Successful establishment of third-line antiretroviral therapy in Malawi: lessons learned

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Setting: Malawi has an extensive national antiretroviral treatment (ART) program, and although less than 2% of all patients receive second-line ART, there are increasingly more patients failing on these regimens.

Objective: To establish a virtual ART committee using limited available local facilities and expertise to recommend third-line regimens based on genotype resistance of samples sent abroad.

Design: A secretariat and a laboratory sample hub were established. The committee started work after locally organizing training courses. Decisions about ART regimens were mainly based on a relatively simple, previously described algorithm, which allowed decisions to be taken without extensive expert knowledge.

Results: Of the 25 applications assessed, 23 samples were sent for resistance testing from June 2017 to April 2018. Major protease inhibitor (PI) resistance was detected in 65% of the samples. PI resistance was found even in patients exposed to PIs for short periods. In particular, patients who received co-administration of PIs and rifampicin frequently showed resistance mutations.

Conclusion: Third-line ART using genotypic resistance testing and algorithm-based treatment regimens are feasible in low-resource settings. Our model can serve as a base for similar programs initiating programmatic third-line ART in other African countries.

According to the 2016 Malawi Population Based Impact Assessments (MPHIA),¹ Malawi continues to have a significant burden of human immunodeficiency virus (HIV) disease. The prevalence of HIV infection among adults aged 15–64 years is estimated at 10.6%. The report established Malawi's significant progress towards the second and third of the UNAIDS 90-90-90 targets: 89.6% of HIV-positive adults aged 15–64 years with known HIV status are reported to be on antiretroviral treatment (ART); 91.2% of those on ART were virally suppressed.¹ Malawi's 2016 national ART guidelines recommended regimens based on two nucleoside reverse transcriptase inhibitors (NRTIs), combined with a non-NRTI, mainly efavirenz (EFV), as first-line ART. As second-line ART, combinations of two NRTIs with a ritonavir (RTV) boosted protease inhibitor (PI) are recommended. ART and viral load (VL) testing is offered free of charge for all patients; however, there are still challenges in the VL cascade.¹

Routine VL monitoring is performed at 6 months, 24 months, and every 2 years thereafter from the ART

initiation date. Confirmed treatment failure occurs after a targeted or repeat VL is >1000 copies/ml, with good adherence in the previous 3 months. After a switch to second- or third-line ART, patients reset their clock for routine VL monitoring.² By April 2018, the VL testing coverage for Malawi was 62% for routine scheduled VLs.³

The proportion of patients receiving second-line ART in Malawi remains very low. In 2017, only 13 352 (1.8%) of the 725 002 patients alive on ART were treated with a PI-based second-line regimen.⁴ Nevertheless, patients with high VL on second-line ART are seen. Socio-economic factors such as younger age groups, social instability, disclosure and depression, as well as adverse drug reactions are known to increase the risk of failing ART.⁵ While the national guidelines have a provision for third-line ART (darunavir [DRV], raltegravir [RAL] and etravirine [ETR]), the process of switching patients was not defined. Our report describes the successful implementation of a third-line committee and the lessons learned in the process.

SETTING AND INTERVENTION

In September 2016, a third-line ART committee was formed under the guidance of the Ministry's Department of HIV/AIDS (DHA). Several implementing partners were involved, but Partners in Hope Medical Centre (PIH) and the Lighthouse Trust (LH) took leading roles and performed key activities for the committee.

Based in Lilongwe, PIH has been providing HIV and TB care since 2004. PIH became a PEPFAR partner in 2009 and supports HIV care in eight districts in Malawi. PIH has over 5000 patients in care and offers outreach community services. PIH's VL laboratory is accredited through the Centers for Disease Control and Prevention's laboratory program; it also provides microscopy, hematology, biochemistry, and TB diagnostics, including Xpert® MTB/RIF testing (Cepheid, Sunnyvale, CA, USA) and the TB MGIT® System (BD, Franklin Lakes, NJ, USA).

LH Trust operates two Centers of Excellence for HIV Care in Lilongwe, one on the grounds of Kamuzu Central Hospital, Lilongwe, since 2002 and a second clinic at the Bwaila District Hospital, Lilongwe, Malawi, since 2007. At the end of 2017, these sites were treating more than 25 000 patients on ART. Since the end of 2017, LH has also been operating the ART clinic in Queen Elizabeth Central Hospital in Blantyre, Malawi, with over 12 000 patients. Referral-level ART is provided, including differentiated care for patients

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KEY WORDS

HIV; treatment failure; protease inhibitor resistance; resource-limited setting

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FIGURE 1 Third-line ART algorithm: adults. PI = protease inhibitor; ATV = atazanavir; LPV = lopinavir; DRV/r = ritonavir-boosted darunavir; TDF = tenofovir; AZT = azidothymidine; ABC = abacavir; 3TC = lamivudine; RAL = raltegravir; ETR = etravirine; ART = antiretroviral therapy.

with advanced HIV disease. TB, sexually transmitted infections, family planning and hypertension treatment are fully integrated in all three clinics.

After forming the third-line committee, the implementing partners mainly managed the day-to-day activities. Existing experience and evidence from the South African third-line ART Committee was reviewed. A focal point with a data clerk (secretary) acting as the administrative focal person to manage applications was established at the LH clinic and an email address for submission of applications created (3rdline@lighthouse.org.mw). As genotyping facilities were not locally available, a contract was negotiated with the National Health Laboratory Service (NHLS) in Johannesburg South Africa. NHLS has a state of the art genotyping program, including equipment capable of using dried blood spot samples (DBS) for genotyping. A hub for sample logistics was established in the laboratory at PIH. In cooperation with Right to Care, a 2-day training course on HIV resistance testing and third-line ART was organized in November 2016 for the committee members (15 participants) and in May 2017 for a wider audience of district medical officers (25 participants) from the various districts. The committee members included physicians and clinicians who were familiar with managing HIV, with four pediatricians and seven others with experience seeing adults and children.

The following mechanism to send applications and samples was established: A “third-line application form” was developed and made available to ART clinicians in all large clinics and district hospitals to report patients failing on second-line ART. The secretary would receive and forward the application electronically to three committee members in a rotation schedule based on the age of the patient, who decided on a majority basis whether the documented facts (e.g., viral load results, adherence) justified resistance testing. If approved, the secretary informed the treating clinician by email to collect a DBS sample which was collected using the private logistics company (G4S Logistics, Malawi) and transported to the dispatching laboratory at PIH. The DBS sample would then be packaged for air travel and sent to the NHLS laboratory in Johannesburg, South Africa, by the same logistics company. As samples could only be used for resistance testing within 2 weeks from collection, samples were sent individually and not batched. The associated shipping costs were US\$25.50 per sample and the cost per genotype for resistance of the reverse transcriptase and protease genes were US\$129, as was negotiated with G4S and NHLS through PIH.

Resistance results were returned from the laboratory via email to the secretary. The results were sent to the same three committee members for review and to recommend a third-line regimen. To determine the drug combination, a relatively standardized decision algorithm (Figure 1) was applied following reported experience from South Africa,⁶ but experts were allowed to suggest alternatives as required. The recommendations were collected by the secretary who informed the treating clinician about the recommended regimen along with standardized drug information and informed the supply chain at DHA about the required drugs and clinic location.

The following cascade of indicators were reported quarterly: number of applications received, number eligible for genotyping, number of samples received, number of genotyping results, number of samples with PI resistance and number of patients who were switched to third-line ART.

RESULTS

During the period after establishment of the third-line ART mechanism, 25 applications were received from June 2017 to April 2018; the number of samples varied from 1 to 7 per month (median 2 samples/month). Nineteen (76%) applications were received from the LH clinic, four (16%) were from PIH Medical Centre; only two samples (8%) were received from other institutions. All applications were approved by the committee for resistance testing either directly or after further adherence counselling without subsequent viral suppression. In two samples, the laboratory was unable to amplify RNA. In 15 (65%) of the remaining 23 samples, major PI mutations were detected and third-line ART

TABLE 1 Cascade of third-line indicators reported for the period June 2017–April 2018

	<i>n</i> (%)
Application forms received, <i>n</i>	25
Number eligible for genotyping	25 (100)
Samples received	25 (100)
Number with genotyping results	23 (92)
Samples with protease inhibitor resistance	15 (65)
Number of patients who switched to third-line treatment	15 (+1 for toxicity) (100)

TABLE 2 Demographics and ART information on third-line patients

	All applications (<i>n</i> = 25) <i>n</i> (%)	With protease inhibitor resistance (<i>n</i> = 15) <i>n</i> (%)
Female sex	16 (64)	9 (60)
Age, years, median [IQR]	43 [39–46]	43 [41–49]
WHO Stage III/IV at ART initiation	13 (52)	7 (47)
WHO Stage III/IV at application	10 (40)	7 (47)
Time on first-line ART, months, median [IQR]	54 [43–84] min: 21	54 [44–90] min: 21
Time on second-line ART, months, median [IQR]	33 [19–45]	33 [20–50]
On second-line ART for <12 months	4 (16)	2 (13)
On second-line ART for <24 months	9 (36)	6 (40)
VL at application, median [IQR]	206 000 [49 431–737 000]	703 000 [366 281–1 340 000]
VL at application > 10 ⁵ copies	17 (68)	13 (87)
More than 2 high VL before application	13 (52) 3 high VL (<i>n</i> = 9); 4 high VL (<i>n</i> = 4)	9 (60) 3 high VL (<i>n</i> = 7); 4 high VL (<i>n</i> = 2)
Any previous TB treatment reported	9 (36)	5 (33)
Previous TB treatment during protease inhibitor regimen	6 (24)	5 (33)
Any previous side effects reported	6 (24)	3 (20)
Any adherence problems reported	6 (24)	3 (20)
HBsAg-positive	4 (16)	2 (13)

ART = antiretroviral therapy; IQR = interquartile range; WHO = World Health Organization; VL = viral load; TB = tuberculosis; HBsAg = surface antigen of the hepatitis B virus.

recommended (Table 1). Third-line ART was recommended for one patient due to toxicity of NRTIs despite absence of significant PI resistance.

The characteristics of the patients with a third-line application and with PI resistance are given in Table 2. Of the applications, 64% were for female patients. The median time on PI-based second-line ART was 33 months (interquartile range [IQR] 19–45), but in two patients, PI resistance was detected after less than 12 months of PI exposure (3 and 10 months, respectively). Previous TB treatment was reported in nine of the applications. Six of these patients received rifampicin (RMP) based TB treatment while on a PI-based second-line ART; in five of these six patients, significant PI resistance mutations were discovered. Only a minority of patients (24%) reported adherence problems. Previous side effects were reported infrequently (24%), with no difference in those with detected PI resistance. Two patients (13%) were reportedly HBsAg (surface antigen of the hepatitis B virus) positive, and TDF/3TC (tenofovir disoproxil fumarate plus lamivudine) was maintained as the NRTI backbone drugs.

The mean turnaround time (TAT) from receiving the initial application until communication of the final recommendation was 50 working days (range 21–166). For patients with samples that amplified RNA directly from the first sample, the mean time from application to recommendation was 29 working days (range 21–56); this was 102 working days (range 67–166) when a second sample was required.

The recommended third-line regimens are summarized in Figure 2. All patients received ritonavir-boosted DRV (DRV/r) and a dual NRTI backbone. In 80% of the patients, RAL was added, and ETR was also prescribed in 20%.

The total operational costs (excluding drug costs) from June 2017 to April 2018 was US\$3862.50.

DISCUSSION AND LESSONS LEARNED

It has been shown that up to 22% of patients receiving second-line ART in Malawi do not achieve HIV RNA suppression by 6 months. Although many cases are due to poor adherence, major

PI resistance at the time of second-line failure is prevalent.⁷ In adult patients with second-line ART failure in Namibia, only 41.5% harbored ≥ 1 HIV drug resistance mutations to the standard regimen;⁸ in Uganda, more than 60% of patients with suspected treatment failure did not have significant resistance patterns,⁹ highlighting the fact that optimized adherence may prevent unnecessary testing and switching to costly third-line ART. Nevertheless, the need for third-line ART is increasingly rec-

FIGURE 2 Patients on different third-line regimens. ART = antiretroviral therapy; PI = protease inhibitor; DRV/r = ritonavir-boosted darunavir; 3TC = lamivudine; AZT = azidothymidine; TDF = tenofovir; ABC = abacavir; RAL = raltegravir; ETR = etravirine.

TABLE 3 Lessons learned

- 1 Legal framework needs to be understood
- 2 Only few samples initially but budgets drained over time
- 3 Mainly referral sites to send samples
- 4 Storage and transport problems lead to failure of amplification
- 5 Patients are lost and die even when turnaround time was reasonable
- 6 Protease inhibitor resistance happens in less than 1 year
- 7 Very high viral load does not preclude protease inhibitor resistance
- 8 Previous protease inhibitor and rifampicin combination may lead to resistance
- 9 Side effects are a valid reason for third-line drugs
- 10 Third-line regimens are complex and consist of many tablets
- 11 Third-line ART regimen can be “semi-standardized”

ART = antiretroviral therapy.

ognized in resource-limited settings in Latin America¹⁰ and Asia,¹¹ and modeling suggests genotype assays and third-line ART could increase survival and be cost-effective compared to population-based approaches in Africa.¹² In our intervention, third-line ART was prescribed successfully using a focal secretary and a “virtual” committee. This allowed semi-individualized decisions on resistance testing and third-line drug regimens using mainly electronic communication between committee members. As Malawi has a critical shortage of health care workers,¹³ and providers with advanced experience in ART are scarce, our model allowed the use of existing expertise with minimal effect on the experts. A relatively large number of committee members, in total 14, were involved in the decision-making processes of different patients, which stimulated capacity building and reduced impact on the individual expert.

The following lessons were learned during the implementation process and the first months of the operation (Table 3).

- 1 In the initial phase, a delay was created due to the lack of clarity on the legal process of sending patient samples out of the country. It was initially felt that this would need ethics approval, but as it was not part of any study, no ethics boards felt responsible. It was concluded in accordance with the DHA that as part of routine patient services, samples could be sent without further approval.
- 2 Despite training of district-level staff, applications were mainly received from central referral-level ART sites. It was observed that peripheral sites preferred to refer patients instead of sending samples, which is likely due to the centers of excellence available at all tertiary hospitals and access to more experienced physicians and diagnostics. Further attention and training is needed to develop a more efficient up- and down-referral system that can effectively capture those suspected of second-line failure and connect them with the appropriate management.
- 3 The total number of samples was low and remained low during the observed period, which may be related to the availability and TAT for VL monitoring in these areas. Nevertheless, the numbers drained the budget, and in April 2018 the process had to be temporarily halted due to a lack of funding; this highlighted the need to include third-line activities in future budgets.
- 4 Adequate storage and transport were found problematic due to transport delays of >2 weeks; RNA could thus not be amplified in some samples. Follow-up samples from the same patients were resent urgently to minimize delays. The median TAT from

application to recommendation of regimen was 29 working days when the laboratory was able to amplify RNA directly, which is considered excellent given the logistic challenges faced. The TAT increased significantly in case of resent samples. The time to dispense a third-line regimen was generally within 1 week, depending on the location of the patient; this may have been influenced by the fact that many applications were sent from referral-level sites. Despite these reasonable time intervals, one patient was unfortunately lost during the process and one died before receiving the result.

- 5 Given the fact that RTV-boosted PIs have a high genetic resistance barrier,¹⁴ it was initially considered to restrict resistance testing to patients who were on PI-based ART for at least 2 years to save costs. It was further hypothesized that patients with PI resistance would show detectable VL but not “very high” VL levels, as the mutations should reduce viral fitness.¹⁵ This was suggested as another potential screening tool to limit the number of samples to be sent. Both assumptions were not confirmed; we found significant PI resistance in 40% of patients with <2 years of PI treatment, and 87% of the samples with significant PI resistance showed very high VLs (>10⁵ copies/ml). A similar experience in Zimbabwe did not find an association between VL at resistance testing with major PI resistance-associated mutations.¹⁶
- 6 Five of six patients who previously received RMP-based TB treatment while on a PI-based ART were found to have significant PI resistance mutations. This underlines the risk of insufficient drug levels when combining PIs with RMP,¹⁷ although Malawian guidelines recommend double dosing of LPV/r while on RMP. In failing patients who received this drug combination, resistance testing is recommendable.
- 7 One patient was eligible for third-line therapy, not because of resistance virus but due to multiple severe side effects to other drugs. The availability of third-line drug choices in the public system allows treatment of this small but difficult patient group.
- 8 Due to the lack of fixed-drug combinations, the pill burden of third-line regimens is high, especially when DRV, RTV, RAL, ETR and the NRTI backbone drugs are all prescribed (11 tablets per day). As the high pill burden is a known risk factor for poorer adherence,¹⁸ extensive adherence counseling for patients are required.
- 9 The decision algorithm for the selection of third-line ART was found to be practical and applicable without extensive expert knowledge, which is not widely available in many settings. The proportions of patients receiving the different drug combinations (Figure 2) are similar to findings reported from South Africa,⁵ suggesting similarities in the patient population as well as in the virological resistance patterns. This algorithm could therefore be recommended for wider use in similar settings.

CONCLUSION

Third-line ART using genotyping resistance testing and algorithm-based treatment regimens are feasible in low-resource settings. Even when samples need to be sent out of the country, acceptable TATs can be achieved if logistics are optimized. Our model of a virtual committee made use of existing expertise in the country without excessive burden on the experts. Although adherence needs to be optimized before submitting samples, significant resistance is detected in a large proportion of patients

failing on second-line ART. Resistance was seen in cases exposed to PIs for shorter periods and patients who receive co-administration of PIs and RMP, testing should be considered.

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Contexte : Le Malawi a un vaste programme de traitement antirétroviral (TAR) national et bien que seulement moins de 2% de tous les patients reçoivent un TAR de deuxième ligne, il y a de plus en plus de patients en échec sous ces protocoles.

Objectif : Etablir un comité virtuel de TAR utilisant les structures locales disponibles, limitées en nombre et en expertise, pour recommander des protocoles de troisième ligne basés sur le test de résistance génotypique des échantillons envoyés à l'étranger.

Schéma : Un secrétariat et un plateforme des échantillons ont été établis. Après une formation locale, le comité a commencé à travailler. Les décisions relatives aux protocoles de TAR ont été principalement basées sur un algorithme relativement simple, précédemment décrite, qui a permis de prendre des décisions sans connaissances expertes majeures.

Marco de referencia: Malawi cuenta con un extenso programa nacional de tratamiento antirretroviral (TAR) y aunque menos de 2% de todos los pacientes recibe TAR de segunda línea, cada vez más pacientes presentan fracaso con estos esquemas terapéuticos.

Objetivo: Instaurar un comité virtual de los TAR, recurriendo a los establecimientos y la pericia locales disponibles que son escasos, para recomendar las pautas de tratamiento de tercera línea basadas sobre las muestras enviadas al extranjero con el fin de realizar las pruebas de genotipos de resistencia.

Métodos: Se creó un secretariado y una plataforma de muestras de laboratorio. El comité comenzó a operar después de las sesiones locales de capacitación. Las decisiones sobre los esquemas de TAR se fundamentaron en su mayor parte en un algoritmo relativamente sencillo descrito con anterioridad, que facilita la

Résultats : Des 25 candidatures évaluées, 23 échantillons ont été envoyés pour un test de résistance de juin 2017 à avril 2018. Une résistance majeure aux inhibiteurs de la protéase (PI) a été détectée dans 65% des échantillons. Même chez les patients exposés aux PI pendant de courtes périodes, une résistance aux PI a été constatée ; les patients qui ont reçu une administration conjointe de PI et de rifampicine, en particulier, ont fréquemment présenté des mutations de résistance.

Conclusion : Le test de résistance génotypique des TAR de troisième ligne et les protocoles de traitement basés sur ne algorithme sont faisables dans des contextes de faibles ressources. Notre modèle peut servir de base à des programmes similaires initiant des TAR de troisième ligne dans d'autres pays d'Afrique.

toma de decisiones sin necesidad de amplios conocimientos de expertos.

Resultados: De junio del 2017 a abril del 2018 se analizaron 25 solicitudes y se remitieron 23 muestras para estudios de resistencia. Se detectó resistencia a los principales inhibidores de la proteasa (PI) en 65% de las muestras. La resistencia se detectó incluso en pacientes expuestos a PI durante períodos cortos. En los pacientes que habían recibido de manera concomitante PI y rifampicina se observaron con frecuencia mutaciones de resistencia.

Conclusión: En los entornos con recursos limitados es factible administrar tratamientos con TAR de tercera línea con base en un algoritmo y las pruebas genotípicas de resistencia. Este modelo puede servir como fundamento a los programas similares que inician el TAR programático con medicamentos de tercera línea en otros países africanos.