PERSPECTIVE

Urgent need to improve programmatic management of patients with HIV failing first-line antiretroviral therapy

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Introduction: Delayed identification and response to virologic failure in case of first-line antiretroviral therapy (ART) in resource-limited settings is a threat to the health of HIV-infected patients. There is a need for the implementation of an effective, standardized response pathway in the public sector.

Discussion: We evaluated published cohorts describing virologic failure on first-line ART. We focused on gaps in the detection and management of treatment failure, and posited ways to close these gaps, keeping in mind scalability and standardization. Specific shortcomings repeatedly recorded included early loss to follow-up (>20%) after recognized first-line ART virologic failure; frequent delays in confirmatory viral load testing; and excessive time between the confirmation of first-line ART failure and initiation of second-line ART, which exceeded 1 year in some cases. Strategies emphasizing patient tracing, resistance testing, drug concentration monitoring, adherence interventions, and streamlined response pathways for those failing therapy are further discussed.

Conclusion: Comprehensive, evidence-based, clinical operational plans must be devised based on findings from existing research and further tested through implementation science research. Until this standard of evidence is available and implemented, high rates of losses from delays in appropriate switch to second-line ART will remain unacceptably common and a threat to the success of global HIV treatment programs.

Despite the availability of viral load (VL) testing in a growing number of low- and middle-income countries (LMICs), many antiretroviral therapy (ART) programs fail to switch patients experiencing virologic failure (VF) promptly, resulting in avoidable mortality. These delays also increase the risk for additional antiretroviral drug resistance and transmission of drug resistance. Cohort studies of patients experiencing VF in LMICs help us understand this issue, illustrating several important micro-themes (Table). First, there is significant loss to follow-up (LTFU) early, even before confirmatory VL testing, among patients experiencing VF. Second, confirmatory VL testing, required for second-line ART switch in most programs, is frequently delayed.¹ Third, the time between confirmation of first-line ART failure and initiation of second-line ART is excessive, in some cases exceeding 1 year.¹⁻⁴ How can these gaps be addressed at the clinic level? Although recommendations for managing VF in individ-

ual patients are outlined in country-specific guidelines, there is a lack of translational research in public sector settings to formulate generalizable operational models for overwhelmed health facilities.

Here, we focus on the need for improved recognition and management of first-line ART failure in clinics. We highlight actions that have potential for scalability and standardization (Figure).

STANDARDIZED VIROLOGIC MONITORING—STILL MILES TO GO

Since 2016, the WHO has advocated annual VL monitoring to identify ART failure in adults stably receiving ART. However, the implementation of this recommendation globally, especially in sub-Saharan Africa, has not been uniform.^{5,6} For example, despite access to VL testing, less than 50% of patients on first-line ART in South Africa complete annual VL monitoring.^{1,7} To address this deficiency, non-randomized implementation studies, completed in both South Africa and Botswana, have focused on a workflow that is coordinated by a 'VL Champion'—a designated person charged with providing practical coordinated oversight of facility-based VL monitoring. The VL Champion is tasked with increasing demand for VL testing through patient empowerment and health care worker education. In addition, the VL Champion is expected to provide accurate monitoring of monthly clinic-level VL completion rates and coordinate a dedicated team focused on expeditiously managing patients with treatment failure. Such a strategy has been shown to be cost-effective and scalable, improving VL completion rates in clinics to >90%.^{8,9} Incorporating similar clinic-based implementation strategies may be useful to promote action on behalf of patients experiencing VF in a timely way and improve accounting of the virologic cascade after VF.

MANAGING LOSS TO FOLLOW-UP AFTER ART INITIATION

Early loss to follow-up early after ART initiation

LTFU after the initiation of ART in sub-Saharan Africa occurs at a median of 162 days (interquartile range [IQR] 35–454) based on a systematic review of over 7000 patients.¹⁰ Reasons for early LTFU prior to repeat VL monitoring are multifactorial; however, patient limitations are a predominant determinant to maintain retention in care. Patients with advanced disease

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TABLE Studies reporting first-line ART failure and a template for reporting first-line failure

Author, reference, year conducted; location; study design	Total population on FL-ART <i>n</i>	Initial high VL <i>n</i>	LTFU on FL-ART after initial high VL <i>n</i> (%)	EAC sessions completed <i>n</i> (%)	Second VL* done <i>n/N</i> (%)	Time to VL from initial VF (months) Median [IQR]	Time since ART initiation (years) Median [IQR]	FL-ART first VF <i>n</i> (%)	Resuppressed on FL-ART <i>n</i> (%)	Switched to SL-ART <i>n</i> (% eligible)	Time from confirmed VF to switch days (months) Median [IQR]
Bell Gorrod, ¹⁶ 2012–2017; South Africa; retrospective cohort	NR	NR	NR	NR	5,748	6.4 [4.5–10.4]	2.9 [1.8–4.8]	NR	491 (12)	1768 (31)	12.8 [7.6–21.8]
Fox, ¹⁸ 2000–2008; South Africa; retrospective cohort†	19,645	NR	4,094 (21) Death: 921 (4.7) Transferred out: 1339 (6.9) Uncontactable: 1834 (9.4)	NR	NR	2.7 [1.6–4.7]	NR	1,348 (9.9)	NR	833 (62)	4.6 [2.1–8.7]
Petersen, ² 2002–2011; Uganda and South Africa; retrospective cohort‡	7,975	NR	NR	NR	NR	2.6 [1.7–3.8]	1.4 [0.8–2.6]	823 (10.3)	NR	358 (43.5)	3.8 [2–6.5]
Ssemplija, ³⁵ 2004–2011; Uganda; retrospective cohort‡	3,036	NR	NR	NR	NR	5.6 [5.1–5.6]	1.4 [1–1.9]	124 (4.1)	NR	82 (66.1)	8.1 [3.7–17]
Haas, ⁴³ 2004–2013; 16 sub-Saharan African countries; retrospective cohort‡	56,764§	11,346	NR	NR	5,102/11,346 (45)	NR	NR	5,102 (56.1)	NR	2321 (57.1)	NR
Keiser, ⁴⁴ 2004–2005; sub-Saharan Africa; retrospective cohort†	16,591¶	NR	NR	NR	NR	NR	NR	705 (4.2)	NR	382 (54.2)	16.7 [11–24.8]
Rohr, ³ 2004–2014; South Africa; retrospective cohort	NR	NR	NR	NR	NR	2.9 [1.9–4.9]	1.5 [0.9–2.6]	5,895 (NR)	NR	3706 (63)	3.4 [1.1–8.7]
Johnston, ¹⁵ 2003–2008; South Africa; retrospective cohort	13,537	10,402	NR	NR	NR	4.9 [2.8–6.1]	2.6 [1.7–3.5]	1,668 (NR)#	173 (9.3)	361 (21.6)	NR
Etoori, ²⁷ 2013–2015; Swaziland; retrospective cohort	NR	820 FL-ART	246 (29.7) Death: NR Transferred out: NR Uncontactable: NR	0–252 (30.4) 1–133 (16.1) 2–155 (18.7) 3–288 (34.8)	653 (79.6)	4.6 [3.3–8.9]	2.9 [1.8–4.3]	278 (NR)	375 (46)	120 (43.2)	5.9 [2.3–9.9]
Laurent, ⁴⁵ 2006–2010; Cameroon; RCT	221	NR	NR Death: 32 Transferred out: NR Uncontactable: 17	NR	NR	NR	NR	33 (15)**	NR	13 (39)	8 [6–10]††

* Also termed 'confirmed virologic failure'.

† Overlapping cohort data presumed of the leDEA-SA cohort.

‡ Overlapping cohort data presumed of the RHSP cohort

§ Routine VL monitoring; 19.1% of total cohort.

¶ Routine VL monitoring and immunologic failure.

Cohort inclusion of patients with at least 6 months data after confirmed VF.

** VL failure defined as >5000copies/mL.

†† Time from first high VL.

ART = antiretroviral therapy; FL-ART = first-line ART; VL = viral load; LTFU = loss to follow-up; EAC = enhanced adherence counselling; VF = viral failure; SL-ART = second-line ART; NR = not reported; IQR = interquartile range; RCT = randomized control trial.

FIGURE Proposed interventions to improve management of first-line ART failure. LTFU = lost to follow up; EAC = enhanced adherence counseling; POC = point of care; ART = antiretroviral therapy; VL = viral load.

and low Karnofsky scores often miss appointments without social support.¹¹ Furthermore, people living with HIV are more likely to have socio-economic hardships, as well as medical comorbidities, specifically mental health or substance abuse disorders, creating added barriers ranging from patient readiness to remain engaged to limitations from means of transportation, time away from work, and battling community or family stigma.^{12,13} Without a nationally shared, and readily updated, electronic database, patients with migratory work jobs (e.g., truck driving) often have intermittent follow-up. Attempts to bolster retention in South Africa are demonstrated with universal test and treat models of care; however, these can be complicated if not providing ample counselling to high-risk patients or recognition of resource limitations.¹⁴ The role of early risk assessment for disengagement, the provision of community engagement platforms, and transitioning to electronic-based records with automated alerts to capture and start tracing tactics are all potential areas for improvement.

Loss to follow-up after virologic failure

Loss from care of patients, after initial failure of first-line ART but before confirmatory virologic testing, is common (Table).¹⁵ Even in the better-resourced South African private sector, 42% of patients with VF are lost early after VF, before switching to second-line ART.¹⁶ This presents a high-risk situation as patients with treatment failure typically have immunologically advanced HIV

infection and are at high risk for HIV-related mortality in the absence of switch.¹⁶ One proposed solution for this vulnerable patient group is to improve tracing and re-engagement efforts. Tracing and re-engagement efforts include the collection of complete locator information, system alerts to trigger telephonic and physical tracing attempts, and assigning tracers to every ART clinic. However, outside of a research-supported setting, allocating resources for these additional activities can be challenging. Even within research settings, results for such efforts have been mixed. Prior implementation studies emphasized improved tracing by maximizing contact information, such as collecting landlord or village contacts, as well as mobile app-based communication services, and utilized professional trackers.¹⁷ However, a randomized trial in South Africa found no difference in the prevalence of viral suppression at 12 months with enhanced tracing efforts over national standard of care techniques.¹⁸ Similarly, despite a 22% significant early reengagement with intensive tracing of patients, the effects were transient and engagement returned to pre-tracing levels.¹⁹ These results suggest additional research is needed to define interventions with a more consistent and durable impact on retention. Research that helps to define innovative, low-cost tracing tactics are necessary to both better understand the causes of loss from care, help re-engage those lost, and establish efficacy and cost analyses of those tactics compared to standard-of-care activities.²⁰

Until this research is carried out, low-cost strategies for tracing and re-engagement could include expansion of mobile, app-based services and the allocation of unique identifiers for tracing patients accessing care at another facility. For patients with stable and suppressed VL, expansion of decentralized community-based care models, including adherence clubs, may ensure patient retention in care while being more cost-effective and offloading the clinical resources of centralized health centers.^{21–23} Finally, clinical research studies should be expected to standardize reporting of loss from care to provide transparency of program data for quality improvement. In South Africa, for example, national death registries are accessible and reliable for researchers to further characterize LTFU patients in cohort studies. National VL repositories are also available, which can list patients that may have transferred care and those that are ‘active and alive’. Prioritizing retention and reporting loss of care by its separate constituents are pivotal components to impact the incidence of first-line failure.

Optimizing number and quality of enhanced adherence counseling sessions

Although recommended in guidelines for patients experiencing VF, the benefits of enhanced adherence counseling (EAC) are not certain. After initial VF, current WHO guidelines recommend EAC sessions with VL testing repeated after 3–4 months.²⁴ This recommendation was based on a meta-analysis of heterogeneous studies that reported an estimated 70% re-suppression after VF and EAC.²⁵ The durability of this response is uncertain, considering that the majority of patients with first-line ART failure have major drug resistance mutations.^{26–28} Nonetheless, EAC requires considerable resources and is advocated as a reason to delay switch to second-line ART. In a systemic review of cohort studies from 2012 to 2019, 42% of patients on first-line ART with VF will achieve re-suppression without regimen change, suggesting the possible importance of EAC.²⁹ However, cohort studies evaluating first-line ART failure seldom report EAC capture and outcome.^{29–31}

Furthermore, the number of EAC sessions required to achieve VL re-suppression has not been explored.^{19,20} Published data from cohorts from Zimbabwe and Swaziland have shown that EAC attendance was associated with more frequent repeat VL testing and suppression.^{27,32} When stratified to those that underwent repeat VL testing, the benefit was lost. This suggests that there is a subpopulation in whom early recognition of failure, albeit with adequate adherence to follow up, may benefit from early switch. Interrogation of first-line ART failure algorithms through randomized trials to assess the depth and number of EAC sessions associated with VL re-suppression and resistance would assist in informing practice.

Ensuring timely switch to second-line therapy

Delayed switch to second-line therapy after confirmed first-line ART virologic failure is common (Table).^{29,33} For example, in a South African cohort of 233 patients who were switched to second-line ART, the median time after confirmatory VL to regimen change was 6.4 months (IQR 0–43.3).⁴ Delays between treatment failure and switch are similar in the South African private sector, where median time to second-line switch was over 7 months (IQR 2.1–17.8).¹⁶ Barriers to timely switch are multi-faceted, and include patient and provider unwillingness to substitute a more complex regimen, concern for new adverse events with a boosted protease inhibitor-based regimen, delays in laboratory testing and reporting, drug stockouts, and higher second-line ART costs.

Addressing provider hesitancy and the requirement of physician prescribing of second-line ART are potentially high value clinical interventions. Provider dependence on the level of the VL

at the time of failure as a surrogate for adherence is common and results in continuation of first-line therapy and delays guideline-recommended switch.^{1,2,5,34,35} A sub-study evaluating resistance at the time of first-line ART failure did not identify correlation between the level of HIV-1 RNA copies/mL and the presence or absence of drug resistance mutations.³⁶ In reality, more than 80% of people failing first-line NNRTI-based ART have significant drug resistance.^{26–28} Efforts are needed to increase provider awareness and education to ensure timely switch. The role of a VL Champion, as mentioned, can help facilitate clinical care teams’ awareness of these patients to help standardize workflows.⁸ Furthermore, many ART programs still require physicians to prescribe second-line ART. Empowering nurse providers to switch patients to second-line ART early should be evaluated for impact in reducing switch delays caused by physician staffing limitations.

Current guidelines do not recommend early switch after first recognition of VF given the large barriers for this paradigm shift in approach in LMIC. However, a modelling study comparing early switch after a single elevated VL > 1000 copies/ml vs. standard of care at the time of VF demonstrated the potential for an 18% (range 6–30) reduction in AIDS-associated mortality and a 2.9% absolute increase in maintaining virologic suppression during first- or second-line ART (the ‘3rd 90’ of the 90-90-90 goals).³⁷ Short-term costs could be greater and 18% of individuals would switch unnecessarily even in the absence of antiretroviral resistance mutations. This approach would require a real-world evaluation of efficacy, cost and practicality before adoption.

FURTHER STRATEGIES TO IMPROVE MANAGEMENT OF FIRST-LINE FAILURE

Early resistance testing

Early resistance testing, point of care (POC) VL testing, and the use of POC therapeutic drug monitoring to help estimate adherence have all been raised as potentially important scalable strategies to improve management of VF. Historically, widespread use of HIV-1 genotypic resistance testing in LMICs have been limited by cost and complexity. However, at the time patients are eligible for switch with confirmed failure, resistance to first-line ART in LMIC is likely and well-established.^{26–28} The efficacy, cost-effectiveness and feasibility of resistance testing at the time of first detecting of VF on first-line ART is being evaluated in South Africa and Uganda.¹⁷

Point-of-care testing

The use of POC VL testing demonstrated that access to rapid results and immediate triage of patients significantly improved viral suppression and reduced likelihood of loss from care.³⁸ Such a rapid turnaround of VL testing may have a dramatic impact on patient care given that in some regions of sub-Saharan Africa, VL results can take up to 56 days to reach the provider.³⁹ Furthermore, the use of POC ART drug level monitoring in urine and hair is a potential non-invasive adherence marker to help triage real-time failure and ART switch strategies.^{17,40} If efficacious and scalable, the inclusion of one or more of these new interventions into algorithmic work flows have the potential to empower clinicians to make quick, evidence-based decisions to switch ART regimens.

VIROLOGIC FAILURE IN THE ERA OF DOLUTEGRAVIR-BASED FIRST-LINE ART

Many countries have implemented guidelines to switch to first-line dolutegravir-based ART and adapted the algorithmic work-

flows for VF on a dolutegravir-based regimen.⁴¹ The relative contributions of adherence, acquired antiretroviral drug resistance, and drug intolerance will be different from NNRTI-based first-line ART VF and is beyond the scope of this perspective. However, the respective components already addressed such as 1) early recognition of VF, 2) ensuring patient retention, and 3) timely response to VF, are just as relevant. The dolutegravir roll out is an opportunity to develop concomitant strategies to evaluate further or scale up proposed interventions (Figure). For example, patients experiencing VF on dolutegravir-based regimens are expected to have more EAC sessions according to the adapted guidelines in South Africa, given the robust barrier to antiretroviral resistance with dolutegravir-based regimens.^{41,42} However, further evaluating the impact of EAC, both in terms of frequency and impact of individual patient characteristics, is essential to improve the clinical evidence behind standardized workflows for providing optimal patient care while assuring judicious resource allocation.

CONCLUSIONS

Patients with first-line ART VF represent a high-risk group requiring evidenced-based, simplified, and standardized algorithms to sustain the long-term benefits of ART. As the population of people accessing ART, and the provision of virologic monitoring expands in the sub-Saharan African region, simultaneous strengthening of response pathways to treatment failure is critical. The switch from efavirenz- to dolutegravir-based first-line ART will not diminish the need for maintaining high VL completion rates.

To determine the best way forward, implementation science is key and should be focused on the benefits (and costs) of patient tracing, resistance testing before regimen switch, drug concentration monitoring, adherence interventions, and streamlined response pathways for those failing therapy. Until this evidence is available and programmatic guidelines reflect the results, missed opportunities in the identification and management of VF, as well as delays in appropriate switch to second-line ART, will remain unacceptably common and a threat to the success of global HIV treatment programs.

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Introduction : Le retard d'identification et de réponse à un échec du traitement antirétroviral de première ligne (TAR) dans des contextes de ressources limitées menace la santé des patients infectés par le VIH. Il est nécessaire de mettre en œuvre un parcours de réponse efficace, standardisé dans le secteur public.

Discussion : Nous avons évalué les cohortes publiées décrivant des échecs virologiques sous TAR de première ligne. Nous nous sommes concentrés sur les failles de la détection et la gestion de l'échec thérapeutique et les façons de combler ces failles en gardant à l'esprit la flexibilité et la standardisation. Les lacunes spécifiques enregistrées à répétition incluaient pertes de vue précoces (>20%) après reconnaissance de l'échec du TAR de première ligne ; retard fréquent du test de confirmation de la charge virale ; et enfin, délai excessif entre la confirmation de l'échec du TAR de première ligne et

l'initiation du TAR de deuxième ligne, dépassant un an dans certains cas. Nous discutons ensuite des stratégies mettant l'accent sur le traçage des patients, les tests de résistance, le suivi des concentrations de médicaments, les interventions visant à améliorer l'adhérence et les parcours de réponse rationalisés pour les patients en échec du traitement.

Conclusion : Des plans globaux, fondés sur des preuves, opérationnels doivent être élaborés à partir des résultats de la recherche existante et ensuite testés grâce à la recherche scientifique en matière de mise en œuvre. Jusqu'à ce que ces plans soient disponibles et mis en œuvre, des taux élevés de pertes dus à des retards de passage à un TAR de deuxième ligne resteront beaucoup trop fréquents et menaceront le succès des programmes mondiaux de traitement du VIH.

Marco de referencia: El retraso en la detección del fracaso del tratamiento antirretrovírico (TAR) de primera línea y la respuesta al mismo, en los entornos con recursos limitados, pone en peligro la salud de los pacientes con infección por el VIH. Es necesario introducir en el sector público una vía de respuesta normalizada que sea eficaz.

Métodos: Se evaluaron cohortes publicadas que describían fracasos virológicos del TAR de primera línea. Los autores centraron su interés en las deficiencias de detección y manejo del fracaso terapéutico y propusieron soluciones teniendo presente la posibilidad de ampliación y normalización. Las dificultades específicas notificadas reiteradamente fueron la pérdida temprana durante el seguimiento (>20%), tras haber reconocido el fracaso del TAR de primera línea; el retraso frecuente de una prueba confirmatoria de la viremia; y, por último, el intervalo excesivo entre la confirmación del fracaso del TAR

de primera línea y el inicio del TAR de segunda línea, que en algunos casos excedía un año. Se examinaron estrategias que dan prioridad a la localización de pacientes, las pruebas de resistencia, la supervisión de las concentraciones de fármacos, las intervenciones en favor de la adhesión y la agilización de las vías de respuesta para los pacientes en fracaso terapéutico.

Conclusión: Es indispensable elaborar planes clínicos operacionales integrales basados en la evidencia, a partir de los resultados de las investigaciones existentes y analizados en estudios complementarios sobre la ejecución. Hasta que no se definan estos criterios de referencia y se apliquen, persistirá una frecuencia inaceptable de tasas altas de pérdidas debidas a los cambios inadecuados hacia un TAR de segunda línea, que ponen en peligro la eficacia de los programas mundiales de tratamiento de la infección por el VIH.