

Association of HIV/AIDS Clinician Warm Line Utilization with Diagnosis and Management of Antiretroviral Treatment Failure in Mozambique: A Retrospective Analysis of Program Data

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Abstract

In accordance with global HIV/AIDS goals, Mozambique is attempting to improve management of antiretroviral treatment failure (TF). We sought to determine whether the utilization of a national HIV/AIDS clinician telephone consultation service increased recognition and reporting of TF. In a retrospective analysis of routinely collected program data from telephone consultation logs and Mozambique's national registry of second-line antiretroviral requests, we used linear mixed methods to describe the association between TF-related telephone consultations and submission of second-line requests, which required documentation of the TF diagnosis. The unit of analysis was the health facility. Available data included 1417 consultations (390 [27.5%] TF related) and 2662 second-line requests from 1011 health units (2015–2016 data). In multivariable analyses, each TF-related consultation was associated with an increase of 0.61 (95% confidence interval 0.15 to 1.06) second-line requests. In this setting, TF-related telephone consultation was positively and significantly associated with diagnosis and reporting of antiretroviral TF.

Keywords

HIV/AIDS, Mozambique, teleconsultation service, antiretroviral treatment failure

Background

In the interest of population-level reductions in associated mortality and morbidity, international 90-90-90 goals for care of persons infected with HIV, with or without AIDS, aim for detection of 90% of HIV infections, initiation of antiretroviral therapy (ART) in 90% of infected persons, and suppression of HIV viremia in 90% of those on ART.¹ Attainment of viral suppression (the third “90”) requires systematic monitoring of HIV viral load (VL), followed by timely switching to new ART regimens for patients found to have virologic treatment failure (VF). Scale-up of routine VL monitoring has been challenging in resource-constrained countries with high prevalence of HIV infection.²

Context

The Republic of Mozambique is a sub-Saharan African country with an estimated HIV prevalence of 11.5% in residents 15 to 49 years of age, based on the most recent nationwide survey.³ Public-sector rollout of ART began in 2003. By 2015, ART was available in nearly 1000 health facilities (65% of all Mozambican health

facilities) located in all 11 provinces, and 738 386 adults and 64 273 children were reported to be on treatment.⁴

The backlog of undiagnosed treatment failure (TF) cases may be substantial in Mozambique. Second-line ART regimens were seldom requested during the first decade of ART availability although they were available. Initially, the national HIV/AIDS program prioritized HIV testing and first-line ART initiation, and VL testing capacity was scant. Health worker training did not emphasize—and often did not cover—diagnosis or management of TF, whether defined by clinical, immunologic, or virologic means.

Recently, local clinicians have noted rising mortality associated with advanced AIDS in spite of ongoing ART, and the Mozambican Ministry of Health (MISAU) has sought to

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increase the availability of VL testing and to promote in-service training on TF. Clinician awareness of TF appears to be increasing. In 2015, MISAU's National ART Committee (the Comité TARV) received 2014 second-line ART requests, nearly doubling the preceding year's total of 1188.⁴ But the year 2015 requests corresponded to fewer than 0.3% of the estimated population on ART. In 2 studies conducted in Mozambique, Tilghman et al and Bila et al identified VF in 19% to 23% and in 24% of Mozambican patients on ART, respectively.^{5,6} The International Epidemiology Databases to Evaluate AIDS (IeDEA) collaborative reported that VF was confirmed in 4.23 first-line ART patients/100 person-years at sites that monitored VL routinely in 16 African countries.⁷

In Mozambique, the Comité TARV must authorize all second-line ART switches nationwide. The number of second-line ART requests submitted to the Comité TARV is the only available estimate of the number of TF cases diagnosed by Mozambican clinicians. When submitting second-line requests, clinicians are required to enclose documentation of the available clinical, immunologic, and/or virologic evidence supporting the TF diagnosis for the Comité's review. Thus, submission of the second-line request and reporting of new cases of TF occur simultaneously. Clinicians may switch patients from first-line to alternative first-line regimens in the event of toxicity, drug–drug interactions, or other indication without notifying or seeking the approval of the Comité TARV, but the Comité's approval is required for second-line switches. Thus, if previous published reports of VF prevalence in Mozambique are generalizable, and the number of second-line requests received by the Comité TARV in 2015 is a good estimator of the number of TF cases diagnosed during the preceding year, the magnitude of the unmet need for second-line ART in Mozambique may be over 10 times greater than the number of documented TF diagnoses.

Training gaps for clinicians may explain much of the disparity between probable and confirmed numbers of TF cases. In Mozambique, VL testing capacity is centered in urban provincial capitals, and initial TF trainings primarily enrolled physicians. However, HIV/AIDS care has been decentralized to smaller health units staffed by lower-level health professionals who have not yet been formally trained to detect and manage TF and have limited access to physician support. MISAU responded to the unmet needs of HIV/AIDS clinical support at more peripheral levels by establishing a nationwide, no cost telephone consultation service known as the “Linha Verde.” The model for this “warm line,” established in 2013, was based on experience in both prosperous and resource-constrained settings.^{8–11} Linha Verde clinicians responded daily to questions about HIV prevention, diagnosis, and treatment as well as program management and logistics. They consulted each other and MISAU specialists as needed to respond to complex cases. The Linha Verde also worked closely with MISAU's Comité TARV, and helped the committee disseminate new policy on diagnosis and management of TF (and other HIV-related conditions) through mass distribution of text messages to HIV/AIDS clinicians. The Linha Verde clinicians advised callers on

methods for diagnosis of TF and submission of second-line requests to the Comité TARV but did not travel to clinical sites to confirm diagnoses at the bedside and did not submit second requests on behalf of the callers.

As AIDS treatment capacity has expanded to resource-constrained countries with higher HIV caseloads, many sites have adopted the warm line approach. But there have been few published reports on the clinical impact of these services.¹¹ To the best of our knowledge, the impact of telephone consultation on detection and management of TF has not been measured in sub-Saharan Africa, although studies in the United States and Europe have reported improved management of TF with telemedicine support by expert clinician panels.^{12–14} We sought to determine, through analysis of routine Linha Verde and MISAU program data, whether Linha Verde consultation regarding TF was positively associated with diagnosis of TF as indicated by submission of a request for second-line ART to the Comité TARV.

Methods

The primary aim of this retrospective study was to describe the association between the number of TF-related calls to the Linha Verde and the number of requests for second-line ART submitted to the Comité TARV, for the period January 2015 through May 2016 (for Linha Verde calls) and June 2016 (for second-line requests). Because second-line ART initiation in Mozambique requires the approval of the Comité TARV and the Comité's concordance with the diagnosis of TF, because the Comité TARV's second-line ART application is not used for any other purpose (except rare third-line requests), and because there is no other known Mozambican registry of TF diagnoses that do not result in second-line requests, we regarded submission of a second-line ART request to the Comité as the best available proxy measure of TF diagnosis in Mozambique. We chose the 2015 to 2016 time interval because MISAU policy for use of VL testing was finalized and disseminated in early 2015,⁴ and a marked increase in Linha Verde calls related to TF was noted in the same year. The unit of analysis was the health facility. A secondary aim was to identify constraints to identification and management of TF, through qualitative analysis of TF-related Linha Verde call content.

Sources of Data

The Linha Verde database contained 1 entry per call. Each entry recorded the call date; the caller's age, sex, level of training, and primary health unit affiliation; a summary of the clinical case (if relevant) and the caller's query; and the Linha Verde's response. Each call was assigned a single content category, such as “HIV counseling and testing” or “opportunistic infections” and was secondarily categorized as “directly related to a specific patient” or “general.”

The Comité TARV database contained 1 entry per second-line request. Each entry included the request date, the requesting health facility, the response date, and the committee's decision

(authorization to switch versus rejection or deferral of the decision pending further patient evaluation). Requests were not disaggregated by method of TF diagnosis (clinical, immunologic, or virologic).

The MISAU database contained the names, levels, and locations of all public-sector health facilities providing ART in Mozambique.⁴ The database also included estimated ART caseloads and number of years of ART experience for each health unit.

Identification of Linha Verde Calls Related to TF

Linha Verde content categories relevant only to HIV-negative persons (eg, HIV prevention) were excluded. Two coauthors (M.R. and P.E.B.) each reviewed a random sample of 200 calls from the remaining categories and coded them as related or unrelated to TF. The preliminary coding results were compared and discrepancies were resolved, with further refinement of the coding method. Additional call categories that consistently lacked content relevant to TF (eg, “obstetrics and gynecology” and “isoniazid preventive therapy”) were then dropped. Finally, one coauthor (P.E.B.) reviewed and coded all calls in the remaining (eligible) categories, which included TF, ART, opportunistic infections (OIs), adverse drug reactions (ADRs), and others. Calls regarding specific patient cases were categorized as directly relevant to TF diagnosis if the Linha Verde advised the caller to seek clinical and/or laboratory evidence of TF or to request second-line ART through the Comité TARV or if the Linha Verde helped with the submission of a specific second-line request to the Comité. Calls that did not concern management of individual patients were coded as indirectly relevant to TF if the Linha Verde provided clarification of Mozambican policy regarding prevention, diagnosis, or management of TF or assisted with relevant operational problems (eg, interventions to improve VL turnaround time).

Identification of Challenges in the Diagnosis of TF

While reviewing call content, we also identified challenges to TF diagnosis and management as reported by the callers or detected by the Linha Verde clinicians and Linha Verde efforts to address these challenges. We then ordered the apparent steps at which patients may fall out of the pathway(s) to identification of TF and/or to obtaining authorization for second-line ART.

Inclusion and Exclusion Criteria

We included all health facilities authorized to manage ART by MISAU, all Linha Verde calls in the eligible categories, and all second-line requests submitted to the Comité TARV during the period of interest. We also included calls and requests originating with entities other than health facilities (eg, health worker training institutes and provincial health directorates). We included all health facilities authorized to manage ART even if they did not generate calls or requests. We excluded five health units that were associated with nongovernmental

organizations that had provided VL testing and on-site expert clinician support for many years.

Statistical Methods

In our primary quantitative analysis, we used linear mixed methods to describe the association between number of second-line requests (the primary outcome) and number of TF-related Linha Verde calls, with adjustment for other pre-specified health unit characteristics (health facility level, years of ART prescribing experience, ART caseload and viral load availability, and other Linha Verde call activity). Because of small numbers, we combined hospitals of all types (district, provincial, military, etc.) into a single “hospital” level. “Province” was treated as a random effect. The unit of analysis was the health facility (or other entity registering Linha Verde calls and/or second-line requests), and we conducted our analyses in Stata 11. We also conducted exploratory analyses that disaggregated direct versus indirect Linha Verde TF calls and that considered district-level associations between TF-related Linha Verde calls and second-line requests.

Ethical Considerations

The Mozambican National Bioethics Committee approved the protocol. The Mozambican Ministry of Health approved the use of the Comité TARV database. Data extracted from both the Comité TARV and the Linha Verde databases were deidentified. This endeavor satisfied the University of Washington Human Subjects Division’s definition of a quality assurance initiative and was not formally reviewed.

Results

Health Facilities

Based on Linha Verde, Comité TARV, and MISAU data, we identified 1011 eligible health facilities and other entities that registered Linha Verde calls in the categories of interest, requested second-line ART through the Comité TARV, and/or managed patients on ART. Their characteristics are described in Table 1. In comparison to health posts and rural health centers, hospitals and urban health centers had substantially higher ART caseloads, more years of experience in ART provision, and more access to VL testing.

Linha Verde Calls, Second-Line Requests

We identified 1432 Linha Verde telephone calls in the categories of interest for the period January 2015 through May 2016. Between January 2015 and June 2016, the Comité TARV received 3464 requests for second-line ART approval. Fifteen (1.0%) Linha Verde calls and 802 (23.2%) second-line requests originated from the 5 ineligible health units and were excluded. Of the 1417 remaining Linha Verde calls, 390 (27.5%) were relevant to TF (191 [13.5%] directly and 199 [14.0%] indirectly).

Table 1. Characteristics of Health Facilities and Other Entities by Health Facility Level.

Characteristics	Hospitals (n = 57), n (%) or median (IQR)	Urban Health Centers (n = 112), n (%) or median (IQR)	Rural Health Centers (n = 752), n (%) or median (IQR)	Health Posts (n = 58), n (%) or median (IQR)	Other or Unknown ^a (n = 32), n (%) or median (IQR)	n nonmissing
ART caseload, ^b patients	2037 (993, 3412)	1525 (277.5, 4787.5)	197 (73, 491)	108 (32.5, 256.5)	103 (66, 334)	959
ART experience, years ^b	9.5 (9, 10.5)	5 (2.5, 8.5)	2.5 (1.5, 4.5)	1.5 (0.5, 2.5)	1 (0.5, 2.0)	966
On-site viral load test availability (≥1 month during study period)	2 (3.5%)	10 (8.9%)	0	0	0	971
Within-district viral load test availability (≥1 month during study period)	7 (12.3%)	51 (45.5%)	15 (2.0%)	12 (20.7%)	15 (46.9%)	987
Linha Verde participation ^c						
No calls	8 (14.0%)	43 (38.4%)	576 (76.6%)	48 (82.8%)	6 (18.8%)	1011
≥1 Call	49 (86.0%)	69 (61.6%)	176 (23.4%)	10 (17.2%)	26 (81.3%)	1011
Second-line ART requests						
No requests	17 (29.8%)	54 (48.2%)	643 (85.5%)	57 (98.3%)	29 (90.6%)	1011
≥1 Request	40 (70.2%)	58 (51.8%)	109 (14.5%)	1 (1.7%)	3 (9.4%)	1011

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

^aIncludes health units of unknown level (per Ministry of Health lists) and other entities such as nongovernmental organizations and district health directorates.

^bBased on Ministry of Health statistics.

^cIncludes any Linha Verde call in the categories of interest, regardless of relevance to treatment failure.

Of the 1011 eligible health facilities and other entities, 187 (18.5%) used the Linha Verde but did not submit second-line requests; 68 (6.7%) submitted second-line requests but did not use the Linha Verde; 143 (14.1%) used the Linha Verde and also submitted second-line requests; and 613 (60.6%) did neither. Calls originated in 131 (85.1%) of Mozambique's 154 districts and second-line requests in 101 (65.6%). Health facilities that called the Linha Verde or submitted second-line requests (predominantly hospitals and urban health centers) had median ART caseloads of over 1000 patients and over 8 years of ART management experience, versus medians of fewer than 100 patients on ART and fewer than 3 years of ART experience for other health facilities.

Association of Linha Verde Calls and Second-Line Requests

In bivariate linear regression analyses (Table 2), the dependent outcome was the number of second-line ART requests submitted to the Comité TARV per health facility. We found that higher numbers of TF-related Linha Verde calls, higher health facility levels, longer duration of ART management experience, higher caseloads, urban location, and greater availability of VL testing were all significantly associated with higher numbers of second-line ART requests. Linha Verde calls lacking TF-related content had a significant but weaker association with second-line ART requests.

Multivariable Models of the Association between Linha Verde Calls and Second-Line Requests

In our core multivariable model (Table 3), the strength of the association between the number of TF calls to the Linha Verde

and the number of second-line requests submitted by the same health unit was diminished (compared to bivariate results), but its statistical significance persisted after adjustment for health facility level, cumulative ART experience, ART caseload, and availability of VL testing. In multivariable analysis, each TF call to the Linha Verde was associated with an increase of 0.61 (95% confidence interval [CI]: 0.15-1.06) second-line requests from the same health unit, on average. Individual health units generated as many as 13 TF calls to the Linha Verde during the period of observation.

Exploratory Analyses

We examined the possibility that the association between Linha Verde calls and second-line requests might vary by call type. In a model that included direct TF, indirect TF, and non-TF calls, we found that increased numbers of "indirect" TF calls were significantly associated with second-line requests (coefficient 1.70, 95% CI: 0.80-2.60) while other call types were not (Table 2). Other findings were not significantly changed.

We also suspected that the association between Linha Verde calls and second-line requests might operate at the district as well as the health unit level. Therefore, we repeated the main analyses using the district as the unit of analysis. In the district-based analyses, we used covariates denoting total ART caseload for health units in the district, highest level of health facility in the district (hospital versus other), and greatest number of years of ART experience in the district.

Bivariate analyses of associations between TF-related calls and second-line requests at the district level are presented in Table 4. The magnitude of the association between TF-related

Table 2. Bivariate and Multivariable Associations of Linha Verde Calls, Health-Facility Characteristics, and Number of Second-Line ART Requests by Health Facility.

Covariate	Bivariate					Multivariable (main), n = 955					Multivariable (exploratory), n = 955				
	Categories	Coefficient	P Value	95% CI	N nonmissing	Coefficient	P Value	95% CI	Coefficient	P Value	95% CI	Coefficient	P Value	95% CI	
Treatment failure calls (any type)		3.70	<.001	3.15-4.26	1011	0.61	.009	0.15-1.06	Not included	—	—	Not included	—	—	
Treatment failure calls (direct)		5.14	<.001	4.23-6.06	1011	Not included	—	—	-0.03	—	—	0.943	0.943	-0.93-0.86	
Treatment failure calls (indirect)		4.82	<.001	3.00-6.64	1011	Not included	—	—	1.70	—	—	<.001	<.001	0.80-2.60	
Calls unrelated to treatment failure		1.49	<.001	1.25-1.73	1011	Not included	—	—	-0.11	—	—	0.385	0.385	-0.36-0.14	
Health facility level	Unknown or missing	-0.45	.821	-4.35;3.45	1011	Nonhospital: reference	—	—	Nonhospital: reference	—	—	—	—	—	
	Health post	-0.71	.635	-3.66-2.23	1011	reference	—	—	reference	—	—	—	—	—	
	Rural health center	Reference	—	—	—	—	—	—	—	—	—	—	—	—	
	Urban health center	11.86	<.001	9.67-14.05	—	—	—	—	—	—	—	—	—	—	
	Hospital	11.29	<.001	8.31-14.26	—	—	—	—	4.11	—	—	.001	.001	1.78-6.44	
Years of ART experience	≤2.5	Reference	—	—	966	<10.5: reference	—	—	<10.5: reference	—	—	—	—	—	
	3.5-7.5	1.84	.073	-0.17-3.84	—	—	—	—	—	—	—	—	—	—	
	8.5-9.5	9.05	<.001	7.18-10.91	—	—	—	—	—	—	—	—	—	—	
	10.5-12.5	21.80	<.001	17.72-25.87	—	—	—	—	—	—	—	—	—	—	
ART caseload	<1000	Reference	—	—	959	Reference	—	—	5.77	—	—	<.001	<.001	2.74-8.81	
	1000-4999	6.77	<.001	5.26-8.28	—	—	—	—	Reference	—	—	—	—	—	
	5000-9999	22.14	<.001	19.14-25.14	—	—	—	—	3.43	—	—	<.001	<.001	1.97-4.90	
	≥10 000	112.08	<.001	103.5-120.66	—	—	—	—	12.95	—	—	<.001	<.001	9.90-16.00	
Viral load test availability, months: In same district		0.77	<.001	0.60-0.93	987	0.18	.007	0.05-0.31	87.07	—	—	<.001	<.001	79.17-94.97	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

Table 3. Bivariate Associations of Health Unit Characteristics and Number of Second-Line ART Requests, by Health District.^a

Covariate	Categories	Bivariate			Multivariable		
		Coefficient	P Value	95% CI	Coefficient	P Value	95% CI
Treatment failure calls (direct)		11.21	<.001	9.10-13.32	5.02	<.001	3.15-6.88
Treatment failure calls (indirect)		12.14	<.001	8.76-15.52	–		
Calls unrelated to treatment failure		2.48	<.001	1.93-3.02	–		
Health facility level	No hospitals in district	Reference	–	–	–		
	Any hospital located in district	28.13	.001	11.80-44.47	–		
Maximum years of ART experience (any health unit in district)	<9	Reference	–	–	Reference		
	9.0-10.4	3.88	.659	–13.46-21.22	11.79	.044	0.33-23.26
	≥10.5	48.03	<.001	25.09-70.98	22.22	.002	7.97-36.47
ART caseload (patients; total for district)	<1000	Reference	–	–	–		
	1000-4999	3.56	0.714	–15.60-22.72	–		
	5000-9999	13.98	.244	–9.65-37.61	–		
	≥10 000	77.39	<.001	52.88-101.89	–		
Viral Load test availability (months during study period)	In same district	9.08	<.001	7.36-10.80	4.55	<.001	3.12-5.98

Abbreviations: ART, antiretroviral therapy; CI, confidence interval.

^aNumber of health districts included is 140.

Linha Verde calls and second-line requests appeared to be substantially greater in district-level than in health-facility-level analyses.

In bivariate district-level analyses, the coefficients for association between TF-related calls (direct or indirect) were both >10 ($P < .001$ for each) but were attenuated in multivariable analyses. The presence of a hospital, larger ART caseloads, greater experience with ART, and greater availability of VL testing were again associated with higher numbers of second-line requests. Collinearity involving health-facility-level, ART experience, and patient population was a constraint to the construction of a district-level multivariable model that was directly parallel to that presented in Table 3.

Qualitative Findings: Barriers to Diagnosis and Management of ART TF

The Linha Verde call logs recorded many challenges to the identification of TF and to the submission of second-line requests; they are summarized in Table 4.

The most fundamental challenge to the diagnosis of TF (by clinical, immunologic, or virologic methods) was the callers' lack of familiarity with the concept of TF and with indications and methods for monitoring patient response to ART. In consequence, many calls that were ultimately categorized as TF-related began as queries about presumed ADR or OI, but the Linha Verde clinicians detected possible TF during the case discussion. Additional sets of challenges confronted clinicians who grasped the concept of TF but were thwarted in their efforts to confirm it. When possible, the Linha Verde assisted callers in resolution of nonclinical problems that affected patient care.

Discussion

Because the likelihood of VF increases with duration of ART,¹⁵⁻¹⁹ we anticipated that health facilities with larger numbers of more treatment-experienced patients would have substantially more cases of TF and more second-line requests. These health facilities were usually urban hospitals and health centers that were also more able to confirm TF, through enhanced clinical and laboratory investigations, and so were different than smaller/more rural health facilities in several possibly confounding ways. Still, we found that Linha Verde telephone calls related to TF were significantly associated with submission of second-line requests, which we regarded as a proxy for TF diagnosis, even after adjustment for these factors. Linha Verde calls that lacked TF content were not associated with second-line requests in multivariable analyses, suggesting that the content of the TF call—rather than global differences between health facilities that generated Linha Verde calls and those that did not—drove this association.

The coefficient for association of TF-related Linha Verde calls and submission of second-line requests was 0.61 in our primary multivariable analysis ($P < .01$). Is an increase of 0.6 TF diagnoses per relevant Linha Verde call clinically significant? In the study setting, TF was underdiagnosed, VL testing and TF training were only available in a few sites, and nearly 80% of health units that manage ART submitted no second-line requests at all. We believe that a health unit's transition between never requesting a second-line switch and requesting even one is both clinically and programmatically significant. The magnitude of the observed association between TF-related Linha Verde calls and second-line requests was roughly equivalent to that of 3 months of district-level VL availability; the important role of VL availability in the generation of TF diagnoses is unquestioned in the local environment. Also, our

Table 4. Steps in the Recognition and Management of Probable Antiretroviral Treatment Failure in Mozambique as Documented in Linha Verde Telephone Consultation Records.

Category	Steps	Requirements	Linha Verde Interventions ^a
Monitor for signs and symptoms of treatment failure after ART initiation	<ul style="list-style-type: none"> • Monitor clinical evolution • Monitor CD4 evolution • Monitor HIV viral load 	<ul style="list-style-type: none"> • Patient presents for timely care • Patient's medical record is available • Clinician is able to take appropriate history and conduct physical examination • Laboratory and imaging tests for common conditions are available • Clinician knows when and how to request VL and CD4 testing • CD4 and VL are available with adequate turnaround • Clinician has access to Mozambican policy re clinical staging, CD4 and VL monitoring 	<ul style="list-style-type: none"> • Recommend specific laboratory and imaging studies based on clinician's report • Where indicated test is not available locally, identify nearest site where test is available • Where turnaround times are slow, intervene with laboratory supervisors or help clinician to intervene • Help callers fill out forms to request VL test • Circulate summaries of relevant Mozambican guidelines by text message • Mail training materials and policy documents to callers
Identify possible or probable treatment failure	Synthesize and interpret clinical data	<ul style="list-style-type: none"> • Clinician is able to seek and recognize signs and symptoms of WHO stages III and IV conditions • Clinician is able to recognize favorable and unfavorable patterns of CD4 evolution based on Mozambican definitions of adequate CD4 response • Clinician is able to recognize favorable and unfavorable patterns of VL suppression based on Mozambican thresholds • Clinician is able to recognize deteriorating patients who merit second-line request without delaying to request VL testing 	<ul style="list-style-type: none"> • Review diagnostic criteria for WHO stages III and IV conditions • Identify abnormal CD4 and VL patterns not recognized by clinician • Identify normal CD4 and VL patterns not recognized by clinician • Explain difference in interpretation of venipuncture and dried blood spot specimens for VL • In the event of clinical deterioration, recommend immediate hospital admission, transfer to specialist, and/or immediate second-line request in unstable patient
Evaluate contribution of adherence	<ul style="list-style-type: none"> • Use history and pharmacy records to assess patient adherence • Develop enhanced adherence plan 	<ul style="list-style-type: none"> • Medical record is available • Pharmacy records are available • Local resources exist for enhanced adherence support • Antiretroviral medications are consistently in stock 	<ul style="list-style-type: none"> • Recommend increased adherence support while treatment failure investigation continues • Coordinate with provincial and district medication warehouses to locate the nearest available supply of a medication that is out of stock • Advise callers on correct methods for requisitioning medications before stock-outs occur
If treatment failure is identified, submit request for second-line ART	<ul style="list-style-type: none"> • Obtain paper or electronic form to request second line • Fill out form to request second line • Submit form to request second line • Obtain Comité TARV response to second-line request 	<ul style="list-style-type: none"> • Available medical record with data necessary to fill out form • Available paper form • Mailing address of committee (electronic or other) • Ability to type • Available electronic form • Available Internet connection • Available e-mail access • Comprehension of queries in form 	<ul style="list-style-type: none"> • Send forms to callers and help callers complete them • Provide addresses for submission of forms • Advise on locations of active Internet connections within the local health system • Review completed forms in order to increase the likelihood of second-line approval (via e-mail)
If second line approved, start second line	<ul style="list-style-type: none"> • Submit formal requisition for medications to central pharmacy when necessary • Prescribe second-line ART correctly (regimen and dose) 	<ul style="list-style-type: none"> • Clinician has access to necessary forms and knows how to fill them out • Clinician knows where and how to submit forms • Clinician is able to calculate correct dosage for second-line antiretroviral medication 	<ul style="list-style-type: none"> • Explain how to fill out and submit requisitions for the second-line medications • Explain dosage calculations for specific patients

Abbreviations: ART, antiretroviral therapy; VL, HIV viral load; WHO, World Health Organization.

^aInterventions initiated by the Linha Verde team in response to observed or reported constraints to diagnosis or management of antiretroviral treatment failure.

exploratory analyses suggest that the magnitude of association between TF-related Linha Verde calls and second-line requests may be even greater at the district than at the health unit level.

The retrospective analysis of routinely acquired programmatic data has well-known hazards.²⁰ However, although observational in nature and not collected specifically to support research, the Comité TARV database represents nearly all TF cases reported in Mozambique. Our health facility sampling frame was derived from official MISAU lists updated annually. Similarly, the Linha Verde data were observational and initially collected for programmatic, not research, purposes. But all Linha Verde calls were handled by a 3-clinician team based in the same office in Maputo, and all clinicians used the same methods for logging calls. We read each call summary in its entirety before classifying the call.

Because we worked with deidentified versions of the databases, we were not able to link Linha Verde calls and subsequent second-line requests through the use of unique patient identifiers. But because local clinicians were required to provide documentation of TF at the time of submission of a second-line request to the Comité TARV, it is implausible that the direction of causality would be from second-line request to Linha Verde call rather than the reverse.

The observed positive association between TF-related Linha Verde consultation and submission of second-line ART requests (a proxy measure of TF diagnosis) is consistent with observations in more resource-rich settings. For example, a “virtual” pediatric multidisciplinary HIV team in London responded to clinician queries by telephone and e-mail and reported that the team’s advice was followed in 80% of cases¹²; in Spain, “long-distance interactive expert advice” (delivered by e-mail) resulted in 74% clinician uptake of regimen switch advice, with subsequent HIV VL reduction in 59.4% of failing patients.¹³ In the United States, the Extension for Community Healthcare Outcomes networks have successfully used teleconferencing to improve hepatitis C treatment outcomes in rural and other underserved populations; the proportion of patients achieving a sustained viral response to treatment was nearly identical at primary care and academic sites.²¹

The different observed associations of TF-related and TF-unrelated Linha Verde calls with second-line requests were reassuring. We had anticipated that the clinicians and health units that did consult the Linha Verde might be technically stronger than nonusers and that this might have resulted in a positive relationship between all types of calls and our primary outcome. We did not observe this result. With regard to possible differences between direct and indirect TF calls, it is difficult to draw conclusions because of overlapping CIs in bivariate analyses and because of heterogeneity in call content within the 2 categories. However, we did note during our qualitative review of Linha Verde consultation records that many of the indirect TF calls were requests for clarification of new Mozambican policy for diagnosis and management of TF. It is possible that a single policy clarification discussion might have led to more efficient diagnosis and management of multiple patients, whereas patient-specific calls may not have had this

amplifying effect. We also found that both direct and indirect TF calls were initiated much more often in health units that generated at least one request for second-line switch (19.0% made both types of calls) when compared to health units that never requested second-line switches (1.5%); this resulted in collinearity in multivariable analyses. And it is possible that the direct and indirect calls lie within the same causal pathway; for example, an indirect call about new Mozambican criteria for diagnosis of VF might be followed by a second, direct call to discuss a specific patient with VF.

Many recent commentaries on the challenges of 90:90:90 goal attainment in resource-limited settings have noted that overlapping introduction of multiple relevant interventions will be required to support the current global aim of suppressing HIV viremia. This is certainly the case in Mozambique, where the majority of working HIV/AIDS clinicians were never formally trained to diagnose or manage TF and where laboratory tests for HIV viremia are still only sparsely available. Attainment of population-level virologic suppression in Mozambique will require far more than simple installation of VL testing devices; necessary adjuncts will include community involvement, increased health worker training, enhanced monitoring and evaluation, better integration of clinical and laboratory systems, strategic decisions about population and programmatic priorities, and others.²²⁻²⁵ Many of these domains are represented in Table 4, which delineates some of the principal gaps between what Mozambican HIV/AIDS clinicians have been trained to do and what they must do now that diagnosis and treatment of virologic (and other) failure have become feasible. The Linha Verde is attempting to help fill these gaps through rapid dissemination of health policy changes, rapid case consultation, and rapid communication of stockout and other logistical problems to central authorities.

Conclusion

In Mozambique, the population of patients failing ART is thought to be large. One tactic used by MISAU to overcome health worker knowledge and resource gaps in the context of HIV/AIDS is the establishment of a clinician warm line, the “Linha Verde.” Through retrospective analysis of routinely acquired Mozambican program data, we have described a statistically significant association between TF-related Linha Verde calls and second-line ART requests (a proxy measure for new TF diagnoses), persisting even after adjustment for other important covariates and in exploratory analyses that used districts, rather than health units, as the unit of analysis. We have also identified important gaps in clinical knowledge and resources relevant to TF. We anticipate that future efforts will confirm the results of these retrospective analyses through prospective linkage of Linha Verde conversations, second-line ART requests, and patient and/or health worker identifiers.

Our findings suggest that ongoing implementation of Mozambique’s Linha Verde could support many of the multifaceted system changes required for Mozambican attainment of the 90:90:90 goals. We hope that our observations on health

worker knowledge gaps can be used to strengthen the Linha Verde's approach and the development of new initiatives to address the needs of the most peripheral health facilities and health workers and of their patients.

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