Optimize


Jake Price

Experiences Transitioning to New Adult First-Line Antiretroviral Regimens

A MULTI-COUNTRY CASE STUDY

PURPOSE

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 (LMICs). 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 [FDCs]).

As antiretroviral treatment (ART) programs in LMICs advance toward the UNAIDS 90-90-90[1] and World Health Organization (WHO) Treat All targets, ensuring timely access to optimized ARV products is more critical than ever before. Optimized ARV drugs, such as those containing dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF), are expected to bring about improved treatment outcomes and significant cost savings as they are introduced to country programs[2]. However, for these gains to be realized, implementation and uptake of optimized regimens must be well planned and coordinated.

Past transitions to new first-line ARV regimens in LMICs have met with a variety of logistical and implementation challenges, while also yielding a number of good practices. As a new generation of optimized first-line ARV products enters the generic-accessible market, policymakers, health managers and healthcare providers in LMICs can apply lessons learned from past transitions to ensure optimized ARVs reach recipients of care in the most organized and efficient manner possible. **The purpose of this case study is to document and diffuse key lessons learned to date that may inform and facilitate future country-level ARV product introduction activities.**

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METHODS

The cases presented here were constructed from information gathered through desk research, country needs assessments and key informant interviews conducted in 2016 and 2017 under the OPTIMIZE project. Wherever possible, written documentation was used to cross-validate or supplement information gathered through interviews, and vice versa. Information on key challenges and lessons learned was then organized into a stepwise "country transition process" framework consisting of 11 milestones distributed across four domains: **Advocacy, policy, and finance** (drug registration, guidelines revision); **Operational planning and preparation** (transition phasing, communication plans, tendering and procurement of new regimens); **Service delivery support** (directives to staff, mentorship and supervision, demand generation); and **Transition monitoring and visibility** (patient monitoring, pharmacovigilance and stock monitoring).

LIMITATIONS

Implementation challenges at the country level — including facility stockouts, drug expiries, inadequate communication and sensitization regarding new recommendations and resistance to change among patients — are not tracked systematically, so information about these challenges is often anecdotal in nature. Ministries of health (MOH) and country implementing partners feature prominently in accounts of past implementation challenges; however, as these examples illustrate, root causes are complex, and responsibility is shared across a range of global and local institutions and stakeholders. This underscores the need for closer attention to and documentation of key obstacles and bottlenecks encountered as country programs adopt and introduce new ARV regimens.

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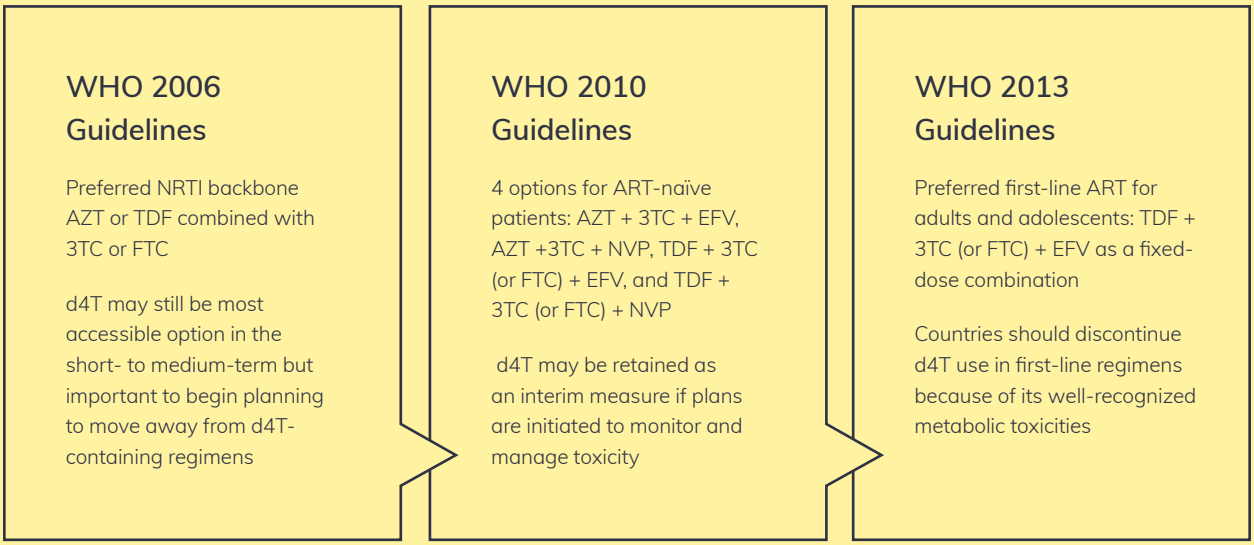
GLOBAL ARV GUIDELINE ISSUANCE AND ADOPTION, 2006 - 2013

Most LMICs update their national ART guidelines based on WHO Guidelines, which are revised and issued every two to four years. Over the last decade, the WHO Guidelines for adult first-line ARV regimens have undergone two major shifts: 1) the phase-out of stavudine (d4T) followed by 2) a recommendation for programs to move towards a fixed-dose combination tablet of tenofovir disoproxil fumarate [TDF], lamivudine [3TC] (or emtricitabine [FTC]) and efavirenz (EFV). Though 3TC and FTC are considered interchangeable[3], in general the lower cost of 3TC compared to FTC makes it a preferable option for most programs and TDF, 3TC and EFV (TLE) is currently the most widely-used regimen globally.

Figure 1 summarizes changes to WHO-recommended "preferred" ART regimens from 2006 to 2013. Starting in 2006, the WHO encouraged a shift away from d4T-containing regimens due to accumulating data on long-term d4T-related toxicities. Both zidovudine (AZT) and TDF with 3TC/FTC were identified as preferred NRTI backbones for adult first-line ART, with an acknowledgement that programs using d4T-based regimens might continue d4T use to avoid undue delays in extending ART to patients in need. At the time, approximately 60 percent of patients were receiving d4T-based first-line ART[4] due to its relative low cost, limited monitoring requirements and availability as a triple drug FDC tablet with 3TC and nevirapine (NVP). It was only in 2010, in the face of increasing concerns about d4T-related toxicities, that the WHO suggested progressive reduction in use of d4T and recommended four new preferred options for adult first-line ART: AZT or TDF in combination with 3TC or FTC plus either NVP or EFV. The WHO consolidated guidelines released in 2013 made a stronger recommendation to discontinue the use of d4T completely, but also placed an emphasis on simplification, recommending TLE – a once-daily, single tablet regimen (STR) that could be used across multiple populations including patients with higher CD4 counts, pregnant and breastfeeding women and patients with TB or Hepatitis B co-infection – as the sole preferred first-line regimen.

Figure 1: WHO Guidelines on first-line ART regimens, 2006 - 2013



The 2013 recommendation to move towards a “universal” adult first-line ART regimen of TLE prompted changes for millions of patients who were on regimens containing d4T, AZT or NVP.

Several country programs, enthusiastic about adopting WHO guidance and facing pressure from both donors and community advocates, forged ahead with the rapid adoption and introduction of TLE. One of the unintended and unforeseen consequences of this rapid shift was a series of global supply shortages caused by inaccurate demand forecasting.[5] Factors exacerbating this issue included manufacturers’ limited production capacity, long required lead times for country orders, and uncertainty among stock managers regarding how to manage existing stocks of older drugs. This necessitated the release of additional WHO guidance recommending a graduated process for transition to mitigate supply chain risks, with the recognition that individual country circumstances may require a more customized approach when it comes to large-scale regimen transitions[6].

From 2006 to 2013, countries continued to use a variety of regimens containing different combinations of AZT, TDF, 3TC or FTC, NVP and EFV delivered in a variety of formulations, including single-drug and dual-drug FDCs (Fig 2). However, since 2013 there has been steady increase in the proportion of adolescents and adults using TLE as first-line ART. This can be attributed to the strong recommendation made by the WHO to move towards a single preferred regimen delivered as an FDC, but also to the decreasing cost of TDF-containing regimens (Fig 3) and increased number of quality assured products available from generic suppliers[7]. At the end of 2015, almost 70 percent of adult first-line patients were on a regimen containing TDF, 3TC or FTC and EFV.

While the transition to TLE has been considered successful from a global perspective, individual country transitions to TLE have been more varied and complex; some programs were slow to adopt and implement a universal first-line regimen, while others moved forward too quickly, with insufficient planning. Both of these scenarios created a sense of disorganization and, in some cases, reluctance by health sector leaders to undertake large-scale regimen changes in the future. However, a number of new processes and innovations also arose to mitigate these challenges. The case studies below present select challenges and good practices that may inform future product introduction at the country level.

Nathan Golon

Fig 2. Evolution in Use of First-Line ARV Regimens in LMIC, 2009-2015[8]

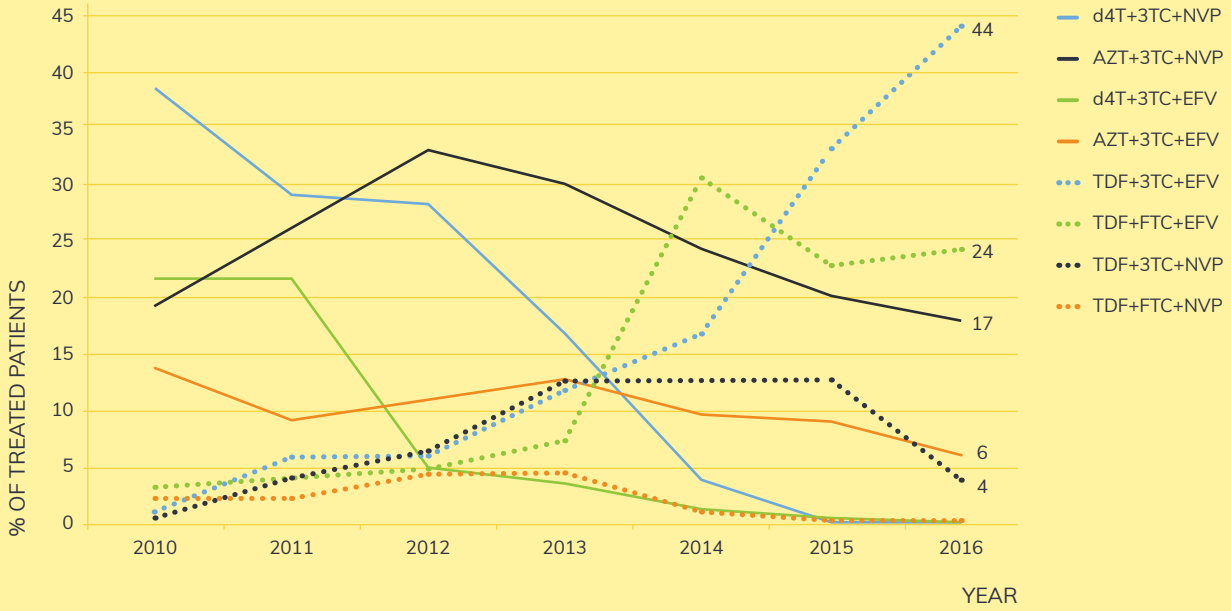
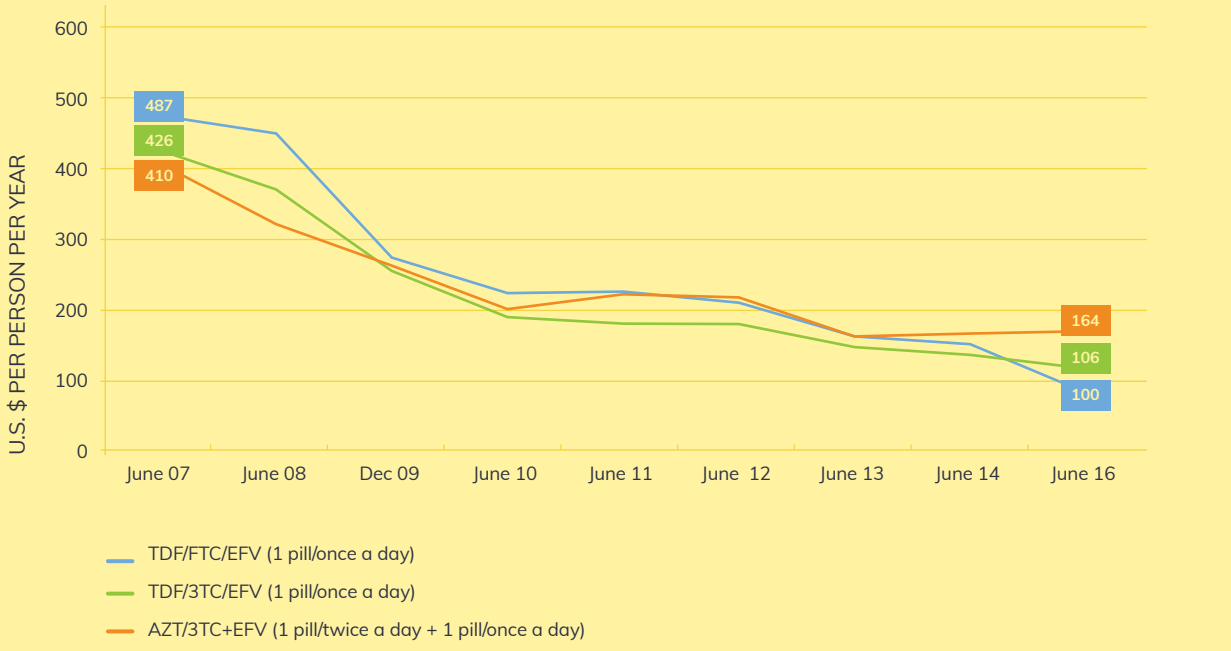


Fig 3. Evolution in Price of Major First-Line ARV Regimens, 2007-2016[9]



A COUNTRY TRANSITION FRAMEWORK

While each country adheres to its own policies and decision-making norms during ARV transitions, most countries must navigate through a common set of processes and milestones when transitioning patients to a new ARV regimen. Figure 4 (below) details the key stages and milestones involved in planning and implementing a typical first-line ARV transition at the country level. Organizing past country transitions into this framework allows for comparative assessment of experiences in multiple transition domains, as well as distillation of key challenges and innovations.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ADVOCACY, POLICY, AND FINANCE

- Drug registration
- Guidelines revision

OPERATIONAL PLANNING AND PREPARATION

- Transition phasing
- Communication plan
- Tendering and procurement of new regimens


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SERVICE DELIVERY SUPPORT

- Demand generation
- Mentorship and supervision

TRANSITION MONITORING AND VISIBILITY

- Patient monitoring
- Pharmacovigilance
- Stock monitoring

ADVOCACY, POLICY, AND FINANCE

Drug Registration:

ARV products must be registered by a country's national drug regulatory authority (NDRA) before they may be imported and used. Because NDRA approval processes can be lengthy (lasting up to three years in South Africa, for example) and unpredictable (with reviewers making ad hoc information requests during the review process), several LMICs rely heavily on drug import waivers to expedite the introduction of ARV products. While waiver protocols vary from country to country, they generally permit the import of drugs of high public health importance on the condition that drug suppliers initiate standard NDRA registration within a specified time frame (for example, within six months of waiver issuance in Mozambique).

Early adoption of new ARV drugs by the private health sector can facilitate public sector introduction. For example, early registration of DTG singles by private sector suppliers in Kenya helped pave the way for subsequent registrations of bio-equivalent products by public sector suppliers.

Though infrequently used, another alternative to standard NDRA registration of ARV drugs is the WHO Collaborative Registration Procedure (CRP), which allows NDRAs in participating countries to securely review WHO technical evaluation files for WHO-prequalified (PQ) medicines in order to make their own determination. Though the CRP reduces the NDRA review time to 90 days, and an additional 30 days are allotted for NDRAs to notify the WHO of their decision. As of September 2017, 19 of 30 countries participating in the CRP have used the process to register at least one ARV product.[10] However it is important to note that the list of WHO PQ medicines is not exhaustive and may not contain all ARVs of interest.

Revision of national guidelines:

Most LMICs require that ARV products be included in the national treatment guidelines before they are imported and used. Revisions to the national treatment guidelines are usually prompted by the issuance of new WHO treatment guidelines, the release of clinical trial data, or a combination of the two. The process of revising national treatment guidelines generally involves multiple iterations of intensive stakeholder consultation and review, and can take from six months (Zimbabwe) to a year (Mozambique) to complete. While it is uncommon to see ARV products introduced to patients before they are included in the national guidelines, there is at least one country where such a precedent exists: in Ethiopia, a directive from the MoH to regional health bureaus is sufficient to initiate a change in ARV prescribing practices.

HIGHLIGHTS

01 — Waivers, private sector adoption of new ARVs, and the WHO CRP can expedite the introduction of new ARV products

02 — ARVs typically need to be included in national guidelines prior to being introduced into the program. However, national guideline revision can be a lengthy process that can take up to a year to a year or longer to be finalized.

OPERATIONAL PLANNING AND PREPARATION

Transition phasing:

Past first-line transitions can be grouped into two broad categories: "phase-out" transitions — wherein an existing drug or regimen (e.g. d4T) is fully supplanted by one or more new regimens — and "phase-in" transitions, wherein a new drug or regimen (e.g. TLE) is introduced for some patients, while other patients remain on an existing regimen (e.g. AZT+3TC+NVP). Both phase-in and phase-out transitions generally require some level of staggered implementation, whether by geography or sub-population, to maintain supply security and avoid wastage of existing stock. Historically, phasing of first-line transitions has varied based on the impetus for transition, national care and treatment priorities, and logistical considerations.

When the Democratic Republic of Congo (DRC) introduced TDF into first-line therapy in 2013, pregnant and breastfeeding women initiating Option B+ were the first to receive the regimen, after which it was gradually extended to other ART patients. In Tanzania, TLE was first introduced for ART-naïve pregnant women and anemic clients, and then expanded to anemic patients on AZT-based regimens, but was not explicitly prioritized for national scale-up. Kenya implemented a phase-in of TLE as the preferred regimen following the release of the 2013 WHO guidelines, though many patients who started AZT-based regimens prior to 2014 remain on their original regimen. Swaziland coordinated an incremental phase-out of d4T to allow for utilization of existing d4T stocks (children were discontinued first). During its phase-out of d4T, Ethiopia transitioned adults before children and utilized geographic staggering, starting in six regions before expanding to all eleven.

Communication plan:

In some cases, informing decentralized managers and healthcare workers about transitions has been a "light touch" affair, with basic parameters (e.g. eligibility criteria) communicated via an MOH circular. In other cases, communications efforts have been more robust, involving conveyance of targets to stakeholders at sub-national levels and/or issuance of a written plan and tools to guide implementation. The "light touch" approach to communicating expectations tends to allow stock quantities to dictate the pace at which patients are transitioned, whereas issuance of sub-national and facility targets seeks to align healthcare workers' actions with the plan in a more proactive manner.

HIGHLIGHTS

01 — Both phase-in and phase-out transitions require a graduated process based on country context.

02 — Stakeholders should agree on step-wise plans for phasing in/out of drugs, including supply chain considerations and clinical eligibility considerations prior to rolling out new ARVs.

Country Spotlight:

DRC

In 2013, in addition to recommending TLE as the preferred adult first-line ART regimen, the WHO introduced Option B+, lifelong treatment for all HIV-positive pregnant and breastfeeding women. Option B+ was rapidly adopted by multiple countries in sub-Saharan Africa, including DRC. DRC linked the introduction of TLE to the rollout of Option B+ by initially limiting TLE use to newly diagnosed pregnant and breastfeeding women, starting in select provinces and gradually scaling up nationwide by 2015. Rollout of TLE to the general adult population was not planned until 2016, when the MOH estimated that stocks of the previously preferred regimen of Zidovudine/Lamvudine/Nevirapine (ZLN) would be exhausted.

The rollout of Option B+ occurred rapidly, in keeping with the national program's accelerated scale-up of prevention of mother-to-child transmission (PMTCT). However, there was confusion about the distinction between Option B+ as a PMTCT intervention and TLE as a new ART regimen. In some facilities, healthcare workers began transitioning all women to TLE thinking that TLE was synonymous with Option B+ even though the transition to TLE was intended as a separate, more gradual process. Healthcare workers also began initiating or switching non-pregnant patients to TLE due to a perception that ZLN was toxic and should no longer be used. This further complicated supply management and caused multiple stockouts of TLE as well as significant wastage of ZLN stocks.

DRC linked the introduction of TLE to the rollout of Option B+ by initially limiting TLE use to newly diagnosed pregnant and breastfeeding women, starting in select provinces and gradually scaling up nationwide by 2015.

Ultimately, the MOH issued an additional circular to correct the perception about ZLN toxicity and clarify the distinction between Option B+ and TLE. In March 2016, the MOH issued further guidance to transition all patients to TLE; however, by the time this directive was issued, 95 percent of PEFPAR-supported sites and 70 percent of Global Fund-supported sites were already using TDF-containing regimens.[11]

In DRC, concurrent implementation of multiple new recommendations was logical, but lack of coordination and agreement across partners regarding the phasing and pacing of changes led to local supply interruptions. This outcome may have been mitigated by clearer communications and anticipation of the enthusiastic demand for new and better treatment options.

Tendering and procurement of new regimens:

Strategic alignment of tendering and procurement actions with transition targets is an indispensable element of sound transition planning. Several countries have found that, in the absence of a target-driven procurement plan adequate to support the desired pace of transition, slower-than-anticipated uptake of new drugs can cause major lags in transition. Kenya's phase-in of TLE, discussed in more detail in the Country Spotlight on page 15, is one example of this.

Another factor that favors timely introduction of new ARV products is efficient tendering and procurement processes that minimize required lead-time for drug orders. Countries that lack access to or opt out of pooled tendering and procurement arrangements such as those supported by PEPFAR and the Global Fund may face barriers with respect to timely introduction of new first-line regimens. South Africa, which funds the purchase of public sector ARVs entirely with government resources, issues multiyear supply and delivery tenders for ARVs in order to secure large volume discounts from multiple suppliers. Because it cannot substantially alter the terms of the resulting multiyear ARV supply agreements, South Africa is limited in procuring new ARV products that enter the market after the agreements are in effect.[12] In addition, past experience in countries with smaller ARV markets has shown that unilateral procurements are more prone to above-market pricing and late delivery from suppliers.

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Country Spotlight:

ETHIOPIA

Following the release of the 2010 WHO Guidelines, Ethiopia's MOH issued a circular to begin the phase-out of d4T by limiting the number of new patients initiated on d4T, while maintaining existing patients on d4T if they were not experiencing toxicity. The complete phase-out of d4T started in September 2012 in a few regions, and quickly expanded nationwide.

The MOH utilized consumption data from an extensive pharmaceutical management information system to inform the pace of d4T phase-out, and facilities prepared bimonthly regimen reports that helped the MOH identify noncompliance and conduct data driven forecasting and quantification. A study carried out from 2012 to 2014 documented a dramatic decrease in use of d4T-containing regimens in the first year of transition. By September 2013, 98 percent of patients had been effectively transitioned to AZT- or TDF-containing regimens (Fig 5).[13]

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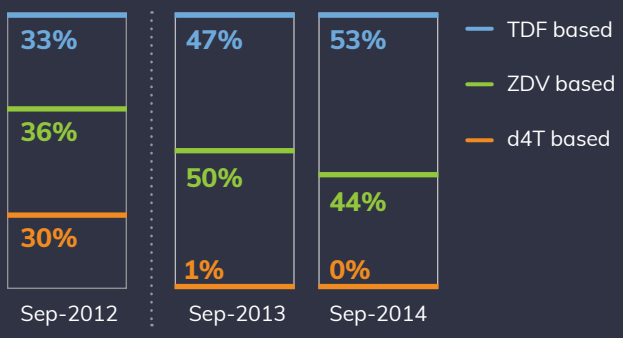
While the complete phase-out of d4T was accomplished rapidly and hailed as a success, the transition of patients to TLE was less efficient. Despite the 2013 WHO recommendation that countries use a once-daily FDC of TLE, MOH guidance on replacement regimens for d4T was non-specific. Fluctuation in prescribing patterns of AZT and TDF, owing in part to fluctuations in local stock availability, was a source of confusion for healthcare workers and patients alike.

At the end of 2016, only 55 percent of patients were on TLE, while 23 percent remained on ZLN. Another 21 percent of patients are taking multiple-tablet regimens with mismatched dosing schedules, such as AZT/3TC twice-daily with EFV once-daily. These patients have not yet experienced the benefits of moving to a simpler, once-daily regimen.

While the carefully monitored phase-out of d4T in Ethiopia was achieved rapidly due to a phased approach and close consumption monitoring at the national level, the transition to TLE was delayed and might have been simplified and expedited through selection of a single replacement regimen and issuance of clear guidance to program managers and healthcare workers.

Figure 5: ARV prescription pattern in Ethiopia, Sept 2012 - Sept 2014



SERVICE DELIVERY SUPPORT

Demand generation:

Targeted demand generation strategies encourage good uptake and adherence during first-line transitions. In some past transitions, clear and accurate information about new ARV regimens and the reasons for their introduction has been proactively communicated to patients only after a pattern of patient apprehension and false rumors emerged, posing a threat to uptake, adherence and retention. During Mozambique's first-line transition to TLE, there were reports that some patients mistakenly took two TLE pills a day (twice the prescribed dose), resulting in increased side effects and demands to return to their previous regimen. This highlights the importance of ensuring that patients — as well as all friends, family and peers involved in their care — receive clear and consistent messages about regimen changes, including changes to dosing schedule or administration requirements.

Demand generation messages are most effective when delivered through multiple channels, both before and during the introduction of new regimens. In countries with powerful civil society networks and people living with HIV advocacy networks, like South Africa, Kenya, and Zambia, network-based sensitization (through meetings, social media campaigns and trainings) has proven highly effective at building demand for new ARV products. In Mozambique, a series of community radio and national television spots — though launched too late — helped to alleviate patient concerns about safety and side effects of TLE. Across multiple countries, clear and consistent interpersonal messages from healthcare providers, pharmacists, and peers have been critical to building patient confidence in new regimens.[14]

HIGHLIGHTS

01 — On-the-job support including mentoring and SMS reminders are successful supplements to training workshops during ARV transitions

02 — Clear and consistent messaging about new regimens across multiple channels is essential to avoid confusion when introducing new ARVs

Country Spotlight:

KENYA

Kenya initiated the phase-out of d4T in 2009, instructing providers to transition patients to AZT- or TDF-containing regimens. By 2010, the proportion of patients on regimens containing d4T, TDF and AZT were 63 percent, 29 percent and 8 percent respectively, and a procurement plan was developed to support a complete phase-out of d4T over a two-year period.[15] Healthcare workers were instructed to substitute TDF for d4T as a single-drug substitution, and a number of patients were transitioned to a two-tablet regimen of TDF/3TC + NVP.

Three years later, in 2013, the progress of the d4T phase-out lagged behind expectations, with only 41 percent of patients transitioned to TDF or AZT[16]. Two explanatory factors were identified: 1) the concurrent but slow introduction of viral load monitoring and accompanying confusion among providers about the need for viral load testing prior to ARV substitution, and 2) lack of clarity among pharmacy managers about how to handle existing stocks of d4T as the drug was phased out. In order to avoid wastage of d4T, pharmacists continued to dispense d4T to patients, and because central procurement was linked to consumption data without a view to the broader transition goals, orders continued to be placed for d4T. Once this issue was identified, a decision was made to cease further procurement of d4T at the national level, and to limit distribution of remaining d4T stocks to facilities that expressed a direct need.

By 2010, the proportion of patients on regimens containing d4T, TDF, and AZT were 63 percent, 29 percent, and 8 percent respectively, and a procurement plan was developed to support a complete phase-out of d4T over a two-year period.

As of July 2016, Kenya had almost one million patients on treatment, and while all new patients are now being initiated on TLE, a significant proportion of experienced patients remained on AZT and/or NVP-containing regimens[17]. Though many patients remain on AZT/3TC/NVP administered as a twice-daily FDC, a significant number are still prescribed multiple-tablet regimens such as AZT/3TC + EFV and TDF/3TC + NVP. This is due in part to procedures that quantify individual drugs instead of complete regimens.

In Kenya, better alignment of central procurement plans with transition targets may have expedited the phase-out of d4T. As Kenya moves toward the phase-in of DTG, anticipated to debut as a triple FDC in combination with TDF and 3TC in early 2018, it may have an opportunity to transition patients on different regimens to a single universal regimen to streamline supply chain management and simplify guidance for healthcare workers.

Mentorship and Supervision:

The actions and practices of healthcare workers — who interface directly with patients and ARV drugs — heavily influence transition outcomes. Empowering them with appropriate guidance, tools and feedback is a top priority. Past country approaches to preparing healthcare workers for transitions vary widely from minimal intervention (in the case of Ethiopia) to large-scale training efforts (in Mozambique). Multiple countries have found that on-the-job support – in the form of enhanced mentorship, supplemental chart reviews or periodic SMS reminders (see Country Spotlight: Mozambique, page 16) – is more effective than traditional training where ARV transitions are concerned.

One key "learning" that emerged from multiple country transitions was the importance of preparing healthcare workers to manage ARV transitions in tandem with other major changes to service delivery models and standards of care. Because the issuance of WHO recommendations is the single most important factor in countries' decision to adopt new ARV regimens, and because the content of WHO recommendations extends to all aspects of patient care, countries often find themselves in the position of implementing multiple guideline changes at the same time. However, past ARV transitions have frequently been planned and managed in isolation, meaning that healthcare workers have not received clear guidance and mentorship on how initiatives like routine viral load monitoring or Test and Start interface with changes to ARV regimens. The Country Spotlight: DRC feature discusses one instance of this phenomenon.

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Country Spotlight:

MOZAMBIQUE

Mozambique first introduced TDF-containing regimens for first-line ART in May 2013, opting for a staggered approach to phase out AZT and scale up TLE over a three-year period. While no formal transition plan was communicated to facilities, provincial managers received periodic instructions on which patient populations were eligible for transition, starting with new patients or those recently initiated on ART at select health facilities. However, the MOH was forced to abandon its incremental phase-in due to a global shortage of AZT, caused by a disruption to the manufacture of its active pharmaceutical ingredient (API). In 2014, the MOH issued revised guidance to transition patients far more rapidly than originally planned, and in a nine-month period the percentage of first-line patients receiving TLE increased from 16 percent to 68 percent.

While the underlying cause of the API shortage was the shutdown of a major API production facility in Beijing, officially attributed to government anti-smog measures, several stakeholders in Mozambique held a concern that the issuance of new WHO guidelines recommending TLE as the preferred first-line regimen may have encouraged manufacturers to switch their production lines from AZT to TLE. Mozambique's supply woes were compounded by shortages of TLE that occurred during the same period, caused by rapid global uptake outstripping supply. Stockouts were frequent and created uncertainty among patients, healthcare workers, implementing partners, and the MOH about the national program's ability to manage future ARV transitions.

Other factors also contributed to Mozambique's rocky transition to TLE. It was reported that not all healthcare workers were adequately trained at the time of the transition, and that patients did not receive adequate information or counseling. High rates of treatment interruption ensued, and there were anecdotal reports of patients mistakenly taking their new TLE regimen twice daily, resulting in increased side effects and TDF-related toxicity. Rumors about a link between TDF and miscarriage also led to reports of women refusing TLE.

A series of community radio and national television spots eventually helped to alleviate patient concerns about safety and side effects of TLE. The MOH also deployed its Linha Verde – a web-based system that broadcasts SMS messages to active healthcare workers throughout the country – to issue periodic reminders to healthcare workers during the transition period.[18]

Mozambique's challenges in transitioning to TLE illustrate why the global community must take a coordinated, considered approach when recommending large-scale changes to ART programs. Global manufacturing capacity, in particular, should be examined and quantified. As national programs often have limited visibility and insight into global manufacturing constraints, improved systems for clearly communicating such challenges in a timely manner may provide programs with additional time to modify transition plans according to supply security.

At the country level, it is essential that clear, concrete information on prescribing guidance and transition rationale reach healthcare workers and patients alike. Misperceptions about new drugs need to be addressed quickly to mitigate suspicion or alarm. The effective use of the media allowed Mozambique to rapidly disseminate corrective information across the country; however, programs should develop messaging that anticipates questions and concerns and addresses these through preemptive communication.

TRANSITION MONITORING AND VISIBILITY

Patient monitoring:

Patient monitoring is crucial before and during transitions. Most country protocols specify that patients should be virally suppressed before transitioning to a new first-line regimen; patients who are not virally suppressed should receive enhanced adherence counseling and subsequent re-evaluation to determine whether they can transition or should instead be switched to second-line therapy. Where viral load testing is not available, CD4 count and clinical/immunological criteria may be used to make this determination. In some past transitions (including transition to TLE in Swaziland and Mozambique), compliance with this guidance was inconsistent and patients were transitioned without evidence of viral suppression, leading to concerns about development of multidrug-resistance. Once a patient has switched, close clinical and laboratory monitoring may be needed to ensure timely detection, reporting and resolution of adverse events (AEs) or other treatment complications.

While healthcare worker training is typically viewed as an essential component of transitions, many countries have found that on-the-job mentoring, supplemental chart reviews, user-friendly job aids and periodic SMS reminders (for example, those disseminated through the Linha Verde in Mozambique) are more effective at supporting good practices such as appropriate patient monitoring than standalone training.

Pharmacovigilance:

In the context of introducing newly available ARVs, it is critical to strengthen pharmacovigilance systems to track drug-related AEs in local populations under conditions of real world use. Many countries have existing pharmacovigilance systems, such as Kenya's Pharmacy and Poisons Board (PPB) that encourage spontaneous submission of either paper-based or electronic reports on drug-related AE's. However these systems may not be well utilized or integrated into the national ART program. Countries may consider strengthening these existing systems and integrating pharmacovigilance into transition activities to support enhanced monitoring of new ARVs. This should include ensuring healthcare workers are sensitized to the importance of reporting AEs and oriented to the process for submitting reports on AEs. At the program level, countries may also consider introducing a national ARV toxicity indicator to monitor the prevalence of treatment-limiting AEs.[19]

Stock monitoring:

Intensified monitoring of ARV stocks during transitions can facilitate a steady supply of drugs and minimize waste due to drug expiries. In some past transitions, MOHs have neglected to issue clear and comprehensive guidance to stock managers and providers regarding the phase-out of existing products in favor of new products. During the phase-out of d4T in Kenya, some stock managers assumed they should exhaust all existing stocks of d4T before transitioning patients, effectively delaying transition. In other cases, repeated supply interruptions during transitions (in DRC, Ethiopia, Mozambique, and other countries) have forced patients to vacillate between old and new regimens or make repeated trips to the pharmacy to fill their prescriptions completely. To avoid these and other challenges in future transitions, countries should ensure that all healthcare workers involved in storing, prescribing and dispensing ARVs are equipped with clear operational guidance and tools for intensified stock management, and that there is an effective mechanism in place to respond to stockouts.

HIGHLIGHTS

01 — Enhanced monitoring of patients is needed to ensure timely detection of adverse events and develop appropriate mitigation strategies

02 — Healthcare workers and pharmacy managers should be provided with clear operational guidance and tools to avoid supply chain challenges such as stockouts, shortages, or wastage of older ARVs

RECOMMENDATIONS AND CONCLUSION

1 ADOPTION AND COMMUNICATION OF REGIMEN SHIFTS

The process of updating guidelines, revising and printing training materials and rolling out countrywide training is a lengthy one, often resulting in significant delay between the issuance of new normative guidance and full implementation. In order to streamline this process when a new recommendation is introduced, programs may consider issuing a brief circular or "rapid advice document" highlighting critical recommendation changes in lieu of a full guideline revision process to save resources and expedite implementation.

At the facility and community level, healthcare workers and patients often have limited understanding of the supply chain implications of prescribing practices. Both healthcare worker training and community advocacy efforts would benefit from supplementation with additional information on the specifics of the national transition plan to avoid wastage of existing resources and mitigate the risk of stockouts. In addition, partner organizations must also be informed of national plans to ensure patients are transitioned at the appropriate pace and the transition is coordinated across the health system's functional areas (e.g. procurement planning, stock management, pharmacovigilance).

2 PHASED TRANSITION PLANNING

In general, new drug or regimen introductions generally require some level of phased implementation, whether by geography or subpopulation. In 2017, the WHO recently published a technical update and policy brief to provide guidance on transition to new antiretroviral drugs in HIV programs[20,21] though they stress the need to consider clinical, operational and programmatic factors. A one-size-fits-all approach to transition planning and preparation may not be feasible or desirable, given that health system capacity to adopt and absorb new ARV products and patient monitoring practices differs greatly across programs, and not all regimen changes involve the same degree of change to clinical and stock management practices. Regardless of these variables, country programs should strive for an integrated transition plan accompanied by monitoring tools to facilitate tracking of transition progress and outcomes by key clinical, pharmacy, laboratory, logistics and civil society stakeholders.

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3 QUANTIFICATION AND SUPPLY SECURITY

Intensified monitoring of ARV stocks during transitions can facilitate a steady supply of drugs and minimize waste due to drug expiries. Consumption data should not be relied upon for accurate forecasting during phase-in periods. However, accurate and detailed information about the distribution of patient populations is often lacking, thereby also limiting the utility of morbidity-based forecasting methods. Additionally, in some past transitions lack of clear and comprehensive guidance to both stock managers and providers regarding the phase-out of existing products in favor of new products resulted in additional challenges. To avoid supply chain challenges in future transitions, countries should ensure that all healthcare workers involved in storing, prescribing and dispensing ARVs are equipped with clear operational guidance and tools for intensified reporting of stock levels and that there is an effective mechanism in place to respond to facility-level stockouts.

4 DEMAND GENERATION MANAGEMENT

Targeted communication and demand generation strategies can promote strong uptake and adherence. Clear and accurate information about new ARV regimens and the reasons for their introduction should be proactively communicated to patients before and during transitions. Conversely, demand generation activities should incorporate the learning that gradual phase-in approaches have resulted in overprescribing by healthcare workers who did not appreciate the aggregate impact of their individual prescribing practices on national supply plans. Clear communication and rationale for phased approaches in conjunction with community engagement during the planning process can mitigate threats to a smooth transition to new optimized regimens.

5 FACILITY-LEVEL CAPACITY

Empowering healthcare workers with appropriate guidance, tools, and feedback should be a top priority. Decision-making protocols and user-friendly algorithms should be easy to use and, given the heavy workloads found in many ART clinics, should allow for rapid identification of patients that should be transitioned to a new regimen. Low-cost, highly scalable technologies like Mozambique's SMS-based Linha Verde are a valuable resource for communicating helpful clinical reminders to healthcare workers in a timely manner.

Transition protocols should also consider the realities of available clinical resources. For example, some would recommend confirmation of viral suppression before substitution of a new drug, particularly when the drug is of a new class or has a different resistance profile to their current regimen (e.g. TDF and AZT).[22] At the program level, requiring viral load testing prior to regimen change should be carefully assessed with a view to its impact on uptake before concrete guidance is issued.

Significant resources are now being put towards the accelerated uptake of new optimal regimens with concurrent phase-out of older, less efficacious options in the expectation that this will enable programs to achieve 90-90-90 targets. However, this goal will not be fully realized without considerable attention to challenges at the implementation level as previous large-scale ART transitions have demonstrated. Programs may be hesitant to report implementation challenges, particularly for drug expiries as these may be construed as poor utilization of resources. These largely undocumented events preclude in-depth understanding for large-scale program transitions. However, greater insight into implementation challenges will create a more effective feedback loop whereby ARV supply can be better matched with program-level demand while avoiding disruptions to patient care and treatment.

ENDNOTES

1. 90 percent of people living with HIV know their status; 90 percent of diagnosed people living with HIV are on antiretroviral treatment GI (ART); 90 percent of ART patients are virally suppressed.

2. Ripin D, Prabhu V, A cost-savings analysis of a candidate universal antiretroviral regimen. Curr Opin HIV AIDS. 2017, 12:403-407.

3. WHO Technical Update on Treatment Optimization. Pharmacological Equivalence and Clinical Interchangeability of Lamivudine and Emtricitabine: A Review of Current Literature http://apps.who.int/iris/bitstream/10665/70936/1/9789241503815_eng.pdf, Accessed July 7, 2017

4. WHO Global ARV and Diagnostic Use Survey in 2016 in Low and Middle-Income countries, presented at Joint WHO/UNAIDS Annual Consultation with Pharmaceutical Companies, Partner Organizations and Stakeholders. March 28-29, 2017, Geneva Switzerland

5. Malati C, Rosenfeld J, Mowafy S et al. Dealing with large-scale supply lines when introducing new regimens. Curr Opin HIV AIDS. 2017, 12; 408-413

6. World Health Organization. Transition to New HIV Treatment Regimens- Procurement and Supply Chain Management Issues, March 2014. http://apps.who.int/iris/bitstream/10665/85514/1/WHO_HIV_2013.10_eng.pdf?ua=1. Accessed May 5, 2017

7. Amole C, Middlecote C, Prabhu V et al. Can the generic antiretroviral industry support access to a universal antiretroviral regimen? Curr Opin HIV AIDS. 2017, 12; 390-397

8. WHO Global ARVs and Diagnostic Use Survey in 2016 in Low and Middle-Income Countries, December 2016

9. MSF Access Campaign. Untangling the Web of Antiretroviral Price Reductions 18th ed. July 2016. http://msfaccess.org/sites/default/files/HIV_report_Untangling-the-web-18thed_ENG.pdf, accessed July 6, 2017

10. WHO Extranet: Accelerated Registration of Prequalified FPPs. Accessed October 17, 2017: https://extranet.who.int/prequal/content/collaborative-registration-faster-registration

11. https://www.pepfar.gov/documents/organization/257652.pdf Accessed June 28, 2017

12. The Government of South Africa is currently extending its 2015-2017 tender in hopes that a TLD FDC will be available from at least two suppliers in time to include it in the upcoming tender.

13. USAID, SIAPS. Phasing Out Stavudine-Containing Regimens in the Ethiopian ART Program: the Role of Pharmaceutical Information for Decision Making. http://apps.who.int/medicinedocs/documents/s22434en/s22434en.pdf . Accessed July 2, 2017

14. In Mozambican facilities where pregnant women had taken TLE under an Option B+ pilot and had communicated their positive experiences to friends and family members, patients began requesting TLE even before the national transition was underway.

15. Ministry of Medical Services (MoMS) & Ministry of Public Health and Sanitation (MoPHS)/National AIDS & STI Control Program (NASCOP), Kenya. National Forecasting and Quantification for HIV & AIDS Commodities for the Years 2010/11 & 2011/12. June 2010.

16. Ministry of Health/ National AIDS & STI Control Program (NASCOP), Kenya. National Forecasting and Quantification report for HIV & AIDS Commodities for FY 2013/14 & 2014/15. September 2013.

17. National AIDS & STI Control Program, Ministry of Health Kenya. National Quantification report for HIV management commodities for FY 2016/17 to 2019/20 September 2016

18. http://www.linhaverdemisau.co.mz

19. World Health Organization. Consolidated guidelines on person-centred HIV patient monitoring and case surveillance. June 2017. http://www.int/hiv/pub/guidelines/person-centred-hiv-monitoring-guidelines/en/ Accessed December 19, 2017.

20. World Health Organization. Transition to New Antiretroviral Drugs in HIV Programmes: Clinical and Programmatic Considerations. July 2017. http://apps.who.int/iris/bitstream/10665/255887/1/WHO-HIV-2017.23-eng.pdf?ua=1 Accessed September 27, 2017.

21. World Health Organization. Access technical update: transition to new antiretroviral in HIV programmes. July 2017 http://www.who.int/hiv/pub/toolkits/transition-to-new-arv-technical-update/en/ Accessed September 27, 2017.

22. Van de Broucke S et al. Scaling up of triggered viral load in rural Zimbabwe: implications for phasing out of D4T. IAC Washington 2012. http://aids2012.msf.org/wp-content/uploads/2012/06/Scaling-up-of-Triggered-Viral-Load-in-Rural-Zimbabwe-Poster.pdf. Accessed July 6, 2017.

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