Diagnosis and monitoring of HIV programmes to support treatment initiation and follow up and improve programme quality

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Purpose of review
The HIV ‘cascade of care’ breaks down at several points, with delayed HIV diagnosis, late treatment initiation, or interruption, leading to new morbidity and mortality and loss of prevention effects. New approaches are needed at each step.

Recent findings
HIV testing is still not reaching certain communities, resulting in late presentation. Creative ways to reach these communities is being explored, including with self-testing. HIV misdiagnosis is increasingly recognized as undermining testing programmes, highlighting the need for better quality control. More rapid antiretroviral initiation, even on the same day, initiation outside of health facilities, and more efficient defaulter re-initiation, may mean better retention and virological control. New antiretrovirals may address side effects responsible for poor adherence and treatment failure, as well as requiring lower adherence levels. Viral load monitoring expansion is required, but mechanisms are needed to ensure healthcare workers act on detectable results; point of care technologies may partly address this. Side-effect monitoring at a programme level is needed to characterise ‘real world’ effectiveness.

Summary
Integrated monitoring systems, using single patient identifiers and utilizing national laboratory data systems, will allow for better characterization and interventions that limit loss to follow up, and allow better pharmacovigilance and programme performance.

Keywords
antiretrovirals, health systems, laboratory, pharmacovigilance

INTRODUCTION
The much-discussed HIV ‘cascade of care’ has demonstrated marked loss between HIV diagnosis, linkage and initiation of antiretroviral treatment (ART), compromising mortality and morbidity benefits to the individual, as well as public health prevention impact. As large-scale programmes provide more long-term data, opportunities have arisen to reduces losses across the cascade. In an era of tenofovir disoproxil fumarate (TDF; Gilead Sciences, CA, USA) and nonnucleoside reverse transcriptase inhibitor (NNRTI)-based therapy, programmes rely on monitoring and excellent adherence to prevent movement to less well tolerated and nonco-formulated drugs. The UNAIDS Fast Track approach calls for 90% of people with HIV to know their HIV status, 90% of those diagnosed to receive sustained ART and 90% of these to have viral suppression, by 2020 [1]. New antiretrovirals that have better safety profiles while providing a far higher resistance barrier than current drugs will help to reduce some of these programmatic complexities, but do not address the first and second ‘90’ of the UNAIDS 90/90/90 targets, namely diagnosis and linkage to care.

In this article we consider the challenges in the cascade, and consider the role of national
HIV testing will require expansion in innovative and unconventional ways, if missing and under-tested populations are to be reached.

Initiation of antiretroviral therapy outside of health facilities, as well as same-day initiation, hold promise in decreasing loss-to-follow-up between diagnosis and starting treatment.

National laboratory systems have unique strength in characterizing the continuum of care, identifying treatment quality, as well as being a form of pharmacovigilance around drug toxicity and pregnancy, using routine programme data.

Implementation of single patient identifiers should be a national priority for countries.

Laboratories in improving outcomes across the continuum of care, with a call for focus on unique single patient national identifiers, as a means to better assess and improve HIV programme and pharmacovigilance in an era where electronic data systems are making contact and tracking of patients more of an option.

HIV DIAGNOSIS

Key marginalized populations and men are consistently underrepresented in many low-and-middle income countries (LMICs) in testing programmes. Reaching these and other neglected communities is often confounded by social, cultural and legal constraints. Even in countries where high levels of HIV testing and treatment has been achieved, such as South Africa, a vexing problem has been people still presenting late, as evidenced by a consistent proportion of people with HIV initiating ART at a low CD4 cell counts, and the persistence of sentinel diseases such as cryptococcal meningitis, a marker of severe immunodeficiency [2,3]. WHO is discussing a formal definition of late diagnosis to support the collection of consistent data on the extent of the problem, to aid future programme evaluation.

HIV testing yields has also merged as a programmatic complexity, with debates around how often and who needs retesting. In some community-based (including home-based) programs, new case pick up has been moderate, suggesting that more targeted subsequent testing will be required to find missing populations. In addition, community HIV testing requires complex management systems to run, while not solving linkage to care issues unless home-based ART initiation is pursued [4]. PEPFAR programmes, trying to draw out efficiencies as budgets get scrutinised, have set many country programmes targets that stress high yields, often at 10% seroprevalence and above, and unlikely threshold in any community-based programme, even with initial waves in untested communities.

Self-testing for HIV is discussed elsewhere in this series [5], but appears to be a useful adjunct to conventional facility-based testing, despite regulatory and implementation complexities, and concerns about ensuring access to counselling and linkage to care. Multiple studies and large demonstration programmes have demonstrated both acceptability and safety, and improvements in instructional materials have meant that even rural, illiterate populations may be able to perform self-tests accurately [6]. Potential exists for use within work-placed programmes, meaning increased focus on men, as well as address marginal populations uncomfortable accessing conventional testing programmes, and may support the delivery of treatment and prevention interventions, including preexposure prophylaxis. Finally, there remains a need to identify successful models to make HIV self-testing available more widely, including commercially and within public programmes.

HIV misdiagnosis has emerged as a major challenge within programmes, and has been the subject of recent attention by WHO [7]. Even within health facilities, false-positive and false-negative results are commonly reported, undermining confidence in programmes and compromising efficacy of prevention, especially in highly effective intervention areas like PMTCT, where a false-negative result can result in infant infection. Although a range of issues occur contributing to misdiagnosis, the majority of instances actually appear to be result of health care worker error. There is little quality control at facility level in most LMIC countries; other laboratory interventions have relatively robust quality checking and automatic electronic data collection of data, limiting errors; in contrast, HIV rapid tests involve error-prone reading and usually paper-based result transcription by health workers. Finding ways past this is complex, as there is no widely used, effective assessment for this part of HIV programmes.

ANTIRETROVIRAL TREATMENT INITIATION

With the era of ‘test and start’ irrespective of immune status at HIV diagnosis, the CD4 count serves as a guide to the urgency of ART initiation, for starting and stopping of prophylaxis for some opportunistic infections, aiding differential diagnoses in symptomatic patients, arguably aids adherence counselling, and monitoring effectiveness of
testing programmes. The role of CD4 cell count is discussed in detail in this series [8].

Same day ART initiation after HIV diagnosis has emerged as an exciting and innovative strategy, with the recent publication of several randomized controlled trials showing that rapid initiation may substantially improve loss to follow up; these benefits may be of particular benefit to certain groups such as young men, and those attending primary care clinics [9**,10**,11]. Previously, innovations such as same-day ART initiation have not been possible unless expensive and difficult-to-maintain point-of-care machines were available. One of the major losses in the care cascade is after diagnosis, and immediate initiation appears to significantly impact on retention, and improve overall viral suppression rates. Some concern has been aired that counselling processes may be bypassed and sloppy attention to adherence may undermine the results in the real world [12]. However, more data should soon be available to assess this approach.

Re-initiation has emerged as a challenge, as large numbers of people on ART interrupt therapy, either because of treatment fatigue, drug stock outs or changing treatment site, among other challenges [13]. Concerns about NNRTI-resistance caused by long ‘tails’ has thankfully proved not to be a major problem, so re-initiation appears to be well tolerated. Unfortunately, patients are often justifiably nervous about telling healthcare workers that they have interrupted, and may prefer to present as new initiators. Lack of patient tracking systems in almost all LMIC environments means this is a missed opportunity to tackle access and adherence issues in a high-risk group of patients.

Initiation outside of conventional settings – for example through community programmes, mobile testing units or through workplace programmes – all hold promise, and merit further exploration. There are studies currently evaluating home-based initiation, and this may be the next innovation that programmes will need to consider.

**TREATMENT MONITORING**

‘Loss to follow up’, a popular programmatic term, is a misnomer. It masks the fact that LMIC clinics usually lack the most basic infrastructure to track patients and results, even within a facility. Unfortunately, the term indirectly blames patients, and has led to much focus on retention within a specific facility, when, predictably, there is ample evidence they move between facilities to access care. The lack of tracking mechanisms, such as unique patient identifiers has not been widely implemented in LMICs, severely hampering accurate programmatic evaluation. There is a proliferation of tracking systems that consume significant resources, limited linkage of laboratory results, leading to expensive retesting and misdirected results. A single patient identifier is possibly the most important missing programmatic priorities at this stage for everything from drug delivery to measuring toxicity, now that the majority of people with HIV in LMICs have started ART [14].

The importance of viral load monitoring has achieved broad consensus among the HIV treatment community, but has achieved poor penetration outside of South Africa and Botswana [15]. Even where HIV viral load testing is available, healthcare workers either delay, cannot interpret or do not react at all to detectable levels [16**]. The whole point of viral load testing is to rapidly identify virological failure, as fast adherence interventions may salvage NNRTI-based regimens, prevent compromising subsequent regimens through cumulative resistance, and limiting community spread of resistance. The test is expensive and a burden on overstretched laboratories, so not using the results effectively is a huge programmatic waste of resources. Point of care viral load monitoring appears to address some of these operational deficiencies, especially in large ART clinics where healthcare workers can make immediate decisions around a result, either quickly moving undetectable patients to community-based dispensing programmes, verifying in-between results, or triggering focused adherence interventions. Viral loads are an ideal marker of programmatic efficiency, with levels of implementation and suppression a measure of clinical programme success.

Although simple, single assays like CD4 and viral load are easy to implement in either a centralized fashion or as a point-of-care, the oldest assays in the armamentarium, such as haematology and chemistry assays may frequently be the most difficult from an implementation perspective. Chemistry analyzers are frequently designed to do a massive repertoire of tests, making standardization difficult, and assay selection, maintenance and costs difficult to manage. Reflex testing, for instance triggering a full liver function test which contains many expensive parameters, only when a raised ALT is picked up, may conserve costs, but is complex. Creatinine exclusions for TDF can be managed using an estimated GFR in place of a creatinine clearance, but most point-of-care assays are not standardized against reference standards as they are for laboratory tests.

Calls for more availability of HIV resistance testing appears to be somewhat premature, in the light of the poor availability and reaction to viral load
testing above, the effectiveness of first-line and second-line regimens advocated by WHO in second-line without resistance testing guidance from, as well as the expense and complexity of the test. For programmes that provide third-line drugs, genotyping will be important in guiding the selection of these expensive drugs.

**PHARMACOVIGILANCE AND DRUG TOXICITY MONITORING**

Classic pharmacovigilance programmes in LMICs have generally yielded little useful information, probably because of poor resourcing and prioritizing. These systems usually rely on a passive approach, based on healthcare worker initiative, and frequently involve several complex and time-consuming steps involving poorly-available forms and requiring communication devices (scanners, fax machines) usually unavailable at a health facility, with minimal report back to the reporting clinician. Clinical trials can be informative in uncovering common side effects, but are limited by restrictive inclusion criteria during recruitment, often excluding high-risk patients, with limited ability for detecting rare events, and publication bias [17]. No one disputes the importance of pharmacovigilance or a more strategic drug toxicity monitoring; with millions of people starting ART, even rare side effects will affect a large absolute number, and formal mechanisms to describe these are needed. To supplement efforts to reinforce pharmacovigilance, passive reporting from patients via creative technology-enhanced offerings, such as smartphone apps, may improve data collection and interaction with health systems, and may be a substitute or ancillary form of monitoring of programs. Laboratory data can serve as a source of signalling, through exception reporting or analysing patterns of test requests.

Pregnancy registries have not demonstrated any important concerns for commonly used ARVs [18]. Disappointingly, formal monitoring of pregnancy events continues to rely on systems of reporting that are less than optimal, relying on individual clinicians with an interest in the area. Large and relatively well monitored antenatal programmes with good ART coverage, such as South Africa and Botswana, would lend themselves to relatively easy operational research programmes, and seem a missed opportunity to assess real-world maternal and foetal health and ART efficacy in preventing mother-to-child transmission. New energy appears to be being channelled to a registry in South Africa, which is vital, as the country has access to large numbers of patients, as well as more capacity for subsequent investigation than many other hyper-endemic countries.

Major recent issues around commonly used ARVs have been published by research clinicians, rather than formal reporting systems. Efavirenz, a key component of current first-line ART, has had several reports showing new toxicities or characterizing in better detail known toxicities, leading to calls for it to be eased out of use or recommended as back up choice [19]. Patterns of severe liver injury, a rare and previously poorly described toxicity, have recently been documented [20]. Worryingly, this toxicity carries a high mortality if unrecognized, especially as symptoms may be subtle initially, with poor availability of intensive care and liver transplant availability in the region. Several central nervous system, specifically cerebellar complications have also been recently documented in both adults and children [21–23].

Creatinine clearance measurements, both before initiation of TDF as well as during treatment, adds substantial complexity to programmes; the requirement compromises same-day initiation strategies, and is of questionable benefit, as studies have shown that the complication is rare [24], and other factors, including diabetes, age and lower CD4 cell count may be as or even more predictive of renal failure. For this reason, the latest WHO ART guidelines note that creatinine clearance measurements are desirable but stops short of recommending that the test be done as a precondition to receiving TDF-based ART. Careful public health guidance is required in future, weighing the complexity and impact of loss to follow up of delayed assessment of baseline creatinine clearance or dropping it completely, against the rare but serious potential renal side effects. In addition, the possibility of tenofovir adefovamide (Gileas Sciences) replacing TDF appears to promise fewer renal events, and may obviate creatinine testing in future, but has unresolved issues around pregnancy and drug interactions with rifampicin.

Dolutegravir (ViiV Healthcare, Brentford, UK) is listed as an alternative in the 2016 WHO ART guidelines, and an alternative to efavirenz. It is currently being evaluated as a potentially safer, better tolerated and less costly replacement, in large clinical studies in LMICs. However, recent studies and case reports have demonstrated significant neurotoxicity in patients [25,26]. These appear rarely severe, but as with all drugs, the actual frequency and severity of rare adverse events will only become apparent once the drug is used at scale.

Drug stock outs have emerged as a major challenge to programs, reducing the individual and public health benefits described above, while
undermining adherence messaging. Helplines, using civil society, have played a role in South Africa in documenting the extent of these stock outs [27], as well as demonstrating that the use of fixed dose combinations are highly protective against interruptions for both tuberculosis and HIV.

A CALL FOR INTEGRATED NATIONAL LABORATORY SYSTEMS AND SINGLE PATIENT IDENTIFIERS

Many of the challenges above would be addressed, at least partially, through the implementation of a networked National Health Laboratory Services, linking patients with a single identifier [14]. The South African National Health Laboratory System is an example of such a system, and has a tiered national footprint within the state sector [28]. The use of a single patient identifier, despite being national policy, has been delayed, but use of systems to link patients using mathematical probabilistic matching techniques, has allowed for increasing focus, often to a clinic level, on programme outcomes.

Laboratory results, such as HIV viral loads, CD4 cell counts and tuberculosis tests, allow for correlation with clinic-reported numbers on ART, and allow for correlations with clinic algorithms. A clinic reporting starting a certain number of patients a month on ART but not doing that number of CD4 cell counts or not confirming an abnormal creatinine clearance soon after it is sent, or where the tally of drugs delivered does not match the number of viral loads, could lead to intervention. Even more granular quality of care focus could be the expected tuberculosis rate at a national level, measured against the amount of tuberculosis testing done per patient denominator. Movement between facilities could be tracked, and even if clinical referral is not done, seeing the pattern of previous testing can be hugely helpful to health workers.

CONCLUSION

There is substantial improvement required at every step of the HIV treatment cascade. Some innovative interventions suggest that we can improve several steps, although as yet there are no magic bullets. The majority of people with HIV are now firmly established on or restarting ART, not simply initiating treatment for the first time. Attention to the decades of monitoring and drug supply that the programme demands is a challenge. Improving systems using patient identifiers, promoting a more strategic approach to drug toxicity monitoring, and better use of laboratory data for programme evaluation, are important next steps.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest


This systematic review summarizes causes of hospitalization among adults and children living with HIV worldwide.


This study shows that community-based HIV testing can achieve high uptake of testing and appears to be an effective and affordable way to encourage large numbers of people to learn their HIV status. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4672714/.

5. Placeholder for reference to series article on self-testing.


This randomized trial from South Africa demonstrated the public health benefit of rapid ART initiation. These positive results have subsequently been confirmed by other studies.


This cluster-randomised trial from Uganda found that a multicomponent intervention targeting health-care worker behaviour increased the probability of ART initiation 14 days after eligibility ascertainment.


This report from MSF details the operational challenges of scaling up access to viral load.