan Africa

Introduction

The expansion of HIV care and treatment for pregnant and postpartum women in sub-Saharan Africa (SSA) exemplifies a significant achievement in the global HIV response. In southern and eastern Africa, home to 50% of the HIV population globally, antiretroviral therapy (ART) coverage for pregnant women has increased from 47% in 2010 to 93% in 2017 [1]. A variety of tools and evidence-based strategies have emerged to improve the health of pregnant and postpartum women with HIV, encouraging optimism towards achieving the ambitious targets established by the Joint United Nations Programme on HIV/AIDS (UNAIDS): that 90% of people living with HIV (PLHIV) know their status, 90% of diagnosed people are on ART, and 90% of those on ART are virally suppressed by 2020 [2,3]. Progress in the prevention of mother-to-child transmission (PMTCT) of HIV has also been substantial. With adequate adherence, ART carries the potential to virtually eliminate the risk of vertical HIV transmission for pregnant and breastfeeding women. At the country level, achieving ≥95% population-level ART coverage for pregnant women is a process indicator for national elimination of MTCT (defined as MTCT rates <5% in breastfeeding populations or <2% in non-breastfeeding populations) [4-8].

However, progress across SSA has not been uniform, and as our understanding of the HIV epidemic has deepened, critical gaps have been identified, which will need to be addressed in order to achieve the 90-90-90 goals for pregnant and postpartum women. Examples of these gaps include: (1) facility-based HIV testing has been broadly implemented for pregnant women in much of southern and eastern Africa, but central and western Africa are lagging behind [9]; (2) from country to country, the proportions of pregnant women accessing ART vary considerably, with many still far from reaching the second 90, even as others have surpassed it [10]; (3) achieving and sustaining viral suppression throughout pregnancy, delivery and the breastfeeding period remains a challenge in multiple countries [11,12], and as a result, there were still an estimated 180,000 new HIV infections in children in 2017 [1]; and (4) for HIV-exposed infants, gaps in early infant diagnosis remain substantial [13]. In this review, we summarise recent progress, remaining knowledge gaps, and identify the future research needed to achieve and eventually surpass the 90-90-90 targets for pregnant and postpartum women in SSA (Table 1).

First 90: knowledge of HIV status

Globally, an estimated 75% of all PLHIV knew their status in 2017, and across many SSA countries, knowledge of HIV status is higher among women of reproductive age (15–49 years) as compared to men [1]. Universal HIV testing for pregnant women initiating facility-based antenatal care (ANC) has been broadly implemented in many regions in southern and eastern Africa, yet central and western Africa, where the healthcare delivery systems are weaker, have been slower to implement this approach [9]. Further, general knowledge of HIV status among PLHIV in western...
and central Africa is considerably lower than other African regions – at 48%, as compared to 81% in southern and eastern Africa [1]. Stigma and discrimination, test kits stock outs, healthcare worker shortages and user fees all contribute to undermining achievement of the first 90 for pregnant and postpartum women [14]. In addition, as many as 20% of women in SSA are estimated to have no antenatal care, and thus miss antenatal Hiv testing entirely [15]. To complicate matters further, pregnancy and the perinatal period are associated with an increased risk of HIV acquisition [16,17]. In a cohort of over 1300 pregnant women in western Kenya, followed through 9 months postpartum, HIV incidence was 2.31 per 100 person-years [18]. Studies from Tanzania and Zambia [19] demonstrated similar results [20]. A critical testing gap also exists for sexually active adolescent girls, particularly in western and central African countries. For example, in Nigeria, 33% of adolescents (ages 10–19 years), as compared to 52% of adult women, reported being tested for HIV during their last pregnancy [21,22].

Several evidence-based strategies exist to improve HIV testing uptake among pregnant women, with fewer strategies specifically focused in the postpartum or breastfeeding periods. Universal, opt-out testing in ANC clinics has been highly successful in eastern and southern Africa. Repeat testing during pregnancy, and at least once during breastfeeding, is cost-effective, although it has been implemented with varying success [23,24]. Door-to-door testing by lay healthcare workers, and recent approaches integrating immediate ART initiation with community testing, may improve knowledge of HIV status pre-pregnancy, and identify pregnant women who have not enrolled in ANC [25,26]. Testing as part of home-based couples counselling may be particularly beneficial for women who are afraid of knowing their status and disclosing to their partner(s) [26]. Self-testing is an emerging strategy that may be particularly beneficial for sexually active adolescent girls [27–29]. Increased knowledge of personal HIV status among the general population using promising approaches, such as integration of HIV testing within multi-disease health campaigns, is likely to increase the proportion of women who know their HIV status prior to pregnancy and breastfeeding [30,31].

Important research gaps exist that need to be filled in order to improve knowledge of HIV status in pregnant and postpartum women. Identification and assessment of innovative HIV testing strategies that consider the lower HIV prevalence are needed for west and central Africa. Furthermore, approaches to improving uptake of antenatal care in women with low ANC attendance, including community-based peer navigators or thoughtful engagement of traditional birth attendants to promote HIV testing, should be explored. Further work is needed to identify optimal timing and implementation of repeat HIV testing for women, and to better understand structural and individual level barriers to repeat testing [32]. Testing strategies that take into account the unique developmental stage and challenges facing pregnant adolescents need to be identified and evaluated in order to increase testing uptake in this population.

Second 90: uptake of ART

The scale-up of World Health Organization (WHO) recommendations, including Option B+(ART for all women through pregnancy and breastfeeding) and Option B+ (lifelong ART for pregnant women), has yielded remarkable progress in ART coverage for pregnant and postpartum women in SSA (Figure 1). ART access for PMTCT more than doubled in 22 of 42 SSA countries with available UNAIDS Global AIDS Monitoring (GAM) data, and six countries (Botswana, Namibia, South Africa, Swaziland, Uganda and Zimbabwe) have surpassed the second 90 target for pregnant women as of 2016 [4,10]. Yet, wide variations in ART coverage exist within the continent, with fewer than 40% of HIV-positive pregnant women accessing ART in Nigeria and Mali compared to over 95% in Botswana, South Africa and Uganda in 2016 [10]. Furthermore, barriers to retention in care and maintenance on ART have surfaced as key obstacles to achieving the second 90 in SSA [33–36]. Since the implementation of Option B+, pooled retention estimates across SSA suggest that one-in-four women become lost to follow-up within 6 months of ART initiation [37], with women initiating ART during pregnancy up to five times more likely to become disengaged compared to women starting ART because of advanced HIV disease [35]. Adverse birth outcomes as a result of in utero ART exposure are persistent concerns, as various studies have reported increased risk of preterm birth and low birth weight, which are themselves associated with increased newborn morbidity and mortality in resource-limited settings [5,38,39]. Protease inhibitors, and to a lesser extent nucleoside and non-nucleoside transcriptase inhibitors, are most often associated with these adverse birth outcomes. Of particular concern is a preliminary report of increased neural tube defects in women who conceive on the integrase inhibitor dolutegravir, which is a potent and well-tolerated antiretroviral agent, whose use is rapidly growing in SSA [40,41].

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**Table 1.** Research priorities to achieve 90-90-90 for pregnant and postpartum women in sub-Saharan Africa

<table>
<thead>
<tr>
<th>First 90</th>
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<tbody>
<tr>
<td>Identify approaches to detecting acute Hiv infection in pregnancy and postpartum periods</td>
</tr>
<tr>
<td>Determine structural- and individual-level barriers to repeat testing in late pregnancy and breastfeeding periods</td>
</tr>
<tr>
<td>Evaluate strategies to ensure universal uptake of antenatal services, including HIV testing</td>
</tr>
<tr>
<td>Develop innovative testing approaches to identify HIV-positive pregnant/postpartum women in lower Hiv-prevalence regions</td>
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</table>

<table>
<thead>
<tr>
<th>Second 90</th>
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</thead>
<tbody>
<tr>
<td>Further understand barriers to ART uptake and retention in care</td>
</tr>
<tr>
<td>Assess interventions to improve ART uptake and retention in care</td>
</tr>
<tr>
<td>Explore optimal models of integrated HIV and maternal and child health services</td>
</tr>
<tr>
<td>Evaluate differentiated models of care for pregnant and postpartum women on ART</td>
</tr>
<tr>
<td>Develop strategies to identify and mitigate ART-associated adverse birth outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Third 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promote research, country and programme reporting of viral load outcomes during pregnancy and breastfeeding</td>
</tr>
<tr>
<td>Evaluate interventions that promote sustained adherence to ART, focused on postpartum period</td>
</tr>
<tr>
<td>Determine optimal timing and frequency of viral load monitoring in pregnancy and postpartum</td>
</tr>
<tr>
<td>Evaluate biomedical and behavioural approaches designed to achieve rapid viral suppression during pregnancy and breastfeeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early infant diagnosis of HIV for HIV-exposed infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate integrated approaches to ensure universal uptake of early infant diagnosis</td>
</tr>
<tr>
<td>Optimise retention, through the breastfeeding period, of exposed infants</td>
</tr>
<tr>
<td>Establish best strategies to incorporate birth testing and point-of-care EID technologies</td>
</tr>
<tr>
<td>Develop HIV testing approaches for infants of women with acute infection during breastfeeding</td>
</tr>
</tbody>
</table>

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A variety of evidence-based, scalable interventions have been described that could help reach the second 90 in SSA [42]. These interventions span the social, behavioural and structural aspects of PMTCT care at both the facility and community levels [43]. Improved ART uptake and retention has been demonstrated with expert peer support and ‘mentor mothers’ [44,45], individual or group counselling sessions [45], and community health workers who provide supportive supervision, ART counselling and tracing of women who default from care [46-48]. Male partner involvement has also been shown to improve maternal ART uptake [49-51]. Behavioural interventions by way of text message or phone call appointment reminders (mHealth) have been effective in improving ART uptake and retention across multiple HIV populations, and there is promising evidence of their feasibility and potential efficacy in the PMTCT population as well. Economic incentives, such as conditional cash transfer [52] and disclosure support to partners [53] have been less well studied, but may provide additional retention benefits. Structurally, the integration of HIV services into maternal and child health and postnatal services has played an important role in expanding capacity for ART coverage, and may improve retention in care compared to non-integrated services [54,55]. Combination interventions are also increasingly being examined to maximise gains in retention and maintenance on ART [42,56,57]. Finally, although many SSA countries have yet to implement national surveillance for ART-related adverse birth outcomes, researchers in Botswana, through the Botswana-Harvard partnership (Tsepamo study), have established a unique surveillance programme that has contributed key data to inform our understanding about the safety of ART for the mother and fetus [40,41].

Despite important progress, knowledge gaps persist concerning the optimal implementation strategies to achieve the second 90. Overall, the evidence for many of the aforementioned interventions is weak and heterogeneous, with limited duration of effect. Further research is needed to: (1) identify the barriers to care; (2) study the impact of interventions on long-term retention; (3) determine successful integration and differentiated care models for PMTCT; and (4) evaluate strategies to optimise ART uptake while maximising safety. Failure to engage in antenatal and HIV care threatens not only HIV-exposed infants, but the health of women with HIV and their partners.

Identifying barriers to care is critical, including their relative significance, and the optimal social and behavioural interventions to address them, particularly in terms of their cost-effectiveness and scalability for care programmes. Many studies have looked at the impact of interventions to improve adherence and retention for the period up to 12 months post-delivery; however, breastfeeding and PMTCT follow-up can last 18 months or longer in many cultures. Studying the impact of interventions through the conclusion of PMTCT follow-up, and through the transition back to an HIV clinic for postpartum women, is vital to understanding their durability and true effect sizes.

On a structural level, integrated service delivery models that maximise efficiency and efficacy for stable PMTCT clients, including models of differentiated and decentralised ART delivery, and patients’ preferences for such models, need to be rigorously evaluated [58]. High-quality, large, population-based studies to better understand the factors that drive regional variations in ART coverage for pregnant and postpartum women in SSA will also help achieve the second 90 goals for them. Finally, questions remain concerning the timing of ART initiation, and the effects of established and novel ART regimens (e.g. dolutegravir) on adverse birth outcomes (e.g. stillbirth, preterm birth, growth restriction, congenital anomalies) and infant development [41,59-61].

**Third 90: viral suppression**

Achieving and maintaining viral suppression is urgent for pregnant and postpartum women in order to minimise vertical HIV transmission and maximise women’s health outcomes [62]. While routine viral load monitoring among PLHIV on ART is now recommended by WHO, scale-up has been slow. In a study focused on seven of the SSA countries, only one was performing at least one viral load on more than 85% of patients on ART (South Africa [91%]); two countries (Kenya [40%] and Namibia [23%]) tested fewer than 50% of patients on ART, and four countries (Côte d’Ivoire [11%], Malawi [19%], Tanzania [9%], and Uganda [22%]) tested
fewer than 25% [63]. Further, recognition of pregnant and postpartum women as a priority population for monitoring and rapid intervention in the setting of virological failure is lacking [63–65]. As a result, literature on viral suppression among pregnant and breastfeeding women in SSA is sparse and frequently comes from research studies rather than routine care programmes. Additionally, several of these studies were conducted in settings and during time periods when universal ART was not the standard of care, and thus have a mixed population of women who are on ART as well as those on PMTCT prophylaxis [66].

Available data show viral suppression rates at delivery or immediately postpartum have ranged from 30% to 98% in different SSA settings, and are dependent on the viral load threshold used (Table 2). Keeping women engaged in care and optimally adherent to ART following delivery is a well-known challenge, and undermines sustained viral suppression [35,48]. In Malawi, although 70% of women starting ART during pregnancy and breastfeeding had adequate adherence (defined as having ART drugs available ≥90% of days between clinic visits), only one-third of them maintained adequate adherence over 2 years of treatment [67]. Similarly, among women who became pregnant after initiating ART in South Africa, the risk of non-adherence was nearly 50% higher during the postpartum period compared to the non-pregnant period [68,69]. Further, among those who are retained in care, optimal viral control (>90% with VL <50 copies/mL) in the postpartum period is rarely achieved. In Nigeria, only 58% of women attained suppression (<20 copies/mL) at 6 months postpartum [70]. While in a follow-up study of 523 previously virally suppressed (<50 copies/mL) women in Cape Town, only 70% were able to maintain viral suppression through 12 months postpartum [11]. The most promising and longest follow-up comes from the PROMOTE trial in Uganda, in which approximately 90% of women had VL <400 copies/mL at 24 months postpartum [71]; and 5 years later, among a random sample of 200 participants, 90% had maintained viral suppression [72].

Evidence-based approaches to address the main drivers of virological failure are being elucidated. While in many settings, data are lacking or not well utilised to address gaps in the third 90, South Africa’s rapid and successful scale-up of PMTCT has been attributed to the use of data-driven continuous quality improvement interventions that identify problems as they emerge, and empowers frontline staff to create local solutions [77,78]. This strategy is currently being fully evaluated in a cluster randomised trial focused on women initiating ART in pregnancy or during breastfeeding in the Democratic Republic of Congo [57]. A large number of studies have identified that non-adherence in pregnancy and the postpartum period is multifactorial, and may be driven by individual-level and biomedical issues, such as ART toxicity, stigma, mental health, ART toxicity and comorbidities, and structural issues related to healthcare worker attitudes and the availability of supportive services [11,66,72–74,79–84]. Thus, combination strategies that address these challenges are needed. Several studies are currently evaluating behavioural, peer navigation and mHealth interventions that may prove successful in attaining and maintaining viral suppression for pregnant and postpartum women [85,86].

In order to reach the third 90 for pregnant and postpartum women, the lack of data highlighted above, especially data from routine PMTCT implementation at programme and country level, will need to be addressed. Additionally, there is need for evidence-based interventions that improve engagement in care and adherence on ART among pregnant and breastfeeding women, and target previously identified modifiable predictors of viral suppression in this population. In order to achieve the third 90 for pregnant and postpartum women, a research agenda targeted on addressing sustained adherence is vital. Additional research should address the optimal timing and frequency of VL monitoring in pregnant and postpartum women and biomedical and behavioural interventions that rapidly achieve suppression in women with viremia.

**Early infant diagnosis for HIV-exposed infants**

Over 80% of newly infected children acquire their HIV infection through MTCT, yet fewer than 50% of infants exposed to HIV are tested at 6 weeks of age, and up to 45% are lost after initial testing [14,48]. EID is the crucial first step in addressing the alarmingly high mortality rate for infants infected with HIV, and is intrinsically linked with 90–90–90 goals for pregnant and postpartum women [87]. Some countries in SSA have made significant progress scaling-up EID testing; in a report on six SSA countries (Cote d’Ivoire, Democratic Republic of Congo, Malawi, South Africa, Uganda and Zambia) it was noted that the total number of EID tests performed on HIV-exposed infants significantly increased between 2011 and 2015, but testing before 6 weeks of age was poor, ranging between 15% and 62% [88]. In 2016, among the 21 UNAIDS-designated high-burden countries (all of which are in SSA) [90], only three – South Africa, Swaziland, and Zimbabwe – managed to test over 50% of exposed infants within the first 2 months of life [14,89]. Even when infants are tested, turn-around time for test results is so exceptionally long that caregivers may never receive the results [90].

Multiple strategies are gaining evidence of effectiveness in improving the first 90 for exposed infants in SSA. South Africa is the first high-burden country to introduce routine birth testing for exposed infants, and has achieved greater than 90% coverage. Complexities of neonatal HIV treatment, and high rates of early losses to follow-up after birth testing, remain concerns for the introduction of birth testing on a wide scale [91,92]. Point-of-care diagnostics may also be a promising new strategy that avoids the challenges associated with sample transport to centralised laboratories, and facilitates early intervention for positive results [93,94]. mHealth innovations, such as returning test results via short text message (SMS), electronic tracking systems and national web-based result dashboards, such as those being used in Kenya and South Africa, may support improved uptake as well as efficient return of results to providers and caregivers [95–97]. Integration of maternal and child health services, and psychosocial support through peer or community interventions, supports EID and retention of both mothers and exposed infants [49,54,98–101].

Further research into testing strategies that maximise uptake and facilitate early ART for infected infants are needed. How and where to integrate accurate point-of-care technologies into national EID algorithms, including as testing at birth, need to be determined. Strategies for integrating surveillance for acute HIV infection in pregnant and breastfeeding women with EID for infants should be explored. Further evidence is needed for cost-effective psychosocial support models that encourage HIV testing among exposed infants.

**Conclusion**

Despite considerable expansion of quality PMTCT services, and widespread uptake of Option B+, most countries in SSA have not achieved UNAIDS 90–90–90 targets for pregnant and postpartum women. A targeted research agenda as outlined in this paper is an important next step in reaching these critical goals, in order to achieve the elimination of vertical HIV transmission and ensure the health and well-being of women and their families.
Table 2. Summary of studies on the prevalence of viral suppression in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Author</th>
<th>Enrolment period</th>
<th>Region</th>
<th>Design</th>
<th>ART eligibility and naivety status</th>
<th>Timing of enrolment</th>
<th>Analytical sample</th>
<th>Viral load threshold (copies/mL)</th>
<th>Timing of VL sampling</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chagomerana et al. [73]</td>
<td>Jun 2015–Nov 2016</td>
<td>Lilongwe, Malawi</td>
<td>Prospective cohort</td>
<td>ART-naive and experienced</td>
<td>First ANC of current pregnancy</td>
<td>252</td>
<td>&lt;1000</td>
<td>Delivery</td>
<td>84</td>
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<td></td>
<td></td>
<td>&lt;40</td>
<td>Delivery</td>
<td>69</td>
</tr>
<tr>
<td>Chetty et al. [12]</td>
<td>2010–2015</td>
<td>Rural KwaZulu-Natal, South Africa</td>
<td>Prospective cohort</td>
<td>ART-experienced (at least 6 months)</td>
<td>Pregnancy, during first ANC visit</td>
<td>1425</td>
<td>&lt;1000</td>
<td>Pre-pregnancy</td>
<td>89</td>
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<td></td>
<td>Pregnancy</td>
<td>85</td>
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<td>6 months postpartum</td>
<td>84</td>
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<td>12 months postpartum</td>
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<td>25 months postpartum</td>
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<td>&lt;50</td>
<td>Pre-pregnancy</td>
<td>82</td>
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<td>Pregnancy</td>
<td>77</td>
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<td>6 months postpartum</td>
<td>77</td>
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<td>12 months postpartum</td>
<td>76</td>
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<td></td>
<td>25 months postpartum</td>
<td>76</td>
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<tr>
<td>Cohan et al. [71]</td>
<td>Dec. 2009–Mar 2013</td>
<td>District Tororo, Uganda</td>
<td>Randomized control trial (test efficacy of efavirenz vs lopinavir/ritonavir)</td>
<td>ART naive-eligible</td>
<td>Pregnant, 12-28 weeks</td>
<td>389</td>
<td>&lt;400</td>
<td>Delivery (efavirenz arm)</td>
<td>98</td>
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<td></td>
<td>Delivery (lopinavir/ritonavir arm)</td>
<td>86</td>
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<td>48 weeks postpartum (efavirenz arm)</td>
<td>91</td>
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<td></td>
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<td></td>
<td></td>
<td>48 weeks postpartum (lopinavir/ritonavir arm)</td>
<td>88</td>
<td></td>
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<tr>
<td>Gill et al. [74]</td>
<td>Apr 2013–Jan 2014</td>
<td>Kigali, Rwanda</td>
<td>Prospective cohort</td>
<td>ART-naive and experienced</td>
<td>Third trimester of pregnancy and up to 2 weeks post-partum</td>
<td>608</td>
<td>&lt;20</td>
<td>≤4 months under ART</td>
<td>30</td>
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<td>&lt;20</td>
<td>&gt;4 months under ART</td>
<td>66</td>
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<td>&lt;20</td>
<td>&gt;12 months under ART</td>
<td>66</td>
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<td></td>
<td></td>
<td>&lt;1000</td>
<td>&gt;12 months under ART</td>
<td>90</td>
</tr>
<tr>
<td>Hosseinipour et al. [75]</td>
<td>Jan 2003–Mar 2017</td>
<td>Central and southern Malawi</td>
<td>Randomized control trial</td>
<td>ART naive-eligible</td>
<td>Pregnancy or post-partum</td>
<td>1269</td>
<td>&lt;1000</td>
<td>6 months post enrollment</td>
<td>84</td>
</tr>
<tr>
<td>Myer et al. [76]</td>
<td>Apr 2013–May 2014</td>
<td>Cape Town, South Africa</td>
<td>Retrospective cohort</td>
<td>ART naive-eligible</td>
<td>First ANC of current pregnancy</td>
<td>620</td>
<td>&lt;1000</td>
<td>Delivery</td>
<td>91</td>
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<td></td>
<td></td>
<td>&lt;50</td>
<td>Delivery</td>
<td>73</td>
</tr>
<tr>
<td>Myer et al. [11]</td>
<td>Apr 2013–May 2014</td>
<td>Cape Town, South Africa</td>
<td>Prospective cohort</td>
<td>Women who initiated ART during pregnancy and achieved initial viral suppression during follow-up</td>
<td>First ANC of current pregnancy</td>
<td>523</td>
<td>&lt;50</td>
<td>Across follow-up (median 322 days) during the postpartum period: 7 days, 6 weeks, 3 months, 6 months, 9 months, and 12 months</td>
<td>70</td>
</tr>
</tbody>
</table>

ANC: antenatal clinic; cp: copies; VL: viral load.

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6. Kesho Bora Study Group. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of...


Traversing the cascade: urgent research priorities for implementing the ‘treat all’ strategy for children and adolescents living with HIV in sub-Saharan Africa

Leslie A Enane1*, Mary-Ann Davies2, Valériane Leroy3, Andrew Edmonds4, Edith Apondi5, Adebola Adedimeji6 and Rachel C Vreeman1

1 Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA
2 Center for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa
3 Inserm (French Institute of Health and Medical Research), UMR 1027, Université Toulouse 3, France
4 Department of Epidemiology, University of North Carolina at Chapel Hill, NC, USA
5 Moi Teaching and Referral Hospital, Eldoret, Kenya
6 Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

Abstract

Children and adolescents living with HIV (CALHIV) in sub-Saharan Africa experience significant morbidity and alarmingly high mortality rates due to critical gaps in the HIV care cascade, including late diagnosis and initiation of treatment, as well as poor retention in care and adherence to treatment. Interventions to strengthen the adult HIV care cascade may not be as effective in improving the cascade for CALHIV, for whom specific strategies are needed. Particular attention needs to be paid to the contexts of sub-Saharan Africa, where more than 85% of the world’s CALHIV live. Implementing the ‘treat all’ strategy in sub-Saharan Africa requires dedicated efforts to address the unique diagnosis and care needs of CALHIV, in order to improve paediatric and adolescent outcomes, prevent viral resistance and reduce the number of new HIV infections. We consider the UNAIDS 90-90-90 targets from the perspective of infants, children and adolescents, and discuss the key challenges, knowledge gaps and urgent research priorities for CALHIV in implementation of the ‘treat all’ strategy in sub-Saharan Africa.

Keywords: children, adolescents, HIV/AIDS, sub-Saharan Africa, HIV care cascade, HIV care continuum, antiretroviral therapy

Introduction

The ambitious UNAIDS 90-90-90 targets intend that, by 2020, 90% of people living with HIV are diagnosed, 90% of those who are diagnosed are on antiretroviral therapy (ART), and 90% of those on ART are virally suppressed [1]. Central to these targets is achieving them for all people living with HIV, which requires particular attention to vulnerable groups who remain furthest from reaching them [2]. Children and adolescents living with HIV (CALHIV) continue to experience alarmingly high mortality and poorer outcomes in the HIV care cascade compared to adults [2]. CALHIV have much to gain from the ‘treat all’ strategy, and they also have specific needs that must be addressed to ensure its successful implementation [3–6]. Here, we consider the 90–90–90 targets from a paediatric perspective, and discuss the key challenges, knowledge gaps and urgent research priorities in implementing the ‘treat all’ strategy in sub-Saharan Africa. This review is informed by systematic activities to set global HIV research priorities undertaken by both the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), and the International Epidemiology Databases to Evaluate AIDS (iDeA), with adaptation to incorporate current paediatric evidence and the input of stakeholders from sub-Saharan Africa [7].

Challenges throughout the HIV care cascade for infants, children and adolescents

UNAIDS estimates that there were approximately 1.8 million children living with HIV (CLHIV, ages 0–14), and 1.8 million adolescents living with HIV (ALHIV, ages 10–19) globally in 2017, of whom more than 85% lived in sub-Saharan Africa (Table 1) [8]. CALHIV experience complex challenges accessing HIV testing and care and adhering to ART, resulting in late diagnoses, poor viral suppression and high mortality [2]. While deaths have declined substantially among CLHIV, there were 110,000 deaths in this group in 2017 [8]. Meanwhile, ALHIV have been the only age group with increasing deaths in recent years, despite a massive scale-up in the availability of ART [8].

The epidemic among infants and children

Although vertical transmission of HIV has significantly decreased in recent years, global ART coverage for prevention of vertical transmission is currently at 80%, and in 2017 there were 180,000 new paediatric infections [8]. Infants under 12 months and later 24 months of age were the first to have a recommendation for universal treatment in 2008 and 2010, respectively, and they have the most dramatic benefit from immediate treatment [9]. In this context, current gaps in infant diagnosis and treatment are particularly concerning, and contribute to high early HIV-related mortality before the age of 2 years [10]. Paediatric diagnosis is frequently delayed, with the majority of CLHIV in low- and middle-income countries initiating ART at a stage of advanced immunodeficiency [11–13]. Late perinatal diagnosis sets the stage for advanced illness and medical vulnerability, inadequate immune recovery once ART is initiated, development of opportunistic infections, and neurological and inflammatory consequences of uncontrolled HIV [14]. Beyond diagnosis, significant proportions of CLHIV are not accessing ART or achieving viral suppression [2].

The epidemic among adolescents

HIV is a leading cause of death among adolescents in sub-Saharan Africa [15]. The number of ALHIV has been steadily increasing, composed of both adolescents who acquired HIV vertically with long-standing infections and those with recently acquired HIV [16–19]. It is estimated that ALHIV with vertically acquired
infection make up a majority of this age group; however, there are limited available data disaggregated by mode of infection [19–21]. Among adolescents who recently acquired HIV, two-thirds are males, as a result of factors including gender-based inequity and violence, lower HIV education, age-disparate relationships and poverty [22,23]. Adolescence encompasses rapid physiological, developmental, familial and social changes, such that adolescents have specific, evolving needs and capacities (such as the ability to manage one’s own appointments, or to adhere to medications, or to make independent decisions about one’s own care) over these years that extend into young adulthood (ages 20–24)[24]. Adolescents have unique challenges in their HIV care, including those related to access to testing and care, parental consent policies, adolescent disclosure, a shift from dependence on caregivers to independence in care, and transition to adult HIV services [25–27]. Adolescent HIV care is complicated by stigma, fear of HIV status disclosure, mental health needs, and challenges experienced in family, school and clinic environments [27–30]. These factors are exacerbated by the settings of poverty and marginalisation in which many ALHIV live [31]. Improvements to the ALHIV care cascade are urgently needed, not only to improve adolescent outcomes, but also to end the AIDS epidemic, via reduction of vertical and horizontal HIV transmission and prevention of viral resistance.

### Target: 90% of people living with HIV diagnosed

Missed opportunities to diagnose infants and children

While perinatal HIV infection is associated with high mortality in infancy [10], there is a cohort of survivors of untreated perinatal HIV infection who are not diagnosed until reaching advanced illness, even into their second decade of life [16–18]. Current models estimate that two-thirds of infants acquire HIV in utero or at delivery, and experience rapid progression of illness, with a median survival of 1 year; the remaining infants acquire HIV during breastfeeding and are projected to experience slower disease progression, with a median survival to age 14 without treatment [32–34]. Many perinatally infected children are not identified, due to missed maternal HIV diagnoses, gaps in coverage of early infant diagnosis, and failures to diagnose children outside prevention of vertical transmission programmes [11,35]. WHO recommends testing all HIV-exposed infants at 4–6 weeks of age, but early infant diagnosis coverage remains a challenge, with huge geographical heterogeneity in sub-Saharan Africa [36]. In 2015, only 49% of HIV-exposed infants globally had a virological HIV diagnosis within the first 2 months of life [2]. An analysis of HIV programmes in six African countries and Haiti found that the proportion of HIV-exposed infants tested for HIV within 6 weeks of birth surpassed 50% only in South Africa and Zambia, and mean result turnaround times ranged from 22 to 38 days [37]. Moreover, there are missed opportunities to diagnose children seen in other healthcare settings, and a high potential yield for identifying children with previously undiagnosed HIV, particularly in inpatient and nutrition centres [16,35,38]. A study of primary school students found a significant burden of undiagnosed HIV, and important barriers to testing, including parental fears of ‘unmasking’ their own status and of the child experiencing stigma [39]. There is an urgent need to scale up and optimise provider-initiated HIV testing adapted to age, integrated with prevention programmes, HIV, and maternal and child health programmes, and paired with timely treatment initiation.

Most ALHIV have not been diagnosed

Inadequate testing currently presents a significant gap in the adolescent care cascade, and it precludes the subsequent steps of engagement in care and successful treatment. Demographic and health survey data from Congo (Brazzaville), Mozambique, Nigeria and Uganda, including 23,367 respondents aged 15–24 years, showed that 36.5% overall – and only 26.5% of 15–19-year-olds – had ever tested for HIV [22]. As a result of low testing uptake, it is estimated that a majority of ALHIV have not been diagnosed [2]. Population-based HIV Impact Assessments (PHIA) conducted in Malawi, Zambia and Zimbabwe found that only 46% of youths living with HIV (YLHIV, ages 15–24) were aware of their HIV status, compared to 65% of 25–34-year-olds, and 78% of 35–59-year-olds [2,40–42]. Among participants in the SEARCH study in Kenya and Uganda, only 50% of YLHIV were aware of their status at baseline, compared to 67% of older adults [43]. While there are few data on testing in the younger, 10–14-year-old adolescents, a study from Zimbabwe found that

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**Table 1. UNAIDS estimates of children (ages 0–14) and adolescents (ages 10–19) living with HIV in sub-Saharan Africa and globally, in 2017**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage of global total (%)</th>
<th>Number of new infections</th>
<th>Percentage of new infections (%)</th>
<th>Number of AIDS deaths</th>
<th>Percentage of global total (%)</th>
<th>Percentage of children with HIV on ART (%)</th>
<th>Percentage coverage of pregnant women receiving ART for PMTCT (%)</th>
</tr>
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<tr>
<td><strong>Sub-Saharan Africa</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Children living with HIV</td>
<td>1,700,000</td>
<td>94.4</td>
<td>159,000</td>
<td>88.3</td>
<td>97,000</td>
<td>88.2</td>
<td>49.3</td>
<td>81.2</td>
</tr>
<tr>
<td>Adolescents living with HIV</td>
<td>1,540,000</td>
<td>85.6</td>
<td>189,000</td>
<td>75.6</td>
<td>75.1</td>
<td>35,000</td>
<td>92.1</td>
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<tr>
<td><strong>East and Southern Africa</strong></td>
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<td></td>
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<tr>
<td>Children living with HIV</td>
<td>1,200,000</td>
<td>66.7</td>
<td>92,000</td>
<td>51.1</td>
<td>52,000</td>
<td>47.3</td>
<td>59.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Adolescents living with HIV</td>
<td>1,100,000</td>
<td>61.1</td>
<td>120,000</td>
<td>48.0</td>
<td>80.0</td>
<td>22,000</td>
<td>57.9</td>
<td></td>
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<tr>
<td><strong>West and Central Africa</strong></td>
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<td></td>
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<tr>
<td>Children living with HIV</td>
<td>500,000</td>
<td>27.8</td>
<td>67,000</td>
<td>37.2</td>
<td>45,000</td>
<td>40.9</td>
<td>26.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Adolescents living with HIV</td>
<td>440,000</td>
<td>24.4</td>
<td>69,000</td>
<td>27.6</td>
<td>66.7</td>
<td>13,000</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>1,800,000</td>
<td>180,000</td>
<td>110,000</td>
<td>52.0</td>
<td></td>
<td>80.0</td>
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</tr>
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</table>

they were less likely to be offered testing than children aged <7 years, despite the burden of undiagnosed perinatal infection in this group [18,44]. In a study from Botswana, in comparison to older age groups, 10–14-year-olds diagnosed with TB were least likely to have an HIV test; however, of those tested, 52% were HIV-infected [45].

Important barriers to adolescent HIV testing include low perceived risk of infection, fear of stigma, financial costs and gender inequality [46]. These may be particularly significant for younger adolescents. In a mixed-methods study from Zimbabwe, a major reason for providers not offering HIV tests to children aged 6–15 was concern about the suitability of the accompanying caregiver to provide consent [44]. This is a significant challenge in countries of sub-Saharan Africa with generalised HIV epidemics, where a high proportion of children are AIDS orphans, adult migration for work is common, children are cared for by multiple relatives, legal documentation of guardianship is unusual, and policies around consent for HIV testing are varied, without clear guidance on who may give consent [44].

Target: 90% of diagnosed people living with HIV on sustained ART

The treatment gap for infants and children

ART is lifesaving for CALHIV. Highlighting the urgency of early infant diagnosis, linkage to care and prompt treatment, initiation of ART before 3 months of age potentially reduces child HIV-associated mortality by 75% [9,47]. Current estimates are that only 52% of CLHIV globally are receiving ART; 59% in eastern and southern Africa, and 26% in western and central Africa [8]. In an analysis of leDea global cohort data, including 135,479 CALHIV aged 0–19 (over 95% from sub-Saharan Africa), during 2004–2015, 20% were lost to follow-up (LTFU) prior to ART initiation, possibly representing undocumented mortality [48]. Infants had 66% cumulative incidence of ART initiation at 24 months (95% confidence interval (CI) 66–67%); and infants and ALHIV ages 15–19 had the lowest ART initiation of all age groups [48]. ART initiation was lowest in sub-Saharan Africa [48]. Barriers to high ART coverage among CLHIV include delayed diagnosis, limited health worker capacity and poor supply chain for paediatric HIV commodities [3].

The challenge of retention among adolescents

Data from across sub-Saharan Africa have demonstrated poor ART initiation and retention among ALHIV [43,48–51]. In the SEARCH study, only 64% of previously diagnosed YLHIV were on ART at baseline, compared to 81% of older adults [43]. In the analysis of leDea paediatric cohorts, the cumulative incidence of ART initiation was lowest among ALHIV ages 15–19 years, with 62% initiating ART by 24 months (95% CI 62–63%) [48]. Older adolescents were most likely to be LTFU, as has also been reported in studies across sub-Saharan Africa [48,49,52–54]. This finding might reflect that the 15–19-year-old group included those with more recent infection, as ART eligibility at enrolment was correlated with cumulative ART initiation [48]. Adopting the ‘treat all’ strategy could improve retention among ALHIV who were previously not ART-eligible; however, age- and context-specific strategies for improving retention are urgently needed to reach 90–90–90 targets [43,48,55].

Complex barriers to retention for CALHIV

CALHIV experience significant barriers to retention. A cohort study from South Africa found that only 66% of CLHIV were retained in care, with greater attrition in recent years and in infants [56]. A case-control study of paediatric patients in Botswana found that factors associated with LTFU included: age <5 years, advanced HIV disease, greater immunosuppression and not receiving ART [57]. Nearly half of the LTFU patients had dropped out of care after just one clinic visit [57]. Early attrition from care has been reported in other studies of CALHIV, highlighting the need to engage patients on their initial presentation to HIV care [48,50,57,58]. Barriers cited by parents of LTFU CLHIV included beliefs that the child was well, fear of stigma and disclosure issues [57]. Barriers to retention for ALHIV include stigma, illness or death of family members, mental health challenges, substance abuse, poverty, and factors of clinic and school environments [27,30,38,59–61]. Facilitators to retention for CALHIV include social and family support, as well as future orientation and self-sufficiency of adolescents [27,29,60–62].

Target: 90% of people receiving ART with suppressed viral load

Gaps in viral suppression among infants and children

CALHIV have lower viral suppression compared to adults [52,63–66]. Viral suppression is critical to achieving optimal treatment outcomes, including neurocognitive and growth outcomes [63]. Meanwhile, there is a need for expanded access to routine viral load testing. At present, population-based estimates for paediatric viral suppression are lacking, as are data to identify factors associated with virological failure. A South African study found that only half of retained children achieved viral suppression [56].

Emerging data highlight reduced efficacy of specific ART regimens in CALHIV. A South African study demonstrated lower viral suppression for CLHIV when abacavir was used as part of a first-line ART regimen, compared to older, stavudine-based regimens [67]. With shifts in ART regimens, potential impacts on efficacy and adherence should be considered [67]. A lack of appropriate paediatric formulations remains a critical barrier [68]. There are also significant challenges identifying virological failure and HIV resistance in CLHIV, and providing second- or third-line regimens for lifelong ART [7].

Challenges for viral suppression among adolescents

Among YLHIV on ART, the PHIA surveys found that only 79% were virally suppressed, compared to 90% of adults. Given gaps earlier in the cascade, this translated to only 30% of all YLHIV with viral suppression; far below the target of 73% [2]. Similarly, in the SEARCH study, only 26% of all YLHIV had viral suppression at baseline [43]. In a study of adolescents who acquired HIV perinatally in global cohorts, 65% of African ALHIV experienced viral suppression at last visit, where viral load was available [20].

Adolescents have significant, complex challenges adhering to ART. A meta-analysis estimated that 62% of ALHIV and YLHIV globally are >95% adherent to ART, with higher adherence in Africa and Asia, although there was variability in measures of adherence used [69]. A study of Tanzanian ALHIV found an association between mental health difficulties with both stigma and decreased adherence [70]. Among ALHIV in Malawi, barriers independently associated with missed doses in the past week included alcohol use, missed clinic appointments, violence in the home and poor treatment self-efficacy [71].

Research gaps and priorities for CALHIV

Achieving the 90–90–90 targets for CALHIV will require significant improvements along the HIV care cascade, tailored to the
specific needs of CALHIV. CALHIV may be the furthest behind in reaching the 90-90-90 targets, yet the successful implementation of the ‘treat all’ strategy will have immense potential benefits for this population [63]. Earlier diagnosis, initiation of ART and improved quality of care to achieve viral suppression will be life-saving for CALHIV. Improvements to the adolescent care cascade will not only reduce their mortality, but also: reduce transmission to partners, reduce vertical transmission, and foster a healthy productive adulthood, as well as improving maternal and child health outcomes. Linkage of testing to prevention services could have the additional benefit of promoting uptake of prevention measures, including pre-exposure prophylaxis (PrEP) [4]. Improved estimates of the CALHIV epidemic are needed to guide the global response and tailor services to this group. Research is urgently needed to identify cost-effective interventions at each stage of the care cascade and to learn how to implement these at scale. Interesting and informative examples of work in these areas are highlighted.

The need for improved estimates for the paediatric and adolescent epidemics

Despite the burden of HIV among children and adolescents globally, there are significant gaps in the empirical data that guide the response to the epidemic. There is a critical need for accurate estimates for CALHIV, regarding: the number and proportion undiagnosed, timeliness in achieving care cascade stages; treatment outcomes, including HIV drug resistance and outcomes after LTFU and transfer-out; and definitive data on mortality. There is a need for disaggregation of data by 5-year age groups, sex and mode of infection. There is also a need for behavioural surveys to be designed for use among adolescents and disaggregated by age, particularly to address ALHIV from key populations [72].

Importantly, it is not currently known what proportion of ALHIV experienced vertical or horizontal routes of infection, and these groups may have different needs and require different responses for successful diagnosis and treatment [20,21,72]. To describe outcomes among likely perinatally infected adolescents, a recent analysis of 12 global paediatric cohorts evaluated ALHIV who enrolled in care before age 10 years and were not known to have horizontally acquired HIV [20]. Rates of LTFU and transfer-out were significantly higher among African ALHIV compared to other regions, and were likely to include unascertained mortality [20]. Given increasing HIV-associated mortality among adolescents, understanding the causes of ALHIV mortality is critically important.

Adapting HIV diagnosis and linkages to care for paediatric populations

Addressing gaps in paediatric and adolescent diagnosis and linkage to care will require an evaluation of appropriate context-specific interventions, their effectiveness, and their implementation within healthcare systems and service delivery models, including integration of HIV care with prevention of vertical transmission, maternal child health programmes, and paediatric and adolescent healthcare services. Testing innovations, including rapid point-of-care HIV testing for infant diagnosis and expansion of paediatric testing at other entry points to the health system, may enhance timely diagnosis of HIV in CALHIV and decrease the time to ART initiation [73]. Modelling studies evaluating routine HIV testing at birth (to diagnose in utero infection requiring urgent ART), in addition to currently recommended testing at 6 weeks, demonstrated improved outcomes, including ART initiation before 3 months and decreased infant mortality, and cost-effectiveness [74,75]. A study in Botswana showed promise for targeted neonatal testing to diagnose in utero transmission in high-risk infants [76]. There is potential for community-based interventions to enhance uptake of testing and linkage to care. A nested cohort study in Nigeria evaluated a church congregation-based intervention designed to increase uptake of HIV testing among pregnant women, and found that early infant diagnosis was higher and HIV vertical transmission was lower among participants compared to baseline [77]. The SEARCH trial of a community-based testing and treatment programme achieved an increase from 50.3% to 86.5% of YLHIV being aware of their status; although viral suppression remained suboptimal due to reported difficulties with stigma and care logistics while at boarding school [43].

The WHO has developed guidelines for adolescent HIV testing and care directed at policymakers and programme managers, including recommendations to revisit policies around age of consent for HIV testing and facilitating access to care for ALHIV, particularly those from key populations [78]. There is a need to study service delivery interventions and care models to improve access to testing (and repeat testing), linkage to care, and ART initiation with attention to the needs of ALHIV [7]. In South Africa, implementation of an integrated Youth Centre incentivising utilisation of services resulted in greater numbers of young adolescents (ages 12–15 years), particularly males, testing for HIV; among older adolescents, more individuals tested at the community clinic [79]. A systematic review found that provider-initiated infant HIV testing and home-based HIV testing of children and adolescents appear to have high acceptability [80]. Home-based testing in the PopART trial was accepted by 80% of adolescents aged 15–19, and the number of adolescents who knew their status increased from 28% to 89% [81]. Self-testing strategies for adolescents have demonstrated high uptake [82], acceptability [83] and cost-effectiveness [84]. Targeted strategies are urgently needed for adolescents from key populations for increased and repeated testing, enhanced linkage to HIV care for all testing positive, and prevention services for those testing negative, including PrEP [85,86].

Integrating tailored support into service delivery

More research around interventions and service delivery models to improve CALHIV outcomes in the care cascade, including linkage to care and retention on ART, would guide service delivery [3,5,7,27,87]. This should specifically include models to integrate HIV care into other health systems, including maternal child health clinics and general paediatric and adolescent health services. Psychosocial support strategies, such as family support and interventions, disclosure support, and stigma reduction in clinical, school and community settings, should be pursued1. Integrating interventions for mental health issues and substance use disorders into HIV care would mitigate the significant mental health barriers CALHIV face in accessing and continuing in care [28,70].

Though a recent systematic review found that few interventions have been studied to improve retention of ALHIV, promising potential strategies include education and counselling, peer interventions, financial interventions, clinic accessibility and specific adolescent-friendly services [87]. There is a need for rigorous, larger studies to evaluate these potential areas of intervention [87]. A few observational studies have evaluated the impact of adolescent-friendly services on retention in care, with mixed results [27,50,58,88,89]. Potential reasons for this are that adolescent-friendly services may be insufficient to mitigate the complex challenges to retention for many ALHIV, or that ALHIV become LTFU before engaging effectively with these interventions [27]. Differentiated care models have shown promise in improving adult engagement with HIV services, but it is less clear how effective this approach will be for ALHIV [87]. In Zimbabwe, CALHIV managed
within a decentralised HIV care model experienced encouraging retention in care, though only 64% achieved viral suppression [64]. Importantly, strategies are needed to specifically address sexual and reproductive health outcomes of ALHIV, pregnant ALHIV and ALHIV from key populations, and there are few studies in these areas [85,86,90,91]. More data on strategies to support ALHIV to successfully transition to adult HIV services are critically needed to reduce attrition from care at this stage [92,93].

Improving viral suppression and treatment outcomes for CALHIV

There is a very small evidence base for interventions to improve paediatric and adolescent adherence to ART, and consequently, viral suppression [85,86,91,94]. A systematic review of ART adherence interventions for ALHIV ages 13–24 found that, out of a few studies meeting inclusion criteria, most were small, unreplicated pilot studies conducted in the USA [94]. Evidence was found for a phone-based adherence monitor intervention, and for individual and family counselling, to improve viral suppression [94]. The BREATHER trial demonstrated that a ‘weekends-off’ efavirenz-based ART regimen in participants aged 8–24 on first-line ART was non-inferior to a continuous regimen, and had a better safety profile, presenting a treatment option aiming to lessen treatment fatigue, meet lifestyle needs and facilitate adherence [95]. While the introduction of dolutegravir offers promise for ALHIV, given its once-daily dosing, a high genetic barrier for resistance, and lack of cross-resistance to first-generation integrase inhibitors, recent data indicating possible elevated risk of neural tube defects in infants following exposure during conception during conception may impact how it is used in adolescents [96]. Investigational long-acting injectable formulations of ART may have potential future use to facilitate adherence to treatment [97].

Other priority research areas include evaluating the impacts of HIV infection and of ART on paediatric and adolescent clinical outcomes, including virological outcomes, the potential for functional cure with very early ART in infancy, and development of opportunistic infections and non-communicable diseases [7]. Efforts to improve prevention, diagnosis and clinical management of TB and other co-infections will also be critical to improving outcomes.

Conclusions

Dedicated efforts are needed to meet the context- and age-specific needs of CALHIV, including a focus on critical research priorities. Targeted research to strengthen the child and adolescent HIV care cascade in the implementation of ‘treat all’ will translate to improved outcomes for these children and adolescents, followed by transitions to healthy adulthoods.

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Declaration of interests

The authors declare no conflicts of interest.

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References


Mathematical modelling to inform ‘treat all’ implementation in sub-Saharan Africa: a scoping review

April D Kimmel1*, Rose S Bono1, Olivia Keiser2, Jean D Sinayobye3, Janne Estill2,4, Deo Mujwara1, Olga Tymejczyk5,6 and Denis Nash5,6

1 Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond VA, USA
2 Institute of Global Health, University of Geneva, Switzerland
3 Research and Clinical Education Division, Rwanda Military Hospital, Kigali, Rwanda
4 Institute of Mathematical Statistics and Actuarial Science, University of Bern, Switzerland
5 Institute for Implementation Science in Population Health, City University of New York, NY, USA
6 School of Public Health, City University of New York, NY, USA

Abstract

Objective: Despite widespread uptake, only half of sub-Saharan African countries have fully implemented the World Health Organization’s ‘treat all’ policy, hindering achievement of global HIV targets. We examined literature on mathematical modelling studies that sought to inform scale-up and implementation of ‘treat all’ in sub-Saharan Africa.

Methods: We conducted a scoping review, a research synthesis to assess emerging evidence and identify gaps, of peer-reviewed literature, extracting study characteristics on ‘treat all’ policies and assumptions, setting, key populations, outcomes and findings. Studies were narratively summarised and potential gaps characterised.

Results: We identified 16 studies examining ‘treat all’ alone (n=12) or with expanded testing (n=7) and/or care continuum improvements (n=6). Twelve studies examined ‘treat all’ for Southern African countries, while none did so for Central Africa. Four included the role of resistance; one evaluated any key population. A range of health and economic outcomes were reported, although fewer studies formally assessed budget impact. Fourteen studies involved co-authors with any in-country affiliation; one study also had co-authors with local government affiliation. Overall, ‘treat all’ improves health outcomes and is cost-effective compared to deferred HIV treatment; ‘treat all’ with expanded testing or care continuum improvements may provide further health benefits. However, studies generally used optimistic assumptions about the implementation of expanded testing or care continuum improvements.

Conclusions: The modelling literature demonstrates improved health and economic benefits of ‘treat all’. Using mathematical modelling to inform real-world implementation of ‘treat all’ requires realistic assumptions about expanded testing and care continuum interventions across a wide range of settings and populations.

Keywords: HIV, mathematical modelling, treat all, sub-Saharan Africa

Introduction

In September 2015, the World Health Organization recommended ART initiation for all people living with HIV (PLWH), regardless of CD4 cell count [1]. This ‘treat all’ policy is a cornerstone for achieving subsequent UNAIDS 90-90-90 targets [2], that is, 90% of PLWH aware of their status, 90% of individuals with known status receiving ART, and 90% of individuals receiving ART achieving viral suppression by 2020. This, together with evidence-based prevention efforts, can end the global HIV epidemic. In sub-Saharan Africa, where nearly 70% of PLWH worldwide reside [3], ‘treat all’ has been adopted formally in most countries [4].

However, approximately half of sub-Saharan African countries have had limited or delayed ‘treat all’ implementation [4]. Questions remain on local scale-up and potential challenges, such as late presentation to care [5] or health workforce constraints [6]. Consequently, the local health outcomes that can be achieved through ‘treat all’ – and the policy’s value and affordability for specific settings or populations – are uncertain.

Insights into the future outcomes of ‘treat all’ can be gained through mathematical modelling. Mathematical modelling offers a means to use existing evidence to make formal, timely policy evaluations. Model-based analyses allow synthesis of health and/or economic data from multiple sources and permit decision-makers to extrapolate beyond evidence from a single clinical trial, target population, or geographical setting. They also offer a framework for managing uncertainty in the data informing the model and model assumptions, providing a plausible range of potential outcomes.

In 2009, a ground-breaking modelling analysis of ART scale-up in South Africa suggested that the transmission-prevention effects of ART, when implemented in the context of universal HIV testing and immediate ART, could nearly eliminate HIV transmission in a generalised epidemic [7]. While findings depended on optimistic policy scenarios (e.g. 100% annual uptake of voluntary HIV testing), this work ignited policy discussion on the recommendation and implementation of ‘treat all’ policies. The current study aims to summarise the breadth of the mathematical modelling literature seeking to inform ‘treat all’ scale-up, including implementation challenges, in sub-Saharan Africa.

Methods

We conducted a scoping review of peer-reviewed literature using mathematical modelling to examine the scale-up, implementation challenges, and research gaps of ‘treat all’ in sub-Saharan Africa. Scoping reviews provide a broad overview of a particular field of study and identify gaps in knowledge [8,9]. After specifying search terms (Box 1), we identified candidate studies by searching PubMed/MEDLINE, by examining candidate article references, and through co-author recommendation [9]. One analyst identified studies in July/August 2017 and March 2018, and two
This review defines ‘treat all’ as provision of ART immediately after HIV diagnosis, regardless of CD4 cell count. ‘Treat all with expanded testing’ is defined as provision of ART immediately after HIV diagnosis, regardless of CD4 cell count, with additional efforts to diagnose HIV cases. We considered ‘treat all with care continuum improvements’ as immediate ART, regardless of CD4 cell count, with additional efforts to improve care continuum outcomes (e.g. improvements in linkage, retention or adherence), with or without expanded HIV testing. We defined these terms, since the literature uses terms such as ‘treat all’, ‘test-and-treat’, and ‘universal treatment’ inconsistently.

Included studies met all of the following pre-specified criteria: use of a mathematical model to project outcomes over time; assessment of any ‘treat all’ policy; a study objective to examine ‘treat all’ scale-up or implementation; study population including, but not limited to, adults; sub-Saharan African setting; and published in English by 31 March 2018. We excluded studies examining ‘treat all’ primarily as a strategy to prevent HIV transmission (alone or in combination with other prevention interventions), since they do not directly address ‘treat all’ implementation challenges, the focus of the current study. We excluded studies assessing ‘treat all’ as a component of other infectious disease control strategies, studies examining ‘treat all’ in the context of clinical trial design or mathematical modelling methods assessment, and studies that did not model a ‘treat all’ policy for a specific country or countries, although we assigned a country if one was not specified and most data came from a particular locale. No restrictions were made based on type of mathematical model, ‘treat all’ policy or policies evaluated, outcomes examined, or specific key populations modelled or assessed.

Data were extracted on: ‘treat all’ policies assessed and their definitions, assessment of implementation challenges and constraints, policy assumptions (e.g. HIV testing frequency and coverage), other model assumptions, country, region within sub-Saharan Africa [10], and health and/or economic outcomes assessed. We also extracted data on gender and key population(s), which we defined broadly as any vulnerable, under-served, or hard-to-reach population (e.g. female sex workers). We examined involvement of local stakeholders, reporting the number of studies with a co-author having any documented affiliation in the country for which a ‘treat all’ policy was assessed and the number with a co-author having any local government affiliation, including Ministry of Health. Finally, we extracted data on model type, level (e.g. individual, population), inclusion of transmission dynamics, reduced infectivity due to ART, model structural decisions (e.g. age- and/or sex-stratification), and evidence of uncertainty analysis and model performance assessment.

We identified commonalities among studies, summarised commonalities using narrative synthesis, and highlighted potential knowledge gaps to articulate research priorities.

Results

Study characteristics

Sixteen studies met eligibility criteria [11–26] (Figure 1). Fifteen were identified using the database search [11,12,14–26] and one through co-author recommendation [13]. Of the 16 studies, seven have been published since 2015 [12,19,20,22–24,26]. Table 1 shows key study characteristics.

We found wide variation in how ‘treat all’ implementation was evaluated. ‘Treat all’ alone was considered in 12 studies [11,12,15–17,19–24,26]. ‘Treat all with expanded testing’ only was examined in seven studies [13,14,18,19,22,24,25], while ‘treat all with care continuum improvements’ was assessed in six [14,16,17,22,24,26].

Across the seven studies examining ‘treat all with expanded testing’, testing coverage for the general adult population was assumed to be 90% [18,19] or 100% [25] annually, with two studies assuming 90% testing coverage less frequently at every 2 [14] or 4 years [24], another assuming lower testing coverage at 20% and 50% annually [13], and one assuming testing rates were doubled [22].

Studies modelling ‘treat all with care continuum improvements’ did so individually and in combination. Examples included: increasing rates of linkage to care [17]; improving rates of linkage to care and ART re-initiation, while reducing drop-out rates [22]; and improving rates of linkage, re-entry into pre-ART care, and retention on ART, as well as use of point-of-care CD4 testing (routinely and during testing) [24]. Rate adjustments assessed at all steps along the care continuum largely did not appear to be based on empirical estimates from the literature; rather, rates were increased or decreased by a multiplier, e.g. linkage rates doubled or dropout halved.

Few studies examined ‘treat all’ implementation challenges, such as late diagnosis [13,17,24,26] and/or delayed ART initiation [23,26], although two considered ‘treat all’ with explicit resource constraints, resulting in limited treatment slots [19,26]. Additional policy responses – such as task-shifting or international competition to lower drug prices [23], or no availability of more costly viral load monitoring or second-line ART [26] – were also assessed when resources are constrained.

‘Treat all’ implementation was assessed for multiple countries (Figure 2), with most studies reporting outcomes for the overall population in a given setting. Three of four sub-Saharan African regions were represented; 12 studies assessed ‘treat all’ in Southern Africa [12–14,16–21,23,25,26], six in East Africa [12,15,19,20,22,24], four in West Africa [11,12,19,26] and none in Central Africa. Twelve studies either examined ‘treat all’ in the context of South Africa or used primarily South African data [12,13,17–21,23,25,26]. ‘Treat all’ was not assessed sub-nationally in any study. While many models are age- and/or sex-structured, no studies reported outcomes separately by age group (e.g. adolescents) and only one study reported outcomes separately by sex [13]. Similarly, while some studies explicitly incorporated key populations in the model structure, no studies

Box 1. Database search specifications

PubMed/MEDLINE search term:

(“Africa”[Mesh] OR “low income countries” OR “middle income countries” OR “sub-Saharan Africa” OR hyperendemic) AND (HIV OR “human immunodeficiency virus” OR AIDS OR “acquired immunodeficiency”) AND (“test and start” OR “test and treat” OR universal OR “treat all” OR “early initiation” OR regardless OR “combination prevention” OR “multiple intervention”* OR eligib* OR threshold OR expand* OR “fast-track” OR “treatment as prevention”) AND (mathematic* OR simulation OR dynamic* OR compartment* OR “agent-based” OR systems* OR stochastic OR deterministic OR epidemic OR epidemiologic* OR transmission OR cost* OR model* OR modelling OR modelling) Filters:

English language; publication dates 01/01/2009 to 03/31/2018

analysts extracted data in March/April 2018; the first author reviewed a sub-sample of studies to ensure accuracy in study identification and data extraction.
examined ‘treat all’ implementation and outcomes specifically in key populations, although one study examined outcomes for individuals with HIV and hepatitis C and/or B co-infection [21].

Across studies, four reported only health outcomes, one reported only economic outcomes, and 11 reported both. For the 15 studies reporting health outcomes, types of health outcomes included: intermediate health outcomes (e.g. change in CD4 cell count), treatment-related outcomes (e.g. ART coverage) and long-term health outcomes (e.g. number of deaths, life expectancy). Three studies reported modelling of increasing resistance [15,16,25], and one both modelled and reported accumulation of drug resistance and its impact on first- and second-line ART outcomes [16]. Twelve studies reported on any HIV transmission-related outcome (e.g. prevalence [14,18], incidence or new infections [13–20,22,24–26]), although transmission-related outcomes were not the focus of this review.

Among the 12 studies reporting economic outcomes, the type of economic outcome reported also varied. These included: total or cumulative costs, cost-effectiveness (e.g. cost per disability-adjusted life year [DALY] averted), net monetary benefit, optimal set of health interventions under a budget constraint, and other economic outcomes related to affordability (e.g. financing or investment needs). Among studies reporting economic outcomes, cost-effectiveness was most frequently represented; few studies formally examined budget impact.

Studies used a variety of model structures, including single-cohort state-transition models, single- and multi-cohort individual-level microsimulations, and population-level dynamic compartmental models. Fifteen studies modelled HIV transmission and accounted for reduced infectivity due to ART. Analytic time horizons varied from 5 years to lifetime, although were most commonly 20–40 years. Eleven studies reported any uncertainty analysis, while 10 reported any model performance assessment.

Fourteen studies included co-authors with any in-country affiliation. All 14 studies had authors affiliated with universities or research units [11–20,22–24,26]; one of these studies also had a co-author with local government affiliation [23].

Synthesis of findings

Health outcomes

Studies found that implementation of ‘treat all’ increases life expectancy [14,15,21] and saves lives [13,14,19,21,26] versus deferred ART initiation. There appeared to be consensus that ‘treat all with expanded testing’ or ‘care continuum improvements’—in particular earlier diagnosis and/or linkage to care—further improves health outcomes compared to ‘treat all’ alone. However, there was little consistency in the composition of additional interventions, and their levels, that are required for successful ‘treat all’ implementation and achievement of national or global targets. For example, Bacaër et al. found that while ‘treat all with expanded testing’ saves lives and averts new HIV infections compared to ART initiation at a CD4 cell count of <200 cells/mm³, annual testing may not be necessary to end the South African HIV epidemic [13]. However, Olney et al. asserted that combining ‘treat all’ with multiple other strategies that improve linkage, utilise point-of-care CD4 cell count testing including upon diagnosis, and improve pre-ART retention, will avert more DALYs than ‘treat all with expanded testing’ only [24].
<table>
<thead>
<tr>
<th>Author/Ref</th>
<th>Setting</th>
<th>‘Treat all’ policy</th>
<th>‘Treat all’ policy definitions</th>
<th>Key population(s)†</th>
<th>Model structure</th>
<th>Policy assessment</th>
<th>Health</th>
<th>Economic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglaret [11]</td>
<td>Côte d’Ivoire</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>CD4 cell count change; cumulative risk of other diseases; mortality</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atun [12]</td>
<td>Ethiopia, Kenya, Malawi, Nigeria, South Africa, Tanzania, Uganda, Zambia, Zimbabwe</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>FSW, MSM, PWID</td>
<td>–</td>
<td>New infections averted; lives saved; person-years on ART</td>
<td>–</td>
</tr>
<tr>
<td>Bacaër [13]</td>
<td>South Africa</td>
<td>– Yes –</td>
<td>20% or 50% of population tested annually</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>New infections averted; deaths; prevalence; population growth</td>
<td>–</td>
</tr>
<tr>
<td>Bendavid [14]</td>
<td>South Africa</td>
<td>– Yes Yes</td>
<td>90% of population tested every 2 years; 67% or 100% of diagnosed linked to care; 80% or 100% retained in care</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>LMIs gained; number and rates of death; new infections; prevalence; population growth</td>
<td>–</td>
</tr>
<tr>
<td>Braithwaite [15]</td>
<td>Kenya, Uganda</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>FSW</td>
<td>–</td>
<td>Total discounted Ly's and QALYs; AIDS deaths; new infections</td>
<td>Total discounted cost; per-person annual costs; incremental cost per QALY gained</td>
</tr>
<tr>
<td>Cambiano [16]</td>
<td>South Africa</td>
<td>Yes – Yes</td>
<td>80% of ART-eligible in care; 92% retained in care 1 year after ART initiation</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>Number on/off ART, by regimen; incidence; number and % with NNRTI-resistant virus; % with transmitted drug resistance</td>
<td>–</td>
</tr>
<tr>
<td>Eaton [17]</td>
<td>South Africa, Zambia</td>
<td>Yes – Yes</td>
<td>Increased HIV testing and linkage so that 80% of ART-eligible in care</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>Annual incidence per 100 PYs; % new infections averted</td>
<td>Total incremental costs; incremental cost per DALY averted</td>
</tr>
<tr>
<td>Granich [18]</td>
<td>South Africa</td>
<td>– Yes –</td>
<td>90% of adults tested annually</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>Number (%) on ART, PYs on ART; deaths; DALYs; new infections; prevalence</td>
<td>Total costs; cost savings; incremental cost per DALY averted</td>
</tr>
<tr>
<td>Hontelez [19]</td>
<td>Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Tanzania, Uganda, Zambia and Zimbabwe</td>
<td>Yes Yes –</td>
<td>90% of adults tested annually</td>
<td>– –</td>
<td></td>
<td>–</td>
<td>Number with HIV; new infections; number on ART; LYS saved</td>
<td>Annual investment needs; cost per LY saved</td>
</tr>
<tr>
<td>Kuznik [20]</td>
<td>Nigeria, South Africa, Uganda</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>HBV- or HCV-co-infected HBV- or HCV-co-infected</td>
<td>– –</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Martin [21]</td>
<td>South Africa</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>McCleary [22]</td>
<td>Uganda</td>
<td>Yes Yes Yes</td>
<td>HIV testing rates doubled; drop-out rates halved; ART restart rates doubled; linkage doubled</td>
<td>– –</td>
<td>DALS averted; HIV incidence</td>
<td>Incremental cost per DALY averted; net monetary benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer-Rath [23]</td>
<td>South Africa</td>
<td>Yes – – –</td>
<td>–</td>
<td>–</td>
<td>Children &lt;13 years</td>
<td>–</td>
<td>Number initiating ART; number on ART</td>
<td>Total cost</td>
</tr>
<tr>
<td>Olney [24]</td>
<td>Kenya</td>
<td>Yes Yes Yes</td>
<td>90% testing coverage every 4 years; 30% linked if not previously diagnosed/40% linked if previously diagnosed</td>
<td>– –</td>
<td>DALS averted; % deaths averted</td>
<td>Total incremental costs; incremental cost per DALY averted; strategies maximising health gains given a budget constraint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wagner [25]</td>
<td>South Africa</td>
<td>– Yes –</td>
<td>100% of adults tested every 6 months to 4 years</td>
<td>– –</td>
<td>Testing and treatment needed to eliminate transmission; number on ART; number in need of ART, by regimen; reductions in incidence; new infections averted</td>
<td>Annual and cumulative treatment costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walensky [26]</td>
<td>Côte d’Ivoire, South Africa</td>
<td>Yes – Yes</td>
<td>Initial mean CD4 cell count 160–199 cells/mm³; 92% retained in care at 1 year and 70% at 5 years</td>
<td>– –</td>
<td>HIV transmission; deaths; years of life lost</td>
<td>Total costs; budget savings</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* Entries of ‘–’ indicate that no information was reported on a given study characteristic.
† Key population was defined broadly as any vulnerable, underserved or hard-to-reach population.
Studies highlighted circumstances under which ‘treat all’ policies may result in suboptimal or unintended outcomes. For example, Anglaret and colleagues found that compared to deferred ART initiation at a CD4 cell count of 350 cells/mm$^3$, ‘treat all’ improves survival, but this finding may not hold if on-ART retention and treatment adherence is low [11]. Wagner and Blower further suggested that ‘treat all with expanded testing’ may increase drug resistance, increasing the need for more costly second-line ART regimens, compared to universal access to treatment for those meeting lower CD4 cell count eligibility thresholds [25]. Projections from Cambiano et al. concurred, indicating that ‘treat all’ with expansions in diagnosis and retention would increase the number of PLWH with non-nucleoside reverse-transcriptase inhibitor drug resistance by approximately 25% compared to ‘treat all’ without such improvements [16].

**Economic outcomes**

Studies suggested that ‘treat all’, with or without expanded testing, increases per-person costs compared to deferred ART initiation [12,13,15,25,26], is cost-effective at conventional thresholds [17–20,22,24], and may decrease annual population-level economic costs in the longer term [18,23]. These findings were consistent across studies, which relied on different model structures but which all appeared to incorporate assumptions regarding reduced infectivity due to HIV viral suppression while on ART. In optimal conditions – such as high ART adherence and no costs associated with HIV counselling and testing – ‘treat all’ may have lifetime individual cost savings, assuming an annual discount rate of 3% [20]. Under similarly optimistic assumptions of annual HIV counselling and testing at 90% coverage, Granich and colleagues found that the upfront societal investment of expanding ART to all HIV-infected individuals is offset by cost savings of prevented HIV infections in 10 years or more when costs are discounted at 3% annually [18]. Atun et al. further found that upfront investments in ART will reduce costs in the long term, from $5 billion annually in 2015 to $1.8 billion by 2050 [12], when using annual discount rates of 3%.

Multiple studies indicated that simultaneous implementation of improvements along the care continuum may be necessary to efficiently employ limited resources. For example, while Eaton...
and colleagues found that ‘treat all with care continuum improvements’ is cost-effective over 20 years [17], the priority with which ‘treat all’ should be implemented changes depending on current ART coverage. That is, in settings with lower ART coverage, efficiency gains are greater when expanding HIV testing and linkage to care and maintaining a deferred, CD4 cell count threshold-based ART initiation policy; in settings with higher ART coverage, expanding ART eligibility is more efficient [17]. Similarly, Olney et al. suggested that a combination of care continuum improvements, but without expanded HIV testing, averts more DALYs for the same cost than ‘treat all with expanded testing’ only [24].

Emerging work examined ‘treat all’ in the context of affordability or explicit budgetary and health system constraints. Atun and colleagues suggested the resources required to scale up HIV services, including ‘treat all’, in sub-Saharan Africa cannot be met with domestic financing alone [12]. Monteale et al. modelled ‘treat all’ under different scale-up scenarios, including constraints on the number of individuals able to receive ART, and found that while ‘treat all’ is cost-effective compared to ART initiation at CD4 cell count <500 cells/mm³ under most scenarios, extreme supply-side constraints could result in a net health loss if healthier individuals crowd out less healthy individuals [19], assuming no policy that prioritises treatment for those with more advanced disease. Meyer-Rath and colleagues suggested that increases in costs under ‘treat all’ can be offset under different health system constraints, such as allowing for task-shifting and international competition for drug pricing [23]. Finally, Walensky et al. found that in South Africa and Côte d’Ivoire, CD4 cell count-based treatment eligibility criteria instead of a ‘treat all’ policy, which could occur with potential cutbacks in foreign aid, saves approximately $60 million across both countries over 10 years, but substantially increases HIV transmissions and deaths [26].

**Discussion**

A growing mathematical modelling literature from sub-Saharan Africa finds that the implementation of ‘treat all’ improves both individual- and population-level health, is cost-effective, and can reduce long-term population-level costs compared to deferred treatment initiation. While the knowledge base is strongest for ‘treat all’ alone, expanded HIV testing and other improvements along the HIV care continuum are likely required to achieve the full health and economic benefits of ‘treat all’.

The gaps in this literature highlight opportunities to gain further insights into the effective and efficient implementation of ‘treat all’ (Table 2). Despite broad consensus that earlier diagnosis and linkage improve individual and population health [7,28,29], we found little agreement on additional intervention composition or levels, which in many cases were defined optimistically, sometimes with unrealistically frequent testing, high coverage, high levels of retention and rapid ART initiation. Importantly, UNAIDS 90–90–90 targets do not directly address timely diagnosis and/or subsequent ART initiation, which ultimately reduce the time to viral suppression, driving reduced morbidity, mortality and onward transmission. Assumptions in the studies reviewed here largely did not reflect the realities of advanced disease stage at enrolment or the fact that previous ART eligibility expansions, despite resulting in significant increases in timely ART initiation at the original site of enrolment, generally did not achieve full uptake among eligible patients [30]. Similarly, few studies quantified unintended consequences and real-world challenges of ‘treat all’, including development of resistance [31], supply chain challenges [32], the unlikely possibility for crowd-out [30,33], and health system and other resource constraints [34,35]. Modelling studies from South Africa have addressed these issues most comprehensively, although not routinely and rarely in combination. The contextual relevance of future modelling studies would benefit from collaborative involvement not only by in-country researchers, who are largely represented in these studies, but also by local government officials (e.g. Ministry of Health) and other stakeholders who do not regularly conduct research.

Also notable are the settings and populations that remain unaddressed. A minority of studies assessed ‘treat all’ implementation for East and West Africa and none in Central Africa. Despite relatively low HIV prevalence in West and Central Africa, fewer than half of PLWH in these regions know their status, resulting in rates of ART coverage, retention and viral suppression (see Figure 2) that are among the lowest, and AIDS-related deaths among the highest, globally [36]. A greater absence in this literature is seen in assessment of ‘treat all’ by gender, age group and hard-to-reach populations – a concerning finding given that barriers to achieving UNAIDS targets are among the highest for men, adolescents and young adults, and key populations that may require differentiated care [36]. Finally, we found no sub-national ‘treat all’ assessments, which may require tailored interventions and greater country-level coordination [36].

This work complements two previous reviews. Ying et al. reviewed how principles of implementation science can be integrated into mathematical models of HIV prevention to improve universal access to ART [37], while Mikkelsen et al. called for inclusion of health-system constraints in cost-effectiveness analyses on ART scale-up [38]. While our review differs in its focus on modelling of ‘treat all’ implementation, findings are similar: to develop a more nuanced understanding of ‘treat all’ implementation, inclusion of real-world challenges and constraints is warranted but as yet unaddressed in the current modelling literature.

This review also complements a rich literature on modelling studies focusing on the transmission effects of ‘treat all’ or that include ‘treat all’ in prevention packages. The projected transmission effects of ‘treat all’ have been well studied, with a systematic comparison of 12 independent mathematical models finding that ART can reduce new infections when access and adherence are

**Table 2.** Key gaps in the mathematical modelling literature seeking to inform scale-up and implementation of ‘treat all’ in sub-Saharan Africa

<table>
<thead>
<tr>
<th>Gap</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Limited incorporation of unintended consequences and real-world challenges of ‘treat all’, such as late diagnosis, late ART initiation, resource constraints, development of drug resistance, and supply chain disruptions</td>
</tr>
<tr>
<td>•</td>
<td>Inadequate use of realistic assumptions for interventions along the care continuum, such as HIV testing coverage and frequency, that are necessary in addition to ‘treat all’ to achieve 90–90–90 targets</td>
</tr>
<tr>
<td>•</td>
<td>Lack of assessment of the role of timely diagnosis and/or timely ART initiation in not only achieving 90–90–90 targets, but accelerating the time to viral suppression and reducing morbidity, mortality and onward transmission</td>
</tr>
<tr>
<td>•</td>
<td>Little to no examination of ‘treat all’ in Central, East, and West Africa</td>
</tr>
<tr>
<td>•</td>
<td>Nearly absent assessment of ‘treat all’ implementation for men versus women, different age groups, and hard-to-reach or key populations</td>
</tr>
<tr>
<td>•</td>
<td>No sub-national examination of tailored interventions for implementing ‘treat all’</td>
</tr>
<tr>
<td>•</td>
<td>Limited involvement of Ministry of Health, other government officials or additional key in-country stakeholders, beyond academia</td>
</tr>
</tbody>
</table>
high, although longer-term projected outcomes and the efficiency with which ART reduces new infections varies [39]. This compilation adds to empirical evidence from a systematic review finding that ART reduces HIV transmission risk in sero-discordant couples [40]. Similar to our study, this literature confirms that improvements along the care continuum, and specific interventions and implementation strategies that could bring such improvements, are required to achieve the optimal health outcomes and full preventive benefits of ART [39,41]. Results corroborate findings from recent randomised trials: in eSwatini, ‘treat all’ implementation drastically increased viral suppression [42], a necessary precursor for ART to reduce transmissions, but in South Africa, a test-and-treat intervention did not reduce HIV incidence, probably because early diagnosis, linkage to care, and CD4 cell count at ART initiation were sub-optimal [43]. Myriad other modelling work from sub-Saharan Africa has examined the role of ‘treat all’ in combined prevention packages, alongside interventions like pre-exposure prophylaxis and condom distribution [44-49].

Limitations
First, we searched a single database and only reviewed articles in English. Second, we found substantial heterogeneity in the terms used to refer to ‘treat all’ policies, and despite refining our search strategy iteratively to include new terms [8,9], we may not have captured all relevant studies. Third, by excluding studies primarily examining transmission benefits of ‘treat all’, we cannot draw conclusions about the impact of ‘treat all’ on HIV transmission. However, a systematic comparison of 12 independent mathematical models finds that ART reduces new infections, assuming high antiretroviral access and adherence [40]. In this review, we expand on this comparison to understand how mathematical modelling studies have sought to address real-world challenges and constraints across settings and populations in order to scale-up and fully implement ‘treat all’. Fourth, projected outcomes were difficult to compare across studies, given varying model structures, assumptions and timeframes, as well as differing approaches and reporting regarding model performance. Finally, we did not include non-peer-reviewed grey literature.

Conclusions
Mathematical modelling studies can inform the scale-up and implementation of ‘treat all’ policies. While studies have confirmed that ‘treat all’ improves health and is cost-effective, questions surrounding ‘treat all’ implementation remain. Useful analyses will require realistic assumptions and more complete integration of health consequences and constraints, including real-world budgets. Development of country-specific models that address ‘treat all’ implementation sub-nationally and among different sub-populations is critical to ongoing policy assessment and achievement of global targets.

Acknowledgements
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References

Mathematical modelling for ‘treat all’ implementation


HIV drug resistance in sub-Saharan Africa: public health questions and the potential role of real-world data and mathematical modelling

Reneé de Waal¹, Richard Lessells², Anthony Hauser³, Roger Kouyos⁴, Mary-Ann Davies¹, Matthias Egger¹,3,5* and Gilles Wandeler³,5* for IeDEA-Southern Africa

¹Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, South Africa
²KwaZulu-Natal Research Innovation and Sequencing Platform, Department of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa
³Institute of Social and Preventive Medicine, University of Bern, Switzerland
⁴Division of Infectious Diseases and Hospital Epidemiology, University of Zurich, Switzerland
⁵Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland

Abstract

The prevalence of pretreatment resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is >10% in many low-income countries. As a consequence, several sub-Saharan African countries have implemented, or are considering the introduction of, non-NNRTI-based first-line antiretroviral therapy (ART) for treatment-naive and treatment-experienced patients. This is occurring at a time when ART programmes are expanding, in response to the World Health Organization guidelines, which recommend ART initiation regardless of CD4 cell count. Both those developments raise important questions regarding their potential impact on HIV drug resistance and the impact of HIV drug resistance on clinical outcomes. Those issues are particularly relevant to sub-Saharan Africa, where standardised ART regimens are used and where viral load monitoring and resistance testing are often not done routinely. It is therefore essential to forecast the impact of the implementation of ART, and the introduction of drugs such as dolutegravir to first-line regimens, on HIV drug resistance in order to inform future policies and to help ensure sustainable positive long-term outcomes.

We discuss important public health considerations regarding HIV drug resistance, and describe how mathematical modelling, combined with real-world data from the four African Regions of the International epidemiology Databases to Evaluate AIDS consortium, could provide an early warning system for HIV drug resistance in sub-Saharan Africa.

Keywords: HIV drug resistance, universal test-and-treat, dolutegravir, sub-Saharan Africa, mathematical modelling

Introduction

The widespread emergence and transmission of HIV drug resistance (HIVDR) has impaired the success of the currently recommended first-line antiretroviral therapy (ART) regimens including efavirenz in sub-Saharan Africa (SSA). The prevalence of pretreatment non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance ranges from 8% in Cameroon to 15% in Uganda [1]. As many countries in the region consider shifting to dolutegravir-containing regimens, surveillance and monitoring of HIVDR will be key to ensuring the durability of this new drug. The introduction of universal test-and-treat policies [2] will increase the number of individuals on ART from 20 million in mid-2017 to approximately 30 million by 2020. This rapid expansion of ART programmes might impact the occurrence of HIVDR, particularly in under-resourced health systems with little capacity for virological monitoring. In this article we discuss important public health considerations regarding HIVDR in SSA, namely the potential impact of universal test-and-treat policies on HIVDR, and the potential implications of HIVDR on the effectiveness of dolutegravir-based ART. We also identify gaps in current knowledge, and describe how we could address current and future challenges in the field using real-world data from the International epidemiology Databases to Evaluate AIDS (IeDEA), a large consortium of HIV cohorts, and mathematical modelling.

Universal test-and-treat policies and the emergence of HIV drug resistance in sub-Saharan Africa

Randomised controlled trials have shown the benefits of early ART initiation in terms of individual patient outcomes and a reduction in HIV transmission rates [3,4]. However, there are concerns that early ART initiation may increase the prevalence of antiretroviral drug resistance owing to compromised adherence, as patients who feel healthy might be less likely to be fully adherent [5]. Data regarding the impact of early ART on adherence and the development of HIVDR are limited and inconsistent. In a prospective study of 473 patients from Uganda, those who initiated ART with a CD4 cell count ≥250 cells/mm³ were twice as likely to have treatment interruptions of >72 hours in the first 90 days of ART, as assessed by electronic pill bottles. As a consequence, they were nearly three times as likely to have an HIV viral load >400 copies/mL at 120 days than those with CD4 cell count <250 cells/mm³ [6]. However, a study of 900 patients from South Africa found that CD4 cell count at ART initiation was not associated with adherence <95% in the first 12 months on ART (assessed by visual analogue scale and pill count) [7]. In terms of the impact of early ART initiation on HIVDR, in a cohort study from Europe, patients who initiated ART immediately (within 3 months of having a CD4 cell count and viral load measured while AIDS-free), were slightly more likely to develop drug resistance within 7 years than those who initiated ART at CD4 <500 cells/mm³ or <350 cells/mm³ [8]. In contrast, in the HPTN052 trial, which showed decreased HIV transmission between serodiscordant couples with ART initiation at a CD4 cell count of 350–550 versus <250 cells/mm³, the risk of drug resistance was higher in the delayed versus early ART initiation arm [9].

*Corresponding author: Gilles Wandeler, Department of Infectious Diseases, Bern University Hospital, Inselspital, 3010 Bern, Switzerland

Email: gilles.wandeler@insel.ch

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These differences in the effect of timing of ART initiation on the development of HIVDR might be explained by differences in adherence: patients in clinical trials are generally more closely monitored, and may be more motivated to take treatment than those in routine care. Although the evidence that early ART initiation in itself influences the emergence of HIVDR is not compelling, there is reason to believe that the continued expansion of ART programmes might result in increased rates of HIVDR through suboptimal adherence and suboptimal retention in care in the context of resource-limited health systems. Along with HIVDR surveys, adherence monitoring and interventions to improve adherence should be studied in more depth in these settings.

Potential implications of HIV drug resistance on the success of dolutegravir-based antiretroviral therapy in sub-Saharan Africa

In many African countries, the prevalence of pretreatment NNRTI resistance mutations is >10%, the World Health Organization’s threshold for countries to consider implementing non-NNRTI-based first-line ART [1,10]. As a consequence, many SSA countries have either started or are considering implementation of dolutegravir-based first-line ART, although recent concerns regarding its safety in early pregnancy may limit its use in women of childbearing age [11]. It is anticipated that dolutegravir will be used in both ART-naive and ART-experienced patients; the latter will switch from their current NNRTI-based first-line regimens. This raises concerns regarding its use in settings where resistance testing is not standard of care, and where even viral load monitoring may not be performed routinely.

Dolutegravir has a high genetic barrier to resistance and development of resistance mutations has not been shown in clinical trials of treatment-naive patients initiating dolutegravir-containing ART without pretreatment drug resistance [12,13]. In ART-naive patients, dolutegravir was superior to efavirenz and to ritonavir-boosted darunavir in terms of virological outcomes, and much of that superior efficacy was due to dolutegravir’s better tolerability [12,13]. However, in a study of dual therapy with dolutegravir and lamivudine in the US, three out of 120 patients had virological failure at 24 weeks, and one patient developed resistance mutations to both drugs (M184V and R263R/K) [14]. This patient was thought to be poorly adherent to ART as his plasma dolutegravir concentrations were below the limit of quantification on at least one occasion.

In treatment-experienced patients receiving dolutegravir, development of HIVDR is also uncommon, but has been reported in patients on dolutegravir monotherapy. In the DOMONO trial, ART-experienced patients who were virologically suppressed were randomly allocated to switch to dolutegravir monotherapy immediately or at 24 weeks [15]. Eight of 95 participants experienced virological failure and three developed integrase resistance mutations at 48 weeks. In another clinical trial from Spain, two of 31 patients who were randomly allocated to be switched to dolutegravir monotherapy developed integrase resistance [16]. The authors of both studies concluded that dolutegravir should not be used as monotherapy. Of note, ART-experienced patients in the studies described above were virologically suppressed at baseline, and patients with previously documented HIVDR were excluded. Routine viral load monitoring is not carried out in many SSA countries, so it is likely that many patients will switch to dolutegravir-based ART when they are not virologically suppressed. The DAWNING study, a multicentre trial that randomly allocated patients whose first-line ART was failing to receive dolutegravir-based or protease inhibitor-based ART provides some reassurance regarding the use of dolutegravir in patients who are not virologically suppressed [17]. Importantly, all patients had to have at least one active nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) predicted by resistance testing. Dolutegravir-based ART was superior to protease inhibitor-based ART, and no patients in the dolutegravir arm developed resistance mutations.

In summary, based on the available evidence, dolutegravir seems to be highly effective, both in ART-naive and ART-experienced patients, provided that it is combined with a functional NRTI backbone. The TenoRes collaboration, which comprises data from clinical trials and observational studies, reported a prevalence of tenofovir resistance of 57% (370/654), and a prevalence of M184V/I mutation of 61% (401/654) in patients whose first-line ART regimens including tenofovir were failing [18]. Even though the high prevalence of NRTI resistance in patients with failing first-line ART in SSA may have important implications for the use of dolutegravir in settings without viral load monitoring, the long-term clinical significance of NRTI resistance in patients starting dolutegravir is not yet known. Interestingly, HIV-suppressed, treatment-experienced individuals with the M184V mutation switching to a dolutegravir/lamivudine dual therapy do not seem to have an increased risk of virological failure [19]. This finding is supported by results from in vitro studies, which showed that the presence of either of the NRTI resistance mutations M184I/V or K65R prevented the development of resistance to dolutegravir [20].

Gaps in current knowledge: the place for using IeDEA cohort data and mathematical modelling to predict and monitor HIV drug resistance in sub-Saharan Africa

While treatment guidelines and drug prescribing policy are usually based on results from randomised controlled trials, such studies often give little insight into the real-world effectiveness of the interventions evaluated. Clinical trials usually have strict inclusion and exclusion criteria, provide close follow-up and monitoring of patients, and adherence is usually better than in routine care. Observational cohorts are often able to provide generalisable data from many more patients in settings that reflect real-world use of interventions. However, in terms of predicting how HIVDR will affect the success of universal test-and-treat policies and the introduction of new drugs to first-line ART regimens in SSA, both clinical trials and observational cohorts have limitations. The vast majority of studies published to date were conducted in North America or Europe, in clinical settings that differ substantially from SSA. Although we can be confident that dolutegravir-based first-line triple therapy will lead to favourable virological outcomes in SSA, data on its use among patients whose NNRTI-based first-line therapy was failing are insufficient to date.

The scarcity of HIVDR surveillance data in resource-limited settings, together with the fact that those data are usually not linked with observational cohorts, presents challenges for assessing and predicting the transmission of HIVDR. Mathematical models offer a unique opportunity to bridge this gap [21] by combining observational data on rates of HIV diagnosis, treatment, and virological response with cross-sectional HIVDR surveillance data from local settings. Mathematical models have been used to address several key questions regarding HIVDR in various populations, and they are increasingly being used to inform policy [2,10,21]. Box 1 and Table 1 briefly discuss several examples.

The African regional cohorts of the IeDEA consortium provide the ideal platform to explore many of the outstanding research
Box 1. HIV drug resistance mathematical models

The HIV Synthesis Model, developed by Phillips et al, captures resistance to the different antiretroviral classes and its effect on treatment outcome [22-24]. More specifically, it models HIVDR in terms of the presence or absence of every mutation specific to the antiretrovirals in use. Agent-based models such as the HIV Synthesis Model have the advantage of being able to represent complex processes, like the process of acquiring resistance mutations. However, the drawback of using such models is that many assumptions are made but may not be verifiable. This can be avoided by using simpler models, such as compartmental models. Abbas et al [25], Nichols et al [26], and Supervie et al [27] have developed deterministic compartmental models to model HIV drug resistance and calibrated them with data from South Africa, Zambia and Botswana, respectively. These three models capture resistance in a simpler way than the HIV Synthesis Model. The South African Transmission Model (25) has only two layers (absence/presence of resistance) to model resistance, while the HIV-transmission models developed by Nichols et al [28] and Supervie et al [27] represent the main resistance mutations (K65R and M184V mutations for nucleoside reverse transcriptase inhibitors) (Table 1).

Table 1. Examples of how mathematical models have been used to address key HIV drug resistance questions:

<table>
<thead>
<tr>
<th>Model</th>
<th>HIV drug resistance questions</th>
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| HIV Synthesis Model: individual-based model calibrated with sub-Saharan African data | • Assessing the impact of viral load monitoring on HIVDR [29]  
• Predicting the impact of HIVDR on mortality [24,30]  
• Assessing the effectiveness and cost-effectiveness of interventions such as dolutegravir-based ART in settings with a relatively high prevalence of HIVDR [22,23] |
| Deterministic compartmental model calibrated with Ugandan and Kenyan data | • Assessing the impact of increasing second-line ART coverage [28]; and earlier ART initiation [32] on HIVDR |
| South African Transmission Model: compartmental model calibrated to replicate the South African HIV-1 epidemic | • Assessing the impact of PrEP on HIVDR [25] |
| Macha HIV Transmission model: deterministic compartmental model calibrated with Zambian data | • Assessing the impact of PrEP [26] on HIVDR |
| PrEP Intervention Transmission model: compartmental model integrating PrEP and ART and calibrated with data from Botswana | • Assessing the impact of PrEP on HIVDR [27] |
| PrEP intervention model: compartmental model representing the MSM population in San Francisco | • Assessing the impact of PrEP on HIVDR [31] |

Questions highlighted in this article, as they comprise large cohorts of patients on ART from 23 countries across West, Central, East, and Southern Africa [32]. The Consortium collects routine clinical data of patients managed largely in primary healthcare settings, and has a strong capacity for data management and analysis, with a long track record of research that influences policy. Few cohorts measure or collect HIVDR data, but many have the infrastructure to collect them, provided dedicated funding is available.

We have also recently developed a deterministic compartmental mathematical model that comprises three layers: treatment stage (e.g. diagnosis, treatment, viral suppression or failure); disease progression (represented by CD4 count strata); and the presence/absence of HIVDR (in process for future publication). Disease progression at each treatment stage, as well as the transition from one treatment stage to another, are estimated from observational data from the iDeA Southern Africa cohorts and UNAIDS data. The model has the potential to address key questions regarding HIVDR in Southern Africa. Specifically, we aim to describe time trends and drivers of HIVDR, and to estimate how the spread of resistance is affected by alternative interventions. For example, we could assess the impact of enhanced laboratory monitoring (i.e. viral load and resistance testing) on the development of acquired drug resistance under universal test-and-treat conditions. Furthermore, we aim to assess to what extent changes in ART guidelines (e.g. dolutegravir-based first-line ART), can curb the transmission of resistance and improve clinical outcomes. As described above, a key question in this context is the potential impact of NRTI resistance on the effectiveness of dolutegravir-based ART. Finally, we hope to predict the potential development and spread of resistance to dolutegravir. The main difficulty of making such a prediction is the lack of long-term data regarding the impact of dolutegravir resistance on clinical outcomes. Nevertheless, we believe that, by integrating the accumulating clinical data or by making reasonable assumptions on such parameters based on comparable processes or settings [33], mathematical models will be helpful in providing risk assessments, and identifying key knowledge gaps that should be addressed by clinical, epidemiological, and laboratory studies.

Conclusion

Universal test-and-treat policies and the introduction of new drugs such as dolutegravir to first-line ART regimens have the potential to improve patient outcomes and reduce the transmission of HIV in SSA. However, it is important to monitor their implementation, and to forecast their effect on the development of HIVDR. The African regional cohorts of the iDeA global consortium represent an ideal platform to provide data regarding the real-world effectiveness of novel ART strategies and mathematical models have the potential to help predict the emergence of HIVDR in SSA. Such research is essential to ensure positive long-term outcomes, and to inform future programmatic and policy changes, tailored to local settings.

References


