USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTAPS) PROGRAM

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Health facility staff who were trained on the Active Surveillance Study for TLD, Maputo, February 2020. Photo credit: Eunice Dias, MTaPS

Strengthening Pharmacovigilance for Improved Patient Safety in Mozambique

Technical Brief | September 2023 | Mozambique

Monitoring adverse events in patients on an antiretroviral therapy regimen for HIV treatment

Background

The goal of the US Agency for International Development (USAID) Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program (2018–2024) is to help low- and middle-income countries strengthen their pharmaceutical systems to ensure sustainable access to and appropriate use of safe, effective, quality-assured, and affordable essential medicines, vaccines, and other health technologies and pharmaceutical services. Through its work, MTaPS seeks to improve pharmaceutical services, including product availability and patient-centered care, to achieve desired health outcomes.

When Mozambique's Ministry of Health sought assistance from USAID in assessing the safety of the World Health Organization (WHO)-recommended Tenofovir/Lamivudine/Dolutegravir (TLD)—a newly introduced antiretroviral regimen for HIV treatment—MTaPS was called upon to offer technical assistance in safety monitoring of adverse events (AE).

Problem Statement/Challenge

More than 2 million of Mozambique's population of 32 million are living with HIV, with women accounting for

60% of the people living with HIV in the country.[1]

In 2018, Mozambique's national HIV program introduced the WHO-recommended TLD regimen as the first line of HIV treatment in the country, after it was demonstrated to effectively suppress viral load. Some concerns surrounded the use of TLD in pregnant women, based on earlier reports of neural tube defects in babies born to women taking TLD in a Botswana study.[2] Although subsequent studies indicated that these defects were not associated with the new regimen, the WHO recommended continued surveillance for TLD—a standard best practice for new treatments.

When TLD was introduced in Mozambique, the country's national medicines regulatory authority, the *Autoridade Nacional Reguladora de Medicamentos, Instituto Publico* (ANARME, IP), then named the National Directorate of Pharmacy (DNF), had only a spontaneous or passive pharmacovigilance (PV) reporting system in place, allowing health care providers to report AEs in patients. However, no active surveillance system was in place for systematic recording and reporting of AEs associated with the use of medications of interest, including TLD. This severely limited monitoring and collection of drug safety data for evidence-based decision making.

Technical Approach

MTaPS supports low- and middle-income countries with the overall goal of achieving maturity level 3 (out of 4) as per the WHO's Global Benchmarking Tool for evaluation of health regulatory systems, including building or strengthening the country's PV system.

MTaPS' approach for supporting PV includes strengthening the processes for risk identification and characterization, risk assessment/evaluation, risk minimization, and safety communication, and helping countries establish systems to actively monitor the safety of new and/or high-risk medicines and vaccines. In Mozambique, MTaPS collaborated with ANARME, IP and the HIV program to implement active safety monitoring (ASM) of the TLD regimen in the health facilities (HFs) that participated in the study and supported adaptation and deployment of the online Pharmacovigilance Monitoring System (PViMS) tool to support TLD active surveillance data collection from the nine study sites. PViMS allows for recording, reporting, and analysis of data on AEs and other patient information, including medication history and follow-up visits. The application is used by clinicians, regulatory bodies, and implementing partners to monitor the safety and effectiveness of medicines, capturing data such as clinical stage, concomitant medications, test results, co-morbid conditions, and treatment-regimen initiation date, to help improve clinical documentation at participating sites. In addition, PViMS provides for the use of common terms, checklists, and adoption of internationally accepted standard terminologies.

Stakeholder Engagement

To design and implement the PV system in Mozambique and carry out the TLD ASM study, MTaPS collaborated with the national HIV program and ANARME, IP, the University of Washington, and Columbus Consulting. Additional partners included focal persons from the seven provinces where the TLD ASM study was undertaken and the nine participating health care facilities. Funding for this work was provided by the US President's Emergency Plan for AIDS Relief (PEPFAR).

Intervention

MTaPS supported ANARME, IP and the National HIV program to design and implement a PV active surveillance system to study the real-world safety profile of TLD for the management of HIV, including in women of childbearing age. This activity in Mozambique, in turn, could be leveraged to monitor patients who receive other drug regimens of interest and to generate locally relevant information to inform risk assessment.

A prospective study was designed focusing on newly enrolled patients, meaning that when patients came in for care, the information they reported was recorded and evaluated to contribute to increased understanding of side effects that may be related to

[1] https://mz.usembassy.gov/our-relationship/pepfar-us-presidents-emergency-plan-for-aids-relief-2/.

[2] Rebecca Zash et al: Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. NEJM. 2019 Aug 29;381(9):827–840. doi: 10.1056/NEJMoa1905230. Epub 2019 Jul 22.

TLD. Providers were requested to record and report all AEs, regardless of whether they were believed to be associated with the newly introduced drug regimen. In the case of pregnant women or women who became pregnant after starting TLD, pregnancy outcomes were also systematically recorded.

Throughout the process, MTaPS played an active role, supporting country partners and HFs in the design and implementation of the study as follows:

Planning and preparation

- Conducted stakeholder coordination meetings (with the national HIV Program) to solicit input and gain buy-in for the proposed study and PV approach.
- Developed an active surveillance protocol for patients starting TLD treatment. The protocol laid out the study methodology and data collection tools.
- Developed standard operating procedures for study implementation and pilot testing of the data collection forms.
- Obtained approval from the National Commission on Bioethics in Health in Mozambique to implement this safety surveillance study.
- Identified 10 HFs across 7 provinces for the phased introduction of TLD in the country to achieve the sample size of 3,000 enrollees across all facilities. Because one facility was reprofiled as a COVID-19–specialized facility during the COVID-19 pandemic, only 9 facilities implemented the PV system and enrolled patients. Facilities were chosen based on having a high number of patients co-infected with TB/HIV; their experience and/or ability to follow up routinely with patients; serving as a referral site that sees a large number of HIV/TB patients; their ability to collect and manage electronic data; geographic location (to ensure representativeness); and having health professionals with experience in prenatal care, childbirth, and postnatal care.
- Configured the PViMS (an open-source web-based application for passive as well as active surveillance) to the needs of TLD in the Mozambique context.
- Developed and distributed data collection forms to participating HFs.
- Deployed PViMS for data collection in the HFs and supported data transmission from the 9 implementing HFs to the central level. Provided tablet computers to each participating HF to be used for PViMS data entry.
- Facilitated two training courses to equip ANARME, IP and national HIV program staff on data analysis using PViMS and to equip the ANARME, IP with a central system for monitoring adverse events.

Strengthening capacity

- Identified PV, HIV, and maternal, newborn and child health (MNCH) provincial focal persons and trained them as trainers. These provincial focal persons were then responsible for training and sensitizing other HCWs.
- Identified and trained 14 provincial focal persons and 72 HCWs drawn from PV, HIV/AIDS, and MNCH departments through a 3-day site training. These were responsible for training and sensitizing other HCWs from the participating HFs on the study objectives and protocol to build understanding and support.
- Trained ANARME, IP and national HIV program staff as PViMS master trainers, supported cascade training of 34 health workers from nine HFs on PViMS data entry, and trained the ANARME, IP system administration team to administer the tool at the central level.

Enrolling patients and collecting data

- Supported enrollment of patients in nine health care facilities (in Niassa, Manica, Gaza, Nampula, Zambezia, Maputo City and Maputo provinces). Facilities enrolled patients when they began TLD treatment. Participation was voluntary. HCWs explained the study to each patient and obtained informed consent from each participant.
- Supported ANARME, IP and the HIV program to conduct quarterly supportive supervision (in-person and remote) to monitor and support HCWs in the implementing facilities. Supportive supervision focused on topics such as following up with enrolled patients to document AEs, ensuring that patients complete their follow-up visits, and that clinical staff document all follow-up visits to identify challenges and undertake corrective actions.
- Ensured monthly supervisory and monitoring calls to participating sites by provincial focal persons to ensure adherence to the protocol (proper

collection, entry, management, and analysis of safety data generated from the activity) and to support quality and consistency of the process, including data collection.

- Supported ANARME, IP to organize monthly virtual review meetings with all site teams to discuss a status report and emphasize focus on the importance of conducting and recording follow-up visits for the enrolled patients.
- Documented follow-up and progress. Conducted follow-up calls with each study site and generated reports containing key findings on implementation from the different facilities, key implementation challenges, mitigation measures, recommendations, and next steps for proper implementation of the protocol based on each facility's situation. MTaPS, in collaboration with ANARME, IP, the national HIV program, and the MTaPS global expert partner, University of Washington, generated quarterly progress update reports on the enrolled patient numbers, number of follow-up visits, reported AEs, findings of the supervision visits, strengths and challenges in ASM implementation, and recommendations to address the challenges.
- Provided ongoing guidance to the team from ANARME, IP and the HIV program to manage the collected data in PViMS, including data cleaning and periodic data review.
- Trained 9 ANARME, IP staff on causality assessment, including the use of PViMS to conduct the causality assessment for the reported adverse drug reactions (ADRs)/AEs. Supported mid-term causality assessment of reported AEs which will be used to determine the relationship between TLD and the AEs to detect signals, i.e., a possible causal relationship between an AE and TLD where the relationship is unknown or not previously completely documented, to enable better evaluation of the benefit-risk profile of TLD, which can be used for clinical and regulatory decision making.

Closing out active surveillance and analyzing data

The data collection phase of the study concluded on February 28, 2022.

- Supported ANARME, IP to visit the study sites in-person to advise on how to close the ASM activity. Facilities submitted all their study materials (computer, tablets, completed data collection forms, and informed consent forms) to ANARME, IP at the central level for analysis and final storage.
- Supported ANARME, IP to complete data entry of the forms that had not yet been entered into PViMS, to enter the missing information from the manual forms in coordination with the clinicians, and to clean TLD data in PViMS, then reviewed and analyzed the data.
- ANARME, IP conducted causality assessment on the reported AEs.
- MTaPS conducted the analysis and dissemination of the study report. The findings from this study can be leveraged to monitor patients who receive other drug regimens of interest and to generate locally relevant information to inform risk assessment.

Results and Achievements

The targeted enrollment of 3,000 patients was met, and the enrolled patients had at least 3 routine follow-up visits. Data from the physical data collection tools indicated 95 ADR/AEs were reported. The most common reported AEs were headache, insomnia, nausea, and skin rash; however, none was severe. This data provides initial local evidence on the side effect profile of TLD. These results can be used to guide the Ministry of Health and stakeholders in regulatory and clinical decision making or actions.

This study and approach have set the stage for further PV work in Mozambique and can serve as a model for other countries. A joint article was published profiling the TLD study design and implementation in an international peer-reviewed journal to share experience that can serve as a model for other low- and middle-income countries.[3]

The PV system, including PViMS, established to carry out this study has been tested and improved, and allows Ministry of Health partners to use it for further

[3] Mussá M, Gaspar I, Namburete L, et al. Protocol for active safety monitoring of a cohort of patients using a dolutegravir-based antiretroviral regimen in Mozambique. BMJ Open. 2021;11:e050671. Available from: http://dx.doi.org/10.1136/bmjopen-2021-050671.

implementation. The system has been adapted through the course of TLD study implementation, issues have been documented, and documentation is in place to support further PV in the country. Based on the experience with PV for TLD, in April 2022, Mozambique began implementation of PV for the new tuberculosis preventive treatment (TPT) regimens in people living with HIV.

Lessons Learned

- **Foster local (country, facility) ownership of new systems and approaches.** Active PV succeeded—and is being used in Mozambique beyond the scope of the original TLD study—because country partners felt ownership of the PV system/process. Engagement of ANARME, IP and public health programs allowed for strengthening of partner capacity to engage in active safety surveillance.
- **Verify data early.** Collected data should be verified early to allow for correction if needed. MTaPS conducted data verification starting about halfway through the data collection period. Some data entry needed to be corrected at that time, which required involvement of data specialists and led to delays in the study.
- **Assess causality frequently.** Conducting causality assessment at the end of ASM implementation meant that the study sites had completed data collection and transferred relevant documentation to ANARME, IP and some of the HCWs that implemented the study at the HFs had left and so could not be reached to respond to queries.
- **Engage sufficient human resources and plan logistics.** While any active safety surveillance study requires planning from the scientific side—such as protocol development—the planning also needs to take into consideration the huge workload involved in collecting data from facilities and providing them the support they need to properly collect data. When planning, it is important to keep in mind that facility staff may not have the bandwidth to take on study tasks in addition to their daily work and that studies and pilots of new approaches require intense, ongoing supervision and support from implementing partners.
- **Monitor and support human resources.** Human resources turnover is high in HFs, and it was not uncommon for trained staff to leave the facility for a new position without MTaPS' and the ASM study partners' knowledge. Replacement staff came in without training on the protocol and PV, leading to gaps in enrolling patients and collecting follow-up data. Training additional staff at the facility level to allow for back-up coordinators and specifically checking that trained staff are still in place could help address this issue.
- **Be ready to troubleshoot electronic systems.** The PViMS data collection system used for the study initially had some synchronization issues. At first, this discouraged some of the staff responsible for data entry. Preparing for glitches in advance, letting staff know to expect a learning curve with new systems, and having IT support on call to resolve issues can help when introducing new systems.
- **Be flexible in implementation approaches, if needed.** The study protocol called for follow-up of each enrolled patient on a monthly basis during their first three months on the TLD regimen, with subsequent follow-up visits for one year after enrollment for AE monitoring, for a total of at least six AE monitoring visits. However, COVID-19 restrictions prevented many patients from coming back for their next scheduled clinician visit. In response, some planned in-person supervisory visits were substituted with phone calls and the patient follow-up period was extended from six months to one year to allow for tracking and follow-up.

Pathway to Sustainability

MTaPS was a facilitator of the study and active PV monitoring system, but the ownership lay with country partners. By working in lockstep with ANARME, IP and other partners, MTaPS ensured that ANARME, IP learned how to administer the PV study and, more broadly, how to implement active PV monitoring. As MTaPS phased out its work in Mozambique, the program engaged ANARME, IP and other partners in data analysis and discussion of the process to further build country ownership and drive to implement active PV monitoring in the country.

Conclusions

Mozambique now has locally relevant data to assess the overall safety of the TLD regimen, including any risk in pregnant women and demonstrated experience implementing an active PV program. As it phases out its activities in Mozambique, MTaPS is helping partners to document the study findings that help estimate the incidence rate of AEs and risk factors for development of AEs and ADRs among participants in the active surveillance study. The findings will inform country guidance on TLD use and help to identify AEs that practitioners should be alert for when patients are placed on TLD regimens. Furthermore, MTaPS has prepared a final report on the TLD study results that will be disseminated by ANARME, IP and the national HIV program to key health sector stakeholders to foster discussion of challenges and lessons learned and ensure their understanding of the value of the PV work and their support for continued development of PV in Mozambique. MTaPS is also providing support for the continued PV ASM study of TPT. In the longer term, country partners may want to investigate further opportunities to streamline data collection for PV, for example, by moving away from paper-based forms to increased digitization. The Ministry of Health/ANARME, IP may also want to seek ways to leverage the PV experience with TLD and TPT to benefit patients outside of the HIV program.

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About USAID MTaPS:

The USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program (2018–2024) enables low- and middle-income countries to strengthen their pharmaceutical systems, which is pivotal to better health outcomes and higher-performing health systems. The program is implemented by a consortium of global and local partners, led by Management Sciences for Health (MSH), a global health nonprofit.