Optimize

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Mozambique Needs Assessment for Optimized Antiretroviral Drugs and Regimens

The analysis and recommendations presented in this assessment are based on the best available information as of March 2017 and may require adaptation to align with future developments.

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Background

OPTIMIZE, a project supported by the U.S. Agency for International Development (USAID) through the President's Emergency Plan for AIDS Relief (PEFPAR), aims to accelerate the development, testing, and market introduction of optimized antiretroviral (ARV) products to support the best possible treatment outcomes for people living with HIV in low-and middle-income countries (LMIC). Optimized ARV products are those that are 1) effective, safe, well-tolerated, and easy to use for LMIC priority populations (including children, pregnant women, and tuberculosis [TB] patients), and 2) adapted to resource- and infrastructure-constrained environments (i.e. affordable, heat-stable, and available in fixed-dose combinations [FDC]). Optimization offers extensive health benefits, including improved adherence and decreased treatment failure due to higher tolerability, lower toxicity, reduced drug resistance, and fewer side effects; increased patient compliance thanks to smaller tablet sizes; and decreased HIV transmission and incidence as a result of earlier and more sustained viral suppression.

The optimization process consists of a combination of global interventions to bring optimized ARV products to market rapidly and local preparations to ensure they reach patients in LMIC efficiently and effectively. At the local level, some past transitions to new ARV products have been hindered by issues such as national policy and regulatory barriers, tendering, and procurement challenges, supply chain interruptions, slow uptake by prescribers, and patient apprehension. To avoid these and other stumbling blocks during the transition to optimized ARV products such as those containing dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) in the next two to three years, countries require a foundational understanding of their capacity and readiness in key domains relating to new product introduction.

The **OPTIMIZE** Country Needs Assessment assesses national capacity and readiness across four functional domains: 1) Policy, Advocacy, and Finance; 2) Planning Processes and Tools; 3) Service Delivery Capacity; and 4) Transition Monitoring and Visibility. Drawing on quantitative and qualitative data, the

ABBREVIATIONS

ADR	Adverse drug reactions
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
CMAM	Central de Medicamentos e Artigos Medico (Central Medical Stores)
CNCS	Conselho Nacional de Combate ao HIV e SIDA (National AIDS Control Council)
CRP	Collaborative Registration Process
CSW	Community sex worker
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir
EFV	Efavirenz
ePTS	Electronic Patient Tracking System
FDC	Fixed-dose combination
HTLV	Human T-lymphotropic virus
LMIC	Low and/or Middle Income Countries
LIMS	Laboratory Information Management System
M&E	Monitoring and Evaluation
MISAU	Ministério de Saúde (Ministry of Health)
MRS	medical record system
MSM	Men who have sex with men
NDRA	National Drug Regulatory Authority
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
PMTCT	Prevention of mother-to-child transmissio
PPM	Pooled Procurement Mechanism
pppy	Per patient per year
PSM	Procurement and Supply Management
PWID	People who inject drugs
RVLM	Routine viral load monitoring
SISMA	Sistemas de Informaçã (National Health Information System)
TAF	Tenofovir alafenamide fumarate
TAFxD	Tenofovir alafenamide fumarate/ Lamivudine or Emtricitabine/Dolutegravir
TDF	Tenofovir Disoproxil Fumarate
TB	Tuberculosis
TLD	Tenofovir/Lamivudine/Dolutegravir
TLE	Tenofovir/Lamivudine or Emtricitabine/ Efavirenz
ToT	Training of trainers
TWG	Technical Working Group
USAaID	United States Agency for International Development
VL	Viral load
WHO	World Health Organization

Assessment assigns a “need rating” of low, moderate, or high to each of four sub-domains and identifies priority bottlenecks or weaknesses where action is required to ensure that the transition to a DTG-containing FDC (e.g. tenofovir/lamivudine), commonly referred to as TLD, and other optimized products maximizes health and budgetary benefits.

Increasing LMIC access to optimized ARVs requires predictable and consistent supply from multiple manufacturers, as well as significant and sustainable cost savings vis-a-vis current regimens.

Operational Framework

This assessment is structured around four functional domains of product introduction and scale-up that were identified as strongly influencing the organization and success of past ARV transitions. These domains were formed based on input from multiple stakeholders consulted a stakeholder landscape analysis, which Optimize conducted in 2016.

DOMAIN 1

ENABLING ENVIRONMENT (POLICY, ADVOCACY, AND FINANCE)

Are national policies, advocacy platforms, and financial processes ready to facilitate new product introduction?

DOMAIN 2

PLANNING PROCESS AND TOOLS

Do tools and processes for forecasting, tendering, target-setting, and transition monitoring require updating or adaptation?

DOMAIN 3

SERVICE DELIVERY CAPACITY

Are ART service delivery models and health care workers prepared to support the introduction of new ARV products and enhanced patient monitoring?

DOMAIN 4

TRANSITION MONITORING AND VISIBILITY

Are rigorous monitoring processes in place for: regimen change and patient outcomes, ARV stock levels, overall transition progress?

Methods

Desk Review

Much of the contextual and quantitative data for the needs assessment was drawn from relevant reports and other literature, including peer-reviewed journals, official government announcements, and popular media coverage.

Key Informant Interviews

Interviews were conducted from March 23, 2017 to April 4, 2017. Interviews were held in-person in Maputo and Nampula provinces. Interviews were recorded and ranged in length from 30 to 60 minutes, with the vast majority of the latter duration. Interviewer notes and recordings were kept confidential per protocol, and in order to elicit candid responses interviewees were assured that comments would not be attributed on an individual basis.

Twenty-one interviews were conducted with respondents representing a wide range of sectors (Figure 1), and areas of expertise (Figure 2). The full list of interviewees can be found in Appendix 1.

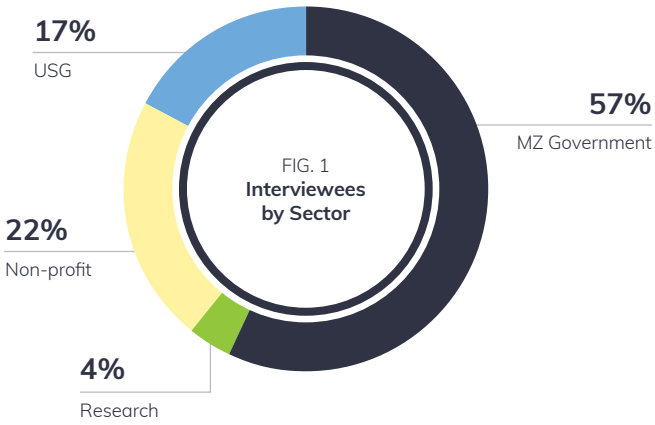

FIG. 1
Interviewees by Sector

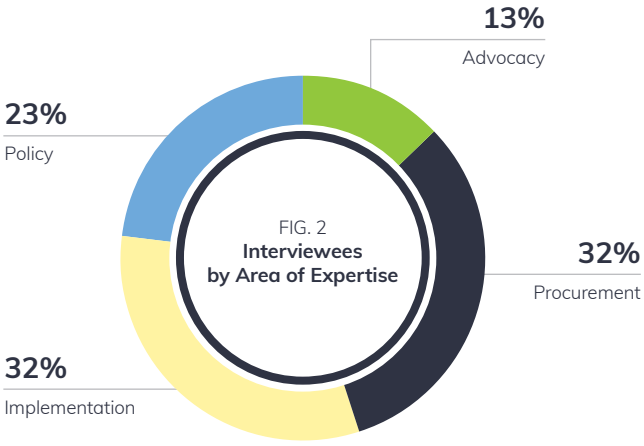

FIG. 2
Interviewees by Area of Expertise

Country Context

Mozambique faces a generalized HIV epidemic characterized by an adult prevalence of 13.2% that is higher among women (15.4%) as compared to men (9.2%) and in the Southern provinces (25.1%) as compared to the Northern provinces (3.7%).[1] Of approximately 1.6 million people living with HIV in Mozambique, 64% of adults and 70% of children are receiving antiretroviral therapy (ART).[2] Key populations include commercial sex workers (CSW), men who have sex with men (MSM), prisoners, and people who inject drugs (PWID). Other priority populations include active military, as well as miners and long-distance truck drivers who migrate between Mozambique and South Africa.

In June 2013, Mozambique began initiating new ART patients on a FDC of 300mg tenofovir disoproxil fumarate (TDF) + 300g lamivudine (3TC) + 600mg efavirenz (EFV), or TLE600, in accordance with the 2013 World Health Organization (WHO) consolidated treatment guidelines. Mozambique experienced a severe interruption in the supply of zidovudine (AZT)-containing formulations due to a global shortage of the main active pharmaceutical ingredient for zidovudine (AZT), the drug that preceded TDF in first-line therapy. In the absence of adequate AZT supply, the Ministry of Health (MISAU) was forced to sharply accelerate the pace of the transition to TLE600; as a result, the proportion of first-line ART patients on TLE600 in Mozambique skyrocketed from 16% to 68% in just nine months.[3] Today, 84% of adult ART patients are on TLE600; Stavudine (d4T) has been effectively phased out, and the remainder of adults still receiving AZT+3TC+nevirapine (NVP) cannot switch to a TDF containing regimen due to hypertension or other conditions for which TLE600 is contraindicated.[4]

Though the phase-in of the TLE600 FDC in Mozambique met with severe logistical challenges, the regimen is in many respects a good match for the country's HIV care and treatment needs. TLE600 is safe and effective in adolescents and adults, including pregnant women, who account for a significant proportion of ART patients in Mozambique. TLE600 is also safe and effective in patients with TB/HIV co-infection (estimated at 52% in Mozambique[5]) and doubles as an effective therapy for Hepatitis B.

TLE600 also has its drawbacks, including large pill size, frequent neuropsychiatric side-effects and a sub-optimal barrier to resistance particularly for EFV. EFV's low genetic barrier to resistance is of special concern in Mozambique, where retention, adherence, and viral suppression rates are low[6] and evidence from small-scale studies[7] suggests that ARV drug resistance is increasing.

Increasing rates of patients on ART who are hospitalized and/or have opportunistic infections are also suggestive of an increasing burden of treatment failure. Furthermore, the need for creatinine clearance monitoring in TLE600 patients with renal impairment presents a logistical challenge, since biochemical evaluation is not widely available at the point of service.

Mozambique has a massively overstretched health workforce, with only 66 health care workers per 100,000 people[8] (compared to the WHO standard of 230). Despite task-shifting policies that have delegated HIV care and treatment functions to clinical officers and nurses and introduced multi-month scripts for stable ART patients, it is not unusual for providers at large health facilities to see upwards of 100 ART patients in a single day. Most ART patients, in turn, spend a full day at the health facility for each appointment, and must make additional trips to obtain laboratory results or pick up medication. ARV drugs occupy a tremendous portion of central and provincial drug warehouse space, and distribution of ARVs to health facilities is dependent on logistical support from implementing partners, as the central medical stores (CMAM) do not have adequate capacity (in terms of trucks and personnel) to cover these routes. Although routine viral load monitoring (RVLM) is included in Mozambique's 2016 Standard Treatment Guidelines ("where possible"), coverage is low and is not expected to increase dramatically in the near term.

1. IMASIDA 2015 (Inquérito de indicadores de imunização, malaria, HIV/SIDA em Mocambique).
2. NAP Report, 2016.
3. Interview with PSM. 9-month period in question ran from February to October 2014.
4. Interviews with PSM and CMAM.
5. PEPFAR Mozambique FY16 COP SDS.
6. 12-month ART retention is 66% according to the FY16 COP SDS. Viral suppression rate is as low as 35%, per head of National HIV Program.
7. Vubil et al., *J AIDS Clin Res* 2016, 7(10). DOI: 10.4172/2155-6113.10000623. Rupérez et al. *J Antimicrob Chemother* 2015; 70(9): 2639-2647. DOI: 10.1093/jac/dkv143.
8. MISAU 2012.

Optimization in Mozambique: Special Considerations

As described above, Mozambique's response to the national HIV epidemic has stretched several pillars of its health system — human resources, medical commodities management, and service delivery — to their limit. In addition to weighing the clinical and public health benefits of optimized ARVs under ideal conditions, MISAU officials and other stakeholders must take into account a range of health system and programmatic challenges as they assess which combination of emerging ARV products offers the best fit for Mozambique. This means carefully evaluating optimized ARV products':

- Potential for simplified transport and storage
- Laboratory monitoring requirements (e.g. for patients with Hepatitis B co-infection, and given the limited availability and extended turn-around times of viral load monitoring)
- Potential for simplified dispensing and administration, especially in the case of pediatric regimens
- Effectiveness and barrier to resistance under conditions of suboptimal adherence due to patient or programmatic barriers
- Compatibility with regimens prescribed in South Africa (for miners and long-distance truck drivers who migrate between countries)

Mozambique's response to the national HIV epidemic has stretched several pillars of its health system — human resources, medical commodities management, and service delivery — to their limit.

I. Enabling Environment (Advocacy, Policy, and Finance)

Shared understanding of optimization benefits:

Despite active monitoring of global developments in ARV optimization by the National Therapeutic Committee (Comité TARV), many stakeholders in Mozambique have limited knowledge of ARV optimization generally and of the specific benefits of DTG and TAF.

Many ART patients lack a foundational understanding of both the HIV life cycle and the mechanisms of action through which different classes of ARV drugs combat HIV in the body. This lack of knowledge has, in the past, led some ART patients to regard new ARV drugs with apprehension or suspicion, and to misattribute any real or perceived changes in their health to the new drugs. Central and decentralized stakeholders (including program managers, implementing partners, providers, and pharmacists) possess varying levels of knowledge about ARV optimization. While several individuals were well acquainted with the emerging evidence on DTG and TAF, the majority of stakeholders interviewed stated that they had limited or no knowledge of the benefits of newer drugs such as DTG and TAF compared to EFV600 and TDF. When presented with an overview of the clinical advantages of these two drugs, stakeholders expressed strong interest in learning more. Several stakeholders conveyed a desire for periodic updates on 1) the latest evidence from regional clinical trials of DTG, TAF, and other optimized drugs, 2) experiences in countries proceeding with introduction DTG and/or TAF on either a pilot or full-scale basis, and 3) availability of optimized ARV products from generic manufacturers.

Political will and popular support for optimization:

All stakeholders conveyed openness to evidence-based innovation in the area of ARV optimization. However, several stakeholders also noted that Mozambique has multiple priorities with respect to HIV care and treatment; increasing retention and viral suppression rates are chief among these. Interviewees signaled that the surest path for establishing optimization as a national priority is to link it directly to improvements in retention and viral suppression, thus ensuring that planning and implementation of new product introduction align with and reinforce existing systems and initiatives. They underscored that strong engagement from national leaders within the therapeutic committee, the national HIV program, and the care and treatment technical working group (TWG) is critical to introducing optimized ARVs, and that involvement of community and religious leaders, people living with HIV and those involved in their care — including clinical providers, peer educators, support group members, and family members and friends — is essential to ensuring strong uptake of and adherence to optimized products.

Civil society advocates noted that TLE600 is still widely perceived as a "new" regimen by people living with HIV, and the introduction of a different first-line regimen could lead to "transition fatigue" among some patients. They also stated that they would welcome a measured transition to an FDC that was available in a smaller pill size and had fewer or less severe side effects than TLE600. Stakeholders noted that early and substantive consultation with networks of people living with HIV about adoption of optimized ARV products will be important in order to educate recipients of care about clinical benefits, generate demand, and head off false rumors about side effects such as those that have plagued past ARV transitions.

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The Comité TARV, which leads the updating of Mozambique's standard treatment guidelines for ART (STG) sees the gathering, evaluation and dissemination of information on the best available ARV products as a core part of its work. The committee will hold a technical consultation in May 2017 to review current evidence on new treatment options and how they relate to Mozambique's priorities and needs.

Comprehensive updates to the STG — including coordinated revision of preferred and alternative first-, second-, and third-line therapy for children, adolescents, and adults — have been a precondition for advancing ARV optimization in Mozambique. Historically, updates to the STG have occurred every two to three years, and are generally

prompted by changes to WHO Treatment Guidelines and newly available scientific evidence. An expert meeting in May will be an important preliminary step in this process, but additional information gathering, expert exchange and consensus-building will be needed before formal revisions occur. Once initiated, the process of updating the STG can take up to one year from start to finish though it is unclear if the optimization opportunities discussed at the recent meeting will be introduced prior to the next formal STG revision.

Financial requirements and resources:

Given Mozambique's heavy reliance on donor funding for procurement and last-mile distribution of ARV drugs, as well as the uncertainty surrounding future PEPFAR funding levels, identifying ways to extend lifesaving ART to more people living with HIV with fewer resources will be critical for the future of the national ART program. By adopting an optimized first-line ARV regimen containing either DTG (TLD) or DTG and TAF (TAFxD), Mozambique could realize direct per patient per year (pppy) cost savings of USD $22 to USD $41 among first-line patients. Even if actual pppy savings fall at the lowest end of this range, aggregate savings at scale would total USD $17.5 million each year — enough to provide ART to more than 200,000 additional patients. Optimization would also bring supplemental indirect savings in the form of decreased drug transport costs (due to smaller pills) and decreased expenditure on second- and third-line ARV (due to anticipated reductions in the treatment failure rate).

While there are some up-front costs associated with planning and implementing a first-line ARV transition, such as on-the-job training mentorship and intensified patient monitoring during the transition period, these can be minimized through advance planning and coordination as well as leveraging of existing platforms like Mozambique's Linha Verde, a combined toll-free hotline and SMS broadcast service designed to disseminate national ART norms to providers throughout the country.

Transparent, streamlined drug registration process:

Mozambique's national drug regulatory authority (NDRA), the Pharmaceutical Department of MISAU, is responsible for evaluating new drug applications submitted by drug manufacturers and deciding whether to approve or deny those applications. The standard pathway for registering ARV drugs is "complete" or "full" registration, which typically takes between 12 and 18 months to complete and — if successful — results in a registration that is valid for five years. Mozambique observes two expedited alternatives to the standard registration process: 1) the WHO Collaborative Registration Procedure (CRP), which requires just three to four months per product and 2) drug import waivers, which allow for immediate import of certain products judged to be of high public health importance. Mozambique has participated in the CRP since 2013 and has used it to register several pharmaceutical products, including three ARV products from MacLoed's in 2016. Should manufacturers not use the CRP and choose to go though Mozambique's NDRA for registration there could be delay in the introduction of new products. However, the NDRA has granted waivers for numerous ARV products in the past, allowing Mozambique to import those products while the suppliers pursue full registration. Stakeholders viewed both the CRP and drug waivers positively and saw them as important mechanisms that facilitate timely introduction and steady supply of ARV drugs in Mozambique.

Streamlined tendering and procurement process:

100% of ARV drugs for Mozambique's public health system are currently funded by international donors (as of 2016, 72% were financed by the Global Fund and 28% by PEPFAR[9]). ARV procurement planning is coordinated through the national Quantification TWG, while tendering and procurement are managed by donor procurement agents on a rolling basis via the Pooled Procurement Mechanism (PPM) and Procurement and Supply Management (PSM) project. CMAM is not directly involved in the tendering and procurement of ARV drugs, but does facilitate customs clearance for ARVs purchased by the Global Fund and PEPFAR.

Because tendering and procurement of ARVs in Mozambique are managed on a rolling basis and independently of the broader national drug tendering and procurement cycle, tendering and procurement requirements are not expected to pose a barrier to the efficient introduction of optimized ARV products. However, advance planning that explicitly links logistical schedules for procurement and distribution of optimized products to the phased rollout of those products to patients at health facilities will be essential to ensuring a smooth transition.

9. PEPFAR Mozambique FY16 COP SDS.

Treatment guidelines readiness:

Before a new ARV product can be imported to or prescribed in Mozambique, it must be included in the national STG. The Comité TARV leads the revision of the STG with input from international experts, the national care and treatment TWG, and other stakeholders. The current STG, published in 2016, establish a CD4 threshold of ≤500 as the standard for initiating ART and specify that pregnant and breastfeeding women and their partners, children <5 years, and patients with TB, Hepatitis B or Human T-lymphotropic virus (HTLV) co-infection, should be initiated regardless of CD4 count. With respect to "what to start", the 2016 STG retain two regimens — TLE600 and AZT+3TC+NVP — as preferred first-line options for adults, and stipulate alternative first-line regimens and second-line options for each of these regimens. Pediatric regimens are even more complex due to the need for age- and weight-specific formulations and dosing. Three optimized ARV drugs that are included in the 2015 WHO consolidated guidelines — DTG, EFV400, and atazanavir/ritonavir (ATV/r) — are omitted from Mozambique's 2016 STG, while darunavir/ritonavir (DRV/r) is included only as part of a complex third-line regimen.

Pediatric regimens are even more complex due to the need for age- and weight-specific formulations and dosing.

Since issuing the 2016 STG, MISAU has initiated Test and Treat in select urban areas, with the intention of scaling up nationally over time. With the initiation of Test and Treat, some providers have started to place less importance on laboratory monitoring, and due to severe logistical challenges surrounding laboratory monitoring in general (including a shortage of lab technicians to process samples, long distances between health facilities (HF) and laboratories, and excessive turnaround times), some clinicians choose not to order tests at all. This is especially problematic given emerging evidence suggesting significant levels of transmitted drug resistance to EFV in Mozambique, which could lead to a surge in treatment failure among first-line patients on TLE600 MISAU appears to have acknowledged this possibility through a November 2015 SMS broadcast message to medical doctors and clinical officers warning: "First line failure is a matter of time. Monitor clinically and immunologically and use viral load (VL) to confirm."[10]

10. http://www.linhaverdemisau.co.mz/normas_misau.html

Table 1: Enabling Environment (Advocacy, Finance, and Policy)

BENCHMARK: Shared understanding of benefits of optimization — **NEED RATING:** HIGH

JUSTIFICATION: Many stakeholders were unaware or marginally aware of the clinical benefits of DTG and TAF as compared to EFV and TDF.

BENCHMARK: Political will and popular support for optimization — **NEED RATING:** MODERATE

JUSTIFICATION: The national therapeutic committee will hold a technical consultation in May to discuss and evaluate the suitability of several pipeline ARV drugs for Mozambique. There is strong support within the committee for a near-term change to 2L therapy; further evidence on safety and effectiveness in TB patients and pregnant women is needed to secure the committee's support for DTG- and/or TAF-containing 1L therapy.

BENCHMARK: Financial requirements and resources — **NEED RATING:** MODERATE

JUSTIFICATION: Projected pricing for TLD and TAFxD indicates that Mozambique stands to achieve significant cost savings by adopting either regimen for 1L therapy. Initial on-the-job training and intensified patient monitoring costs need to be quantified, but can be minimized through advance planning and leveraging of existing platforms like the Linha Verde (http://www.linhaverdemisau.co.mz)

BENCHMARK: Transparent, streamlined drug registration (or waiver) process — **NEED RATING:** LOW

JUSTIFICATION: The standard registration process for ARV drugs takes 12 to 18 months. However, Mozambique has used the WHO CRP to register multiple ARV products and intends to use it to register additional ARVs in the future. In addition, ARV products are commonly imported under waivers, which allow for expedited procurement, and it is assumed that waivers could be secured for optimized products in the future if suppliers choose to forgo the CRP process in favor of registering with Mozambique's NDRA.

BENCHMARK: Streamlined tendering and procurement process — **NEED RATING:** LOW

JUSTIFICATION: The current tendering and procurement processes used for ARVs are flexible and capable of responding in a timely fashion to changes in the STG.

BENCHMARK: Treatment guidelines readiness — **NEED RATING:** HIGH

JUSTIFICATION: Comprehensive revision of STG is a critical precondition for adopting optimized ARV products. Given the most recent update to the STG occurred in 2016, it is unlikely that another major revision would take place before 2018.

II. Operational Planning and Preparation

Forecasting and supply planning readiness:

The National ARV Quantification TWG, led by CMAM, in collaboration with PEPFAR/PSM and the Global Fund, is responsible for ARV forecasting and supply planning in Mozambique. An offline national pharmaceutical supply management system, SIMAM, is used by central and provincial warehouses as well as by some district warehouses and high-volume hospitals and clinics in Mozambique, and currently captures pharmaceutical stock data from a total of 1,020 HF.[11] However, the quality of ARV stock data is suboptimal due to faulty or incomplete paper-based requisition forms completed at the HF level. Large discrepancies (27% on average, and in excess of 50% in some provinces) persist between pharmacy data on the quantity of ARV drugs dispensed and clinical data on the number of active ART patients.[12] This creates challenges for accurate forecasting of ARV needs in Mozambique and creates the potential for stock surpluses or shortages.

With technical assistance from PSM, CMAM and MISAU are enhancing and expanding the Medicine Logistics Information System for Health Facilities (SIGLUS)[13] , a web-based logistics management system operating on the OpenLIMS (laboratory information management system) platform, to a total of 100 health facilities in 2017.[14] The ARV-specific features of SIGLUS include management of ARV stocks and regimen data. SIGLUS expansion is expected to improve the accuracy and flow of data on ARV stocks, and should also support more accurate ARV forecasting. As of January 2017, SIGLUS was in use at 34 HF in Maputo province, and the national scale-up plan aims to expand it to 84 additional HF in Gaza, Inhambane, Tete, and Zambézia provinces by the end of the year.

A national supply plan for ARV drugs exists for the five-year period spanning December 2016 to December 2021. The primary aim of this plan is to ensure ARV security, rather than to dictate in advance the precise type and quantity of ARVs to be procured; as such, the plan provides high-level assumptions and parameters

SIGLUS expansion is expected to improve the accuracy and flow of data on ARV stocks, and should also support more accurate ARV forecasting.

11. Interview with PSM.
12. Interview with CMAM M&E Director.
13. Formerly the electronic stock management system (ESMS).
14. https://openlmis.atlassian.net/wiki/display/OP/ESMS+Tablet+Project

to guide ARV purchases. Since ARV drugs are ordered on a rolling basis with a standard lead time of 9 to 12 months, the supply plan can be adjusted or adapted to incorporate the purchase of lower-cost optimized ARV products with advance notice of approximately one year.

One potential supply challenge that falls beyond the control of national actors is an interruption in the supply of active pharmaceutical ingredients (APIs) used to manufacture finished optimized ARV products. This eventuality cannot be adequately planned for at the country level, since split tenders are only effective at mitigating the risk of interruptions in the supply of finished ARV products. Given Mozambique's recent experience with an API shortage during the transition to TLE600, many national actors will want assurance that API production for optimized products is sufficiently diversified to avoid a similar situation in the future.

Use of data to inform timing and phasing of product introduction:

Once MISAU has determined which optimized ARV regimens will be included in its STG moving forward, further analysis will be required to determine the optimal pace and targeting for the introduction and scale-up of each regimen, based on a combination of clinical, programmatic, and budgetary considerations. In the past, this step has been folded into the transition planning process, which is led by the planning department of CMAM (see "Comprehensive transition planning").

Comprehensive transition planning readiness:

The planning process for the phase-in of TLE600 as a standard first-line regimen was led by the Comité TARV with involvement from the National HIV Program, CMAM, implementing partners and WHO. Within CMAM, the planning department, which is responsible for coordinating the implementation of new policies and drug regimens, took the lead in developing the written transition plan, balancing clinical input from the Comité TARV and other stakeholders with logistical considerations to create a viable, time-bound transition plan. Several stakeholders stated that the initial plan developed for the phase-in of TLE600 was well designed and appropriately detailed; however, it was also noted that concerns about laboratory monitoring requirements for TLE600 emerged late in the planning process due to a combination of incomplete evidence and insufficient consultation with laboratory stakeholders early in the process. Planning for the transition to TLE600 lasted approximately one year; stakeholders held disparate views about the viability of condensing this timeline for future transitions, with some affirming it is feasible to plan in a shorter time period and others insisting that two years is the minimum requirement. Decentralized stakeholders did not recall using numeric targets for the transition to TLE600; rather, they were informed of the criteria for switching patients and were able to track the percentage of eligible patients who had been switched using the electronic patient tracking system (ePTS).

Once MISAU has determined which optimized ARV regimens will be included in its STG moving forward, further analysis will be required to determine the optimal pace and targeting for the introduction and scale-up of each regimen, based on a combination of clinical, programmatic, and budgetary considerations.

Stakeholders emphasized the importance of unified master planning for future ART transitions, given the broad spectrum of stakeholders who have a role in ensuring transition success. MISAU's Acceleration Plan for HIV/AIDS Response 2013-2015 was cited as a model for collaborative planning that brought together key stakeholders from government, donor agencies, multilateral organizations, and implementing partners to establish a common agenda and roadmap for achieving it. The process for developing the Acceleration Plan was intensive and highly participatory, involving a series of thematic working group sessions, solicitation of written input from provinces, a planning retreat, and a validation workshop over the course of a two-month period.[15] MISAU could apply a similar approach to the planning of future ARV transitions, ensuring active input from clinical, logistical/supply chain, laboratory, and people living with HIV/civil society stakeholders.

15. http://www.sahivsoc.org/Files/5%20-%20Joaquim%20Fernando%20-%20Lessons%20learned%20from%20implementation%20of%20HIV%20AIDS%20acceleration%20plan%20in%203%20provinces%20of%20Mozambique.pdf

Table 2: Operational Planning and Preparation

BENCHMARK: Forecasting capacity and readiness **NEED RATING:** HIGH

JUSTIFICATION: Significant discrepancies between logistical and program data in some provinces present a challenge to develop assumptions for accurate forecasting. SIMAM is widely used but constrained by data quality and data flow issues; SIGLUS offers functional improvements but has not yet been adopted widely.

BENCHMARK: Supply planning capacity and readiness **NEED RATING:** LOW

JUSTIFICATION: A national ARV supply plan exists and there is flexibility within the current procurement processes to accommodate new (lower-cost) ARVs with 9-12 months lead time. NB: Ensuring on-time delivery from ARV suppliers has been a challenge in the past.

BENCHMARK: Use of data to inform product introduction timing and phasing **NEED RATING:** MODERATE

JUSTIFICATION: In the past, scenario modeling has been nested inside of the transition planning process led by the planning department of CMAM and MISAU. As such, it has tended to focus narrowly on phase-in options for a particular regimen or product, rather than on the selection of a comprehensive set of optimized products that, in combination, would be most beneficial for patients and the national program. Consumption data used to inform planning is of inconsistent quality.

BENCHMARK: Comprehensive transition planning readiness **NEED RATING:** MODERATE

JUSTIFICATION: CMAM and MISAU led the development of a sound, detailed plan for the phased introduction of TLE600 (though that plan was rendered unfeasible by the AZT shortage). Planning for introduction of optimized ARV regimens can be further strengthened through early circulation of clinical and programmatic evidence to all stakeholders, early solicitation of input from all stakeholders (to avoid the emergence concerns late in the process), better synchronization of supply chain and clinical activities, and establishment of numeric transition targets at the national and sub-national levels.

III. Service Delivery Support

Clear directives and associated implementation tools:

The 2013 MISAU directive that initiated the phase-in of TLE600 for first-line ART, titled "Introduction of New Norms for Monitoring of HIV-positive Patients," included guidance on cotrimoxazole prophylaxis, criteria for ART initiation, changes to therapeutic regimens for adults and children, and prevention of mother-to-child transmission (PMTCT). The initial guidance for first-line ART specified that clinicians at select facilities should switch adult patients from AZT/3TC/NVP to TLE600 if they met any of the five eligibility criteria: ART naive (including pregnant and breastfeeding women), on ART <6 months, unable to tolerate current therapy, ART naive or on ART <6 months with a new case of TB, or co-infected with Hepatitis B. It also specified which alternative regimens were advised in special cases (e.g. renal failure or a serious psychiatric disorder). The directive did not provide a rationale for the regimen change, nor did it direct providers to communicate these reasons to their patients (though such information may have been covered during the training).[16] Some stakeholders thought that future directives on ARV regimen changes should provide background about the changes; others emphasized the importance of setting clear targets for both the phase-in and phase-out of ARV products to avoid stock surpluses and drug expiries.

Stakeholders affirmed the importance of strengthening community education and demand generation leading up to future transitions.

Training, supervision, and data collection materials — including training manuals, job aids, revised registers, supervision grids, and feedback templates — will need to be updated to reflect changes to protocols for patient management (including clinical and laboratory monitoring), stock management and dispensing, and pharmacovigilance. Given observed weaknesses in patient preparation during the transition to TLE600, special attention should be granted to this subject to ensure that it is an explicit focus of both provider orientation/training and subsequent supervision visits. Based on experience from past transitions in Mozambique (wherein small errors in revised tools have made them difficult to implement at health facilities), any revised data collection materials (e.g. registers) should be thoroughly pre-tested before being mass printed and scaled up.

16. Based on primary analysis of Directive No 1314/002/DNAM/2013.

Training and supervision resources and capacity:

During the first-line transition to TLE600, provider training was a large-scale effort that involved intensive technical, logistical, and financial assistance from implementing partners. Training was conducted according to the national training protocol, which calls for a progressive training-of-trainers (ToT) approach starting at the central level and expanding to the provincial, regional, district, and health facility levels.

Decentralized stakeholders noted that the most influential factor in ensuring compliance with the MISAU directive on the phase-in of TLE600 was on-site supervision and follow-up after the initial training, rather than the training itself. MISAU officials at both the central and decentralized levels expressed openness to a streamlined training approach for future transitions; one decentralized official suggested a model wherein district-level trainers (working in teams of two or more) would orient and prepare providers for the transition through routine on-site supervision and mentorship visits. SMS broadcast messages sent through the Linha Verde were also cited as helpful in explaining the transition process and resolving clinical questions that providers had during the phase-in of TLE600, such as how to monitor renal and hepatic function in patients.

Community education and demand generation:

During the phase-in of TLE600, patients were inadequately prepared for regimen change. Advocates for people living with HIV recalled that some existing patients were switched to TLE600 haphazardly and without explanation. In a few cases, patients did not initially understand that they were to take only one TLE600 pill a day, and proceeded to take twice the prescribed dosage, which led to grave side effects, complaints to dispensing pharmacists, and requests to return to their previous regimens. These experiences underscore the importance of ensuring that all patients are informed of — and understand — the reasons for transitioning to optimized regimens. Scientific treatment education is not currently a priority for the National AIDS Control Council (CNCS) or associations of people living with HIV in Mozambique, but this is due to limited awareness rather than lack of interest.

Stakeholders reported that, during the transition to TLE600, TV and radio spots were launched only after the transition was underway and patient confusion was apparent. Stakeholders affirmed the importance of strengthening community education and demand generation leading up to future transitions. Select approaches favored by stakeholders included: discussion groups for people living with HIV, community radio spots, SMS and other cell phone-based communications (especially for adolescents and young adults), and community-based outreach involving local and religious leaders.

Table 3: Service Delivery Support

BENCHMARK: Updated directives and training, supervision and data collection tools (clinical, laboratory, pharmaceutical)

NEED RATING: MODERATE

JUSTIFICATION: Directives for transition to TLE600 were clear but omitted contextual information about why changes were important and beneficial, as well as instructions for managing stock during the transition period. Some data collection tools have not been adequately vetted during past transitions.

BENCHMARK: Training and supervision resources and capacity

NEED RATING: MODERATE

JUSTIFICATION: A national ARV supply plan exists and there is flexibility within the current procurement processes to accommodate new (lower-cost) ARVs with 9-12 months lead time. NB: Ensuring on-time delivery from ARV suppliers has been a challenge in the past.

BENCHMARK: Community education and demand generation

NEED RATING: HIGH

JUSTIFICATION: In-country experience with scientific treatment education for ART patients is very limited. A coordinated plan and curriculum for patient education and demand generation are urgently needed.

IV. Transition Monitoring and Visibility

Clinical and laboratory monitoring:

The OpenMRS (medical record system)-based electronic patient tracking system (ePTS) managed by MISAU collects information from ART patients' clinical files and aggregates them to generate a range of user-definable cross-sectional reports and cohort analyses. ePTS is now in use at more than 550 health facilities. In PEPFAR-supported districts and health facilities, ePTS data are cleaned on a quarterly basis and are considered more accurate than paper-based records. Select metrics monitored via ePTS include the percentage of newly enrolled ART patients retained at three months and the percentage of stable ART patients receiving multi-month ARV prescriptions and semi-annual clinical appointments. These and other indicators (including CD4 count and TB treatment) can be disaggregated by ARV regimen to support intensified monitoring of patients initiating optimized ARV regimens.

Infrastructure and human capacity to support the scale-up of RVLM in Mozambique are weak and unlikely to improve substantially in the near term.

Infrastructure and human capacity to support the scale-up of RVLM in Mozambique are weak and unlikely to improve substantially in the near term (though PEPFAR included expansion of high-throughput and point-of-care VL in its COP16 plan and budget). Even targeted viral load testing remains inaccessible at many health facilities. As a result, suspected cases of treatment failure are often detected through CD4 trend or clinical management, and are escalated to either the provincial or national therapeutic committee for review before a decision is made to switch a patient to second- or third-line therapy. Poor access to viral load testing poses a substantial challenge to the type of enhanced patient monitoring that may be indicated during ARV transitions.

Stock monitoring systems:

The monitoring and evaluation (M&E) unit of CMAM tracks two standard indicators during ARV transitions: 1) monthly and quarterly stockouts at each provincial warehouse and health facility and 2) the rate of discordance between HIV program data and pharmacy data with respect to current ART enrollment. Stockout data are obtained from SIMAM and the Central Tool, while the rate of discordance is obtained from SISMA (the national health information system). There is no tool or system in place for real-time reporting and monitoring of ARV stockouts or impending expiries, though a stock dashboard is envisaged as part of planned improvements to SIGLUS (discussed under II. Operational Planning and Preparation).

One notable blind spot within the ARV supply chain occurs at the district level. Provincial health services are mandated to deliver ARV drugs to the health facility level on a monthly basis; however, due to logistical and capacity constraints, they typically transport ARV drugs to district depots, and districts perform the last-mile distribution to health facilities (often with support form implementing partners). Because drugs are not formally registered or documented at the district level, they are temporarily "invisible" to CMAM until they arrive at the health facility.

All health care providers in Mozambique are charged with reporting adverse drug reactions (ADR) or events. During the transition to TLE600, pharmacists were among the first to hear about patients' neurological (depression, nightmares) and dermatological side effects, as well as to detect misuse by some patients who mistakenly were taking two pills a day (as they had done with their previous regimen). Mozambique has a clear protocol for reporting ADR, but "refresher" messaging on pharmacovigilance — for example, via the Linha Verde — may be needed to support increase vigilance among health care providers.

Transition plan monitoring:

Technical capacity for effective monitoring of ARV transition progress exists within MISAU, CMAM and implementing partner organizations, but timely flow of information across levels of the health system, and appropriate use of that information to redirect resources and take corrective actions, can be improved. A coordinated and multidisciplinary M&E plan will be needed to ensure rigorous monitoring of progress towards benchmarks and targets for supply chain, clinical, pharmacy, laboratory, and demand generation components of Mozambique's future transition plan (once developed). In addition, a Transition Progress Dashboard that captures key metrics in an easy-to-interpret graphic format would be an asset for visualizing and tracking uptake of optimized ARV products during future transitions.

Table 4: Transition Monitoring and Visibility

BENCHMARK: Clinical and laboratory monitoring escalation/alert procedures (retention, viral suppression, treatment failure)

NEED RATING: HIGH

JUSTIFICATION: OpenMRS-based ePTS is in use at more than 550 facilities; can produce cohort reports and cross-sectional analyses on patient progress and outcomes. Laboratory infrastructure is inadequate to support RVLM in many health facilities, so clinical monitoring is used to identify suspected cases of failure. Furthermore, when treatment failure is suspected each individual case must be reviewed by a provincial or national therapeutic committee which creates significant barriers to timely switch.

BENCHMARK: Stock monitoring systems (stockouts, expiries)

NEED RATING: HIGH

JUSTIFICATION: Fragmented data systems impede effective monitoring of ARV stocks. CMAM analyzes stockouts on a monthly and quarterly basis, but there is no real-time tracking or alert system for ARV stockouts and expiries, nor is there a national tools or dashboard that allows for visualization of current stock location and quantity.

BENCHMARK: Pharmacovigilance reporting and escalation (adverse effects)

NEED RATING: MODERATE

JUSTIFICATION: Pharmacovigilance system exists but limited information exists about how widely it is used by providers.

BENCHMARK: Transition plan monitoring (target attainment)

NEED RATING: MODERATE

JUSTIFICATION: CMAM and MISAU conduct intensified tracking of defined metrics during ARV transitions; however, there are sharp discrepancies between pharmacy- and program-side estimates of active ART patients.

Summary

There is strong interest and political will to optimize antiretroviral therapy in Mozambique. Multiple opportunities exist to introduce new ARV products to further support country level goals to achieve 90-90-90 targets. However, transition planning must take into consideration the country context. This includes current MISAU priorities such as the scale-up of test and treat, strengthening PMTCT, and improving identification of treatment failure.
New introduction plans should also leverage existing systems strengthening efforts and incorporate lessons learned from previous wide-scale ARV transitions.

Challenges identified that may hinder the introduction of new optimized ARVs include:

- Limited access to information about new optimized ARVs amongst many in-country stakeholders
- Recent guidelines revision in 2016 that omitted new optimization opportunities such as DTG-based first line and ATV/r based 2nd line
- Limited visibility into consumption data to monitor uptake of different regimens at district and facility level present a challenge to accurate quantification
- Limited treatment literacy amongst people living with HIV may result in low demand for new ARVs due to “transition fatigue” and inaccurate information
- Limited access to diagnostics, in particular viral load monitoring, may result in the missed identification of treatment failure and the ability to ensure timely regimen switches
- Fragmented data systems for monitoring of stock to prevent stockouts or expiries

Program strengths that will support the introduction of new optimized ARVs include:

- Political will from MISAU to strengthen the HIV program and recognition of both clinical and cost benefits of ART optimization
- Transparent and streamlined registration using waivers or the CRP process will allow expedited procurement of new ARV products
- Flexible tendering and procurement practices allow for new orders to be accommodated in a relatively timely manner
- Protocols for training managers and health care workers are supplemented by an innovative communication platform (Linha Verde) that reaches a wide audience
- Existing pharmacovigilance system in place that will allow for post marketing surveillance of newly introduced ARVs

Multiple opportunities exist to introduce new ARV products to further support country level goals to achieve 90-90-90 targets.

Appendix 1: List of Interviewees

Date	Name	Title	Organization
March 23	Ms. Judite de Jesus Mutoque and Ms. Amélia Mariva Muamba	Coordinator of Association	Hixikanwe People Living with HIV Association in Maputo
March 24	Dr. Sultana Razaco	Drugs Registration Focal Point	NDRA Pharmaceutical department
March 24	Dr. Rolanda Manuel	President, ART Committee	MISAU
March 27	Dr. Marzio Stefanutto	Care and Treatment Advisor	Friends in Global Health
March 27	Dr. Joao Teixeira, Dra. Juliane Pires	Head of Forecasting, Distribution, and quantification	Procurement & Supply Chain Management (PSM)
March 28	Eng. Jaime Fraqueza	Head of Department	Central Medical Stores (CMAM)
March 28	Dra. Kamila Magaia	Head of Distribution Department	Central Medical Stores (CMAM)
March 29	Dr. Ema Chuva	Planning Unit Coordinator	National AIDS Control Commission (CNCS)
March 29	Dr. Ernesto Sambo	Head of Procurement Department	Central Medical Stores (CMAM)
March 29	Dr. Lucrecia V. Mateus	Head of Monitoring and Evaluation Department	Central Medical Stores (CMAM)
March 29	Dr. Jose Filipe	Head of Planning Department	Central Medical Stores (CMAM)
March 30	Dr. Januario Reis	Care and Treatment Unit	USAID/MZ
March 30	Dr. Aleny Couto	Head or Deputy of National AIDS Program	MISAU, National HIV program
March 31	Dr. Ruggero Guiliani	Medical Coordinator	Médecins Sans Frontières
April 3	Dr. Suleimana Isidoro	Provincial Medical Officer	Provincial Health Directorate Nampula
April 3	Dr. Carimo Assane	HIV Program Officer	Nampula HIV Program
April 3	Dr. Joaquim Rodrigues	Head of Provincial Warehouse	Provincial Warehouse Nampula
April 3	Various	Health Center and Public Pharmacy staff	Health facilty warehouse and pharmacy (at 25 Setembro)

Appendix 2: Example Interview Guides[17]

Landscape Analysis: Optimization

1. What is your title? What is your role with [INSERT ORGANIZATION]? How long have you been in this function?
2. Do you think that ARV optimization is important for Mozambique currently? Why or why not?
3. What is the role of [INSERT ORGANIZATION] in ARV optimization?
4. Are you aware of recent advances with respect to the introduction of TLD and TAFxD?
5. Can you list the benefits of TLD? TAFxD?

Past Transition and Future Plans

1. Thinking back to the process for establishing TLE FDC as the standard 1L treatment in Mozambique, did CMAM have a dedicated plan for supply and distribution of this new regimen? Were there any special measures put into place to ensure that it was effectively distributed?
2. What are the biggest challenges encountered with respect to sustaining reliable supply of ARV drugs to all HF in Mozambique? During the transition to TLE FDC, what challenges were experienced with respect to supply and distribution of this regimen? Stockouts, expiries, etc.?
3. What can and should be done to ensure timely distribution of ARV drugs during future transitions?
4. What can and should be done to ensure higher visibility of ARV stock levels at the central and decentralized levels (e.g. stock dashboard accessible to public)? Are there any activities underway or planned to improve stock visibility?
5. Can you describe the process for ARV forecasting? Who is involved, and how often is forecasting done? What are the biggest challenges with respect to accurate forecasting of ARV demand in Mozambique?
6. What is the state of non-facility-based (e.g. community-based) drug distribution/dispensing?

17. Interview questions were adjusted based on the role and expertise of the informant.

Optimize

The **OPTIMIZE** project is a global consortium dedicated to rapidly improving treatment outcomes for people living with HIV by optimizing ARV drugs and formulations and accelerating their introduction in low- and middle-income countries. Founding members of the OPTIMIZE consortium include five leading private and public sector organizations: (1) Wits Reproductive Health and HIV Institute (Wits RHI), an established PEPFAR implementing partner with expertise in research, program implementation, policy, and training; (2) ICAP at Columbia University (ICAP), one of the largest PEPFAR implementing partners, with extensive experience providing site, regional, and national support in the scale-up of HIV services and conducting studies on HIV adherence and retention; (3) Mylan Laboratories Limited (Mylan), a global generic and specialty pharmaceuticals company with drug development and manufacturing capacity to achieve lower yet sustainable pricing; (4) the University of Liverpool (UoL), a leading academic research institution with unique capabilities in Solid Drug Nanoparticle (SDN) technology; and (5) the Medicines Patent Pool (MPP), a United Nations-backed not-for-profit organization with a public health driven approach to lowering HIV medicine prices through voluntary licensing and patent pooling. USAID is proud to support OPTIMIZE, a global partnership with unifying distinct voices to achieve a common goal: accelerating access to simpler, safer and more affordable HIV treatment.

For further information or to request technical assistance from **OPTIMIZE,** please contact Nandita Sugandhi, ICAP Product Introduction Coordinator, at nss14@cumc.columbia.edu or +1(212) 305-7085.

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