

Accelerating Access to Simpler, Safer, and More Affordable HIV Treatment Through ART Optimization

What is antiretroviral treatment (ART) optimization?

At its core, ART optimization is about ensuring that people living with HIV receive the best-available ART in the most efficient and cost-effective manner possible. In low- and middle-income countries (LMIC) – where the HIV-positive population includes significant proportions of women of childbearing age, children, and people living with TB, malaria, and other co-infections – optimization requires drugs that are: (1) effective, safe, well-tolerated, and easy to use for people in these demographic groups and (2) adapted to resource and infrastructure constraints (i.e. affordable, heat-stable, and available in fixed-dose combinations, or FDCs). Optimization is achieved by continuous and coordinated efforts by global and country-level stakeholders to simplify, standardize, and harmonize all categories of antiretroviral (ARV) drugs, including first-, second-, and third-line treatments for infants, children, adolescents, and adults (including pregnant and breastfeeding women, and TB patients).

WHY IS OPTIMIZATION IMPORTANT?

Optimization maximizes the positive health impact of HIV care and treatment services in two key ways:

- 1 ART optimization facilitates improved adherence and retention and lowers the risk of treatment failure by raising ARV drugs' genetic barrier to resistance and enabling patients to stay on more tolerable and affordable first-line regimens longer. This leads to better treatment outcomes and decreases per-patient expenditure by reducing the need for more expensive and harder-to-tolerate second- and third-line ARV drugs.
- 2 By reducing the cost of ARV drugs to patients, insurers, and governments, ART optimization allows countries to extend lifesaving treatment to a greater number of people living with HIV, even with fixed or declining expenditure levels.



It is especially important NOW because...

As momentum towards the UNAIDS 90-90-90 targets and implementation of the World Health Organization (WHO) Treat All recommendation grows, global ARV drug spending is expected to double to \$3.8 billion by 2020.¹ Even as ARV drug expenditures mount, donor funding for ART is leveling off, and growth in funding from most low- and middle-income country (LMIC) governments is insufficient to fill the gap. In this context, it is more important than ever for governments to reduce the cost of procuring and delivering ART. For many countries, optimization represents the best – if not the only – pathway for achieving ambitious 90-90-90 targets and delivering lifesaving ART to all who need it.

**AS MOMENTUM GROWS,
GLOBAL ARV DRUG SPENDING
IS EXPECTED TO DOUBLE TO
\$3.8 BILLION BY 2020.**

How may optimized first-line ART regimens be introduced?

The sequence in which optimized first-line ART regimens are expected to make their LMIC market debuts is dependent on regulatory approvals and study data (see *Anticipated Evolution of First-Line ART in LMIC, 2017-2020* for an estimated timeline for product introduction). Countries may opt to “leapfrog” one or more of these regimens, depending on the timing of country transition plans and procurement cycles.



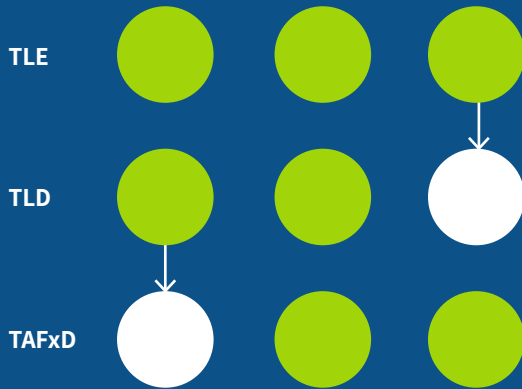
THE NEXT GENERATION OF ANTIRETROVIRAL REGIMENS: MORE EFFECTIVE, LESS TOXIC, AND EASIER TO TOLERATE

The table below profiles four optimized ART regimens (three FDCs and one co-formulation) that will be introduced to LMIC markets between now and 2020 and lists clinical trials currently underway in LMICs to evaluate the safety and efficacy of these products in priority populations including pregnant women and TB patients. The enhanced effectiveness and lower active pharmaceutical ingredient (API) concentrations offered by these regimens will allow patients to enjoy safer, more effective treatment with once-a-day dosing and, in some cases, smaller tablet sizes.

	TLD Tenofovir disoproxil fumarate (TDF)/ emtricitabine or lamivudine (XTC)/ dolutegravir (DTG)	TAFxD Tenofovir alafenamide fumarate (TAF) emtricitabine or lamivudine (XTC)/ dolutegravir (DTG)	Heat-stable DRV/r co-formulation Darunavir/ritonavir	TLE400 Tenofovir disoproxil fumarate (TDF)/ emtricitabine or lamivudine (XTC)/ efavirenz 400 (EFV400)
What does it replace?	TDF/XTC/Efavirenz (EFV), or TLE, the current WHO-preferred 1L regimen	TLE, the current WHO-preferred 1L regimen	Atazanavir/ritonavir (ATV/r), lopinavir/ ritonavir (LPV/r) in 2L regimens	TLE400 is an alternative regimen to TLE
New agent drug class	DTG is an integrase inhibitor	TAF is a nucleotide reverse transcriptase inhibitor	DRV/r is a boosted protease inhibitor	EFV ₄₀₀ is a non-nucleoside reverse transcriptase inhibitor
Dosage informationⁱ	DTG 50mg; no boosting is required	TAF 10mg with a boosting agent	800/100mg once daily or 600/100mg twice daily ⁱⁱⁱ	EFV 400mg
WHO recommended uses^{iv}	Adults, children 6+ years and >30kg (by FDA) ^v	TBD (pending clinical trial results)	Adults, pregnant women, children 3+ years	Adults, adolescents
What will it cost?	US\$78-84 ^{vi} per patient per year (pppy)	US\$73 ^{vii} pppy	US\$413 ^{viii} pppy	US\$99 ^{ix} pppy
Key benefits^x	Highly efficacious, well- tolerated, high barrier to resistance, fewer central nervous system (CNS) and rash events v. TLE	Benefits listed for TLD, plus less bone and kidney toxicity, smaller tablet sizes, and lower cost v. TLE	Once-daily dosing, higher tolerability, potency, and barrier to resistance, fewer side effects v. ATV/r, LPV/r	Fewer CNS, rash, gastrointestinal adverse events, lower cost v. TLE
Trials underway for additional sub-populations	DoIPHIN1: Safety in pregnant women in 3rd trimester. Results expected Q3/2017. ^{xi} DoIPHIN2: Efficacy in pregnant women in 3rd trimester. Results expected 2021. ^{xii} Viiiv: Safety and efficacy of DTG vs EFV in TB patients. Results expected Q4/2017. ^{xiii} ADVANCE: Safety and efficacy in adults and adolescents (including women who become pregnant), compared to TLE, TAFxD. Interim and final results expected Q4/2018 and Q3/2020 respectively. ^{xiv}	IMPACT P2010: Efficacy during pregnancy and up to 48 weeks post-partum, compared to TLE, TLD. ^{xv} Results expected Q3/2018. ^{xvi} ADVANCE: Safety, efficacy in adults and adolescent (including women who become pregnant), compared to TLE, TLD. Results expected Q4/2018. ^{xvii}	Wits RHI: Switch study of DRV/ r400/100mg v. LPV/r. Results expected Q1/2018. ^{xviii} SSAT: Efficacy of DRV/r 400/100 v. DRV/r 600/100 v. DRV/r 800/100. ^{xix} Not yet funded.	Mylan: TB and pregnancy PK study. Pregnancy results expected Q3/2017. TB results expected Q1/2018. ^{xx}

ANTICIPATED EVOLUTION OF FIRST-LINE ART IN LMIC

2017-2020*



If a country adopts all of these products, what health benefits can we expect to see?

Collectively, the benefits of adopting optimized ARV products include:

- Vastly reduced API concentrations, meaning smaller tablets and increased patient adherence^{xxii}
- Higher tolerability, lower toxicity, and fewer side effects, leading to improved adherence and decreased risk of treatment failure
- Earlier and more sustained viral suppression, leading to decreased HIV transmission to partners and infant
- Reduced drug resistance, leading to decreased treatment failure and regimen discontinuation

What are the financial implications of rapid adoption?

GLOBALLY, THE INTRODUCTION OF DTG, TAF, AND EFV400 TO THE LMIC MARKET IS EXPECTED TO YIELD SAVINGS OF UP TO \$3 BILLION BY 2025.^{xxii}

By 2021, countries adopting optimized first-line FDCs containing these drugs can expect to realize annual savings^{xxiii} of up to:

<p>\$22 for each patient transitioned from TLE to TLD</p>	<p>\$41 for each patient transitioned from TLE to TAFxD</p>	<p>\$4 million for every 100,000 patients transitioned (enough to provide ART to more than 50,000 additional people living with HIV^{xxiv})</p>
<p>\$8 for each patient transitioned from TLE to TLE₄₀₀</p>		

Including additional direct savings due to significant decrease in conversion to more expensive second- and third-line regimens.

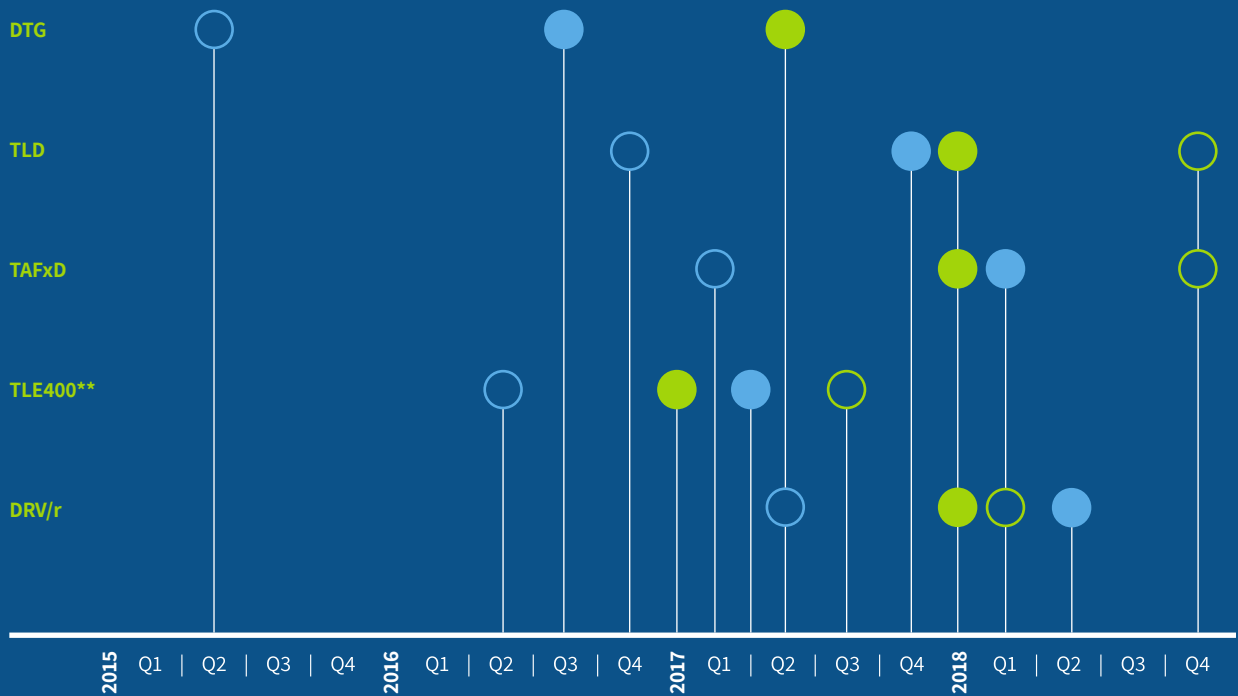
In addition, countries can expect to see indirect savings thanks to lower rates of treatment failure and the need for conversion to more expensive second- and third-line regimens. Both direct and indirect savings will continue to grow over the long-term as market competition intensifies and countries simplify, standardize, and harmonize their treatment protocols and ARV procurement practices.

When will these ARV drugs reach LMIC, and what can we do to get them here faster?

Generic DTG is already available as a single agent. If studies, filings, and approvals proceed as anticipated^{xxv}, TLE400 will be available from at least one generic manufacturer by late 2017, and generic forms of TLD, TAFx_D, and DRV/r will debut in 2018 (see *Introduction Timeline: Key Generic ARV Drugs* for additional details on timing).^{xxvi}

Ministries of Health and their partners can implement a number of preparatory measures to minimize the time between the arrival of these ARV products on the global market and their distribution to ART patients in country. Comprehensive planning with local and global stakeholders can help ensure an efficient transition at a country level. The *Transition Readiness Framework* on the following page outlines key activities that can be undertaken to expedite the introduction of any or all of these optimized ARV products.

INTRODUCTION TIMELINE: KEY GENERIC ARV DRUGS*



- Filled with at least one Stringent Regulatory Authority (SRA)
- Approved by WHO or Food & Drug Administration (FDA)
- LMIC trial data available
- Available from at least one generic supplier

*Timeline is based on best-available information as of March 2017 and may shift. ** LMIC trial data available Q3 2017 for pregnancy, and Q1 2018 for TB.

TRANSITION READINESS FRAMEWORK

1 Enabling environment

- Define and promote public health value proposition
 - Advocate for optimized products (via Technical Working Groups (TWG), stakeholder meetings, and civil society networks)
- Map and/or simplify drug registration procedures
 - Initiate early registration of optimized products (including through WHO Collaborative Registration Process)
- Conduct guidelines analysis and assess budget requirements/impact
 - Revise national treatment guidelines

3 Transition monitoring and visibility

- Conduct intensified patient monitoring and analysis, including cohort analysis
- Conduct intensified stock monitoring
- Increase stock visibility through “stop stockout” campaigns, publications, and web-based tracking tools
- Conduct routine tracking of transition progress against established targets
- Implement QA/QI activities focusing on regimen optimization, viral load suppression, and ARV drug resistance

2 Planning and preparation

- Develop national forecasts incorporating optimized products
- Develop phased implementation plan, including demand generation, communication, and monitoring and evaluation (M&E) plans:
 - Generate demand for optimized products among patients and providers
 - Communicate transition plan, roles, and responsibilities to stakeholders
 - Set national, sub-national, and facility targets & strengthen capacity for transition M&E
- Revise tools and standard operating procedures (SOPs) for training and mentoring clinicians

4 Service delivery support

- Adapt service delivery models to promote differentiated care, linkage, retention, and adherence
 - Institute advanced prescribing practices and differentiated care services for sub-population
 - Integrate new treatment algorithms and treatment preparedness counseling into community ART
- Train and mentor clinicians in SOPs for patient management, regimen tracking, and stock monitoring
- Increase demand among patients through community health days and community meetings

What can we do to ensure the best possible outcomes for patients as we phase in optimized ARV products?

Enhanced monitoring and evaluation of patient outcomes in the early stages of new product introduction is critical. Countries seeking to adopt and introduce optimized regimens should consider designing targeted evaluations, for instance at a subset of health facilities or among a specific population such as pregnant women, as part of the planning and preparation for the introduction of new ARVs. Establishing a feedback mechanism to regularly communicate qualitative and quantitative data

gathered through early evaluations to decision-makers facilitates the inclusion of real-time implementation data in introduction planning, enables the swift identification of programmatic inefficiencies, and ensures vigorous monitoring of patient outcomes during the transition to new ARV regimens. In addition, enhanced monitoring and evaluation enables the compilation of real-world evidence to inform national scale-up and generate global best practices.

ENDNOTES

- i. ARV Market Report: The State of the ARV Market in LMICs, 2014-2020. Clinton Health Access Initiative (2015)
- ii. Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195>
- iii. Currently approved doses for individuals with no protease inhibitor resistance and protease inhibitor resistance, respectively. Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195>
- iv. Ibid.
- v. DTG is expected to be recommended for use in all children in the next several years.
- vi. Medicines Patent Pool (MPP) estimates for 2-3 years post-introduction, based on assumption of moderate API cost reduction
- vii. Ibid.
- viii. Ibid. Lowest theoretical price; actual price may be higher.
- ix. Mylan World AIDS Day press release, December 1, 2015. Available: <http://newsroom.mylan.com/2015-12-01-On-World-AIDS-Day-Mylan-Announces-Plans-to-be-the-First-to-Market-Newly-Recommended-Antiretroviral-Treatment-for-99-Per-Patient-Per-Year>
- x. Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195> and personal communication with Veronique Bortolotti.
- xi. Study completion date from Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195>
- xii. Personal communication with Polly Clayden.
- xiii. Estimated primary completion date: December 2017. NIH Clinical Trials website, updated October 2016. Available: <https://clinicaltrials.gov/ct2/show/study/NCT02178592>.
- xiv. Email communication with Francois Venter and Celia Serenata.
- xv. Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195>
- xvi. Personal communication with Polly Clayden.
- xvii. Email communication with Francois Venter.
- xviii. Email communication with Francois Venter.
- xix. Fit for Purpose: antiretroviral treatment optimization (2016). i-Base. Available: <http://i-base.info/htb/30195>
- xx. Email communication with Kellen Thomas, Mylan.
- xxi. Size, Shape and Other Physical Attributes of Generic Tablets and Capsules: Guidance for Industry. FDA, June 2015. Available: www.fda.gov/.../drugs/guidancecomplianceregulatoryinformation/.../ucm377938.pdf
- xxii. Prabhu, Vineet R et al. "New ARVs Could Represent Over USD 3 Billion in Cost Savings Through 2025." CHAI. Abstract for CROI 2016. Available: <http://www.croiconference.org/sessions/new-arvs-could-represent-over-usd-3-billion-cost-savings-through-2025>
- xxiii. Annual pppy savings estimates for TLD and TAFxT based on MPP estimates of FDC cost 2-3 years post-introduction (assuming moderate API cost reduction), and CHAI midpoint estimates for single-agent ARV savings at scale. Estimates for TLE400 savings provided by CHAI (the TLE400 pricing agreement stipulates pppy pricing of either \$99, or 6-8% below current TLE600 prices, whichever is lower).
- xxiv. Based on assumption that all new patients are initiated on TAFxT at a cost of \$73 pppy.
- xxv. Data on planned filing timelines were obtained from MPP (TAFxT, DRV/r) and Mylan (TLE400) in October 2016 and are subject to change. FDA approval timelines based on assumption of 12 months post-filing and are subject to change. LMIC trial data timelines were obtained from Wits RHI (TLD, TAFxT, DRV/r) and Mylan (TLE400) and are subject to change.
- xxvi. At least one supplier, Mylan, anticipates an earlier 2018 introduction date for TAFxT.



Powered by **OPTIMIZE**, a global partnership 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.



This publication was made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Agency for International Development (USAID) under the terms of cooperative agreement #AID-OAA-A-15-00069. The contents are the responsibility of ICAP and do not necessarily reflect the views of USAID or the United States Government.