PEPFAR ARV Formulation Prioritization March 2017; Latest Revision: November 2018

BACKGROUND

Since the inception of the President's Emergency Plan for AIDS Relief (PEPFAR), the United States Government (USG) has committed to purchasing safe, effective, quality-assured, and low-cost antiretrovirals (ARVs) consistent with applicable international trade law. These ARVs may be manufactured by brand (innovator) and generic (non-innovator) companies.[1]

To help meet this commitment, the U.S. Food and Drug Administration (USFDA) utilized existing review and inspection processes for reviewing new drug applications (NDA) and abbreviated new drug applications (ANDA) for PEPFAR use. NDAs are submitted for new versions (e.g., new fixed dose combinations or formulations) of approved drugs, and ANDAs are submitted for generic drugs. The regulatory pathways for these processes are the same as those for other drugs not procured by PEPFAR. However, the USFDA is able to waive fees for certain NDAs and prioritize review of ARVs that are most needed by PEPFAR. USFDA approval or tentative approval is a prerequisite for ARVs to be eligible for purchase by PEPFAR. Tentative approval means that the ARV meets all USFDA standards of approval for safety, efficacy, and quality; however, existing patents or market exclusivity prevent the ARV from being marketed in the United States.[i]

As of August 17, 2018, the USFDA has either approved or tentatively approved 208 applications (containing 250 ARV products) which include both ANDAs and NDAs for PEPFAR procurement. In addition, after receiving (tentative) approval, manufacturers have submitted modifications to their original applications requesting approval of new/additional manufacturing facilities, increasing the efficiency of the manufacturing processes at existing facilities, and/or extending the shelf life of certain products as well as other changes.

As of September 30, 2017, PEPFAR was supporting nearly 13.3 million people on ARV treatment for human immunodeficiency virus (HIV) infection – a remarkable increase from 1.45 million in 2007.[ii] Accessibility to low cost and effective ARVs has been essential to accomplish these high-impact, life-saving results. The proportion of generic drugs compared to branded drugs procured by PEPFAR increased from 16% to 98% from 2005 to 2017. During this same period, the annual per-patient cost of ARVs for first line treatment fell by more than 92%, from $1,100 to $75.[iii-iv]

As part of global efforts to optimize HIV treatment, PEPFAR actively monitors the research pipeline and identifies ideal characteristics of treatment formulations in a public health context. Currently, PEPFAR is partially reimbursing USFDA to review NDAs for ARVs. The USFDA reviews NDAs according to the Prescription Drug User Fee Act (PDUFA) and ANDAs according to the Generic Drug User Fee Amendments (GDUFA) in the order in which ANDAs are received.

Additionally, the GDUFA and GDUFA II, applies to all ANDAs (generic drug applications) submitted after October 1, 2012. Pursuant to GDUFA and GDUFA II, ANDA applicants are required to pay fees for the review of generic pharmaceuticals.

The PEPFAR ARV Formulation Prioritization Committee seeks to expedite access to new recommended ARV formulations. The Committee implements a systematic and proactive process for prioritizing formulations of ARVs for review by the USFDA, in order to ensure access to critical ARVs for PEPFAR-supported countries, including

(1) maintaining reliable access to currently recommended ARVs and
(2) expediting access to new, high-priority ARVs.

Because generic manufacturers require USFDA approval (ANDA) when there are production process changes (e.g., new facility) to existing products, including current first-line ARVs, these products appear on the prioritization list to highlight the importance of their timely review to minimize supply disruptions. For

anticipated new first-line ARVs, this process is of particular importance as additional safety and efficacy data become available and the Consolidated World Health Organization (WHO) Guidelines evolve. A number of new pharmaceuticals, new combinations of ARVs, new formulations could offer improvement over existing ARVs to meet the needs of patients in a clinical and public health context. As new medications with improved safety and efficacy profiles become available, it is imperative to recommend prioritization of these medications over previously recommended first- and second-line regimens. Ideally, manufacturers are submitting dossiers for formulations that will be used in the field; however, FDA cannot require submission of applications for specific products. In conclusion, this policy will serve as a tool to communicate with FDA and pharmaceutical industry.

RATIONALE

The work of this Committee reflects the collective expertise of all of USG implementing agencies across PEPFAR. It aims to communicate a unified message of PEPFAR's ARV priorities to external stakeholders. It is envisioned that this report would be used to communicate a message to assist pharmaceutical manufacturers to strategically target investments and scale-up capacity of formulations that will be in high demand in PEPFAR programs. Similarly, this report may be used, in conjunction with WHO normative guidelines, in countries during discussions to determine modifications of national HIV treatment guidelines.

COMMITTEE OBJECTIVES and RESPONSIBILITIES

The primary objectives of the Committee are:

1. To prepare a list of prioritized ARVs that are supported by current safety and efficacy data, informed by the HIV research pipeline, and aligned with PEPFAR clinical and public health needs for expedited review by the USFDA.
2. To communicate the prioritized ARV list to manufacturers of ARVs to help guide their research and development programs and submissions for USFDA review.

Functionally, on an annual basis (with interim updates as needed), this Committee will execute these responsibilities by reviewing and updating the prioritization list based on (1) latest list of USFDA approved or tentatively approved ARVs; (2) data on procurement prices, supply, and distribution of ARVs to understand gaps and constraints to market entry; and (3) the most recent WHO recommended regimens to optimize therapy.

METHODOLOGY and LISTS

The Committee[1] convenes to review the experience and impact of the existing version of the PEPFAR ARV Prioritization List and to update the list in light of the latest efficacy and safety data on ARVs, including published clinical trials, conference abstracts, journals, and scientific data from data safety monitoring boards. New information on regulatory procedures at the Drug Controller General of India is also considered. In addition, the Committee reviews the timing of regulatory approval of ARVs for scale up of first-, second-, or third-line treatment services in alignment with WHO treatment guidelines and PEPFAR program priorities; use of ARVs in patients taking rifampicin-containing regimens for treatment of active tuberculosis; use of ARV formulations for infants, children, adolescents, and pregnant and breastfeeding women. This process does not review ARVs for pre-exposure prophylaxis, which may be considered in a different policy document.

The Committee shares relevant experience and policy shifts with USFDA related to scaling up adult and pediatric treatment services as well as in PEPFAR procurement and supply chain innovation as part of PEPFAR 3.0 and its five action agendas (Impact, Efficiency, Sustainability, Partnership, and Human Rights).

ARV formulations are reviewed and categorized according to the following criteria: (updated in October 2017):

[1] The Committee consists of USG representatives from the Office of Global AIDS Coordinator (S/GAC), US Agency for International Development (USAID), Centers for Disease Control and Prevention (CDC), Office of Global Affairs (HHS/OGA), and the USFDA.

1. Primary Priority ARVs meeting at least one of the following criteria (See **Table 1)**:

    a. Recommended as a preferred first-line treatment in the W H O Consolidated Guidelines for HIV Treatment[v] in adults and delivered as a complete treatment regimen, OR

    b. ARVs for children included in the 2018 WHO Paediatric ARV Optimal Formulary and Limited Use List or referenced in the Paediatric ARV Drug Optimization Conference[vi] OR

    c. Essential component of first line-treatment in patients who are concurrently taking medications to prevent or treat HIV associated tuberculosis OR

    d. Modifications to dossier applications of select preferred or alternative first-line ARVs needed to meet demand.

2. Secondary Priority ARVs meeting at least one of the following criteria (see **Table 2**):
    a. Recommended as an alternative first line treatment in the WHO Consolidated HIV Guidelines OR

    b. Recommended as a preferred or alternative second-line treatment in the WHO HIV Consolidated Guidelines OR

    c. Modifications to dossier applications of second-line ARVs needed to meet demand

3. Watch Priority ARVs meeting the following criterion (see **Table 3**):
    a. Approved or tentatively approved by FDA but not currently mentioned in WHO Consolidated HIV Treatment Guidelines OR

    b. Currently studied in clinical trials or pharmacokinetic studies. If study results are favorable, and WHO recommends these ARVs in the Consolidated Guidelines, then such product may be moved to the primary or secondary priority ARV list and introduced expeditiously OR

    c. Recommended as third line treatment for CLHIV

Updates to this document are summarized in Annex 3.

Table 1: PRIMARY PRIORITY ARVs (Abbreviations available in Annex 2)

DRUG or DRUG COMBINATION	DRUG CLASS	STRENGTH (mg)	RATIONALE	LIMITATIONS
DTG/3TC/TDF	INSTI and NRTI	50/300/300	DTG more potent, lower manufacturing costs, improved safety over EFV, superior efficacy to DRV, and non-inferior to RAL, higher genetic barrier to resistance. Preferred first line per 2018 WHO Treatment Guidelines.[vii,viii,ix,x]	There is a drug-drug interaction between DTG and RIP. It is recommended to administer DTG 50 mg every 12 hours when co-administering with RIF. The Tsempano study has identified a potential safety issue related to neural tube defects in infants born to women who are taking DTG at the time of conception.[xi] [xii,xiii,xiv,xv,xvi,xvii]
DTG	INSTI	50	Initiation as a component of first line treatment and used with DTG/3TC/TDF and DTG/FTC/TDF for patients on concurrent therapy with rifampicin.[v]	Only one study recommends increase of DTG dosing to 50 mg twice daily in adults taking rifampicin-containing treatment for HIV-associated TB. [xiii,xiv,xv,xvi,xvii,xviii,xix,xx]
DTG/3TC/ABC	INSTI and NRTI	TBD (chewable, crushable or dispersible form)	The Committee is prioritizing this triple FDC for pediatric patients. Note: The adult formulation is not considered a priority.[vii,xviii]	
DTG	INSTI	10 scored and 50 scored. Both should be chewable, crushable or dispersible.	Harmonized with adult first line, and recommended by WHO as first line for children. Multiple strengths to anticipate dosing requirements through pediatric age bands	WHO weight-band dosing is 50 mg for body weight at least 25 kg, and TBD for weight band of 14 kg to 25 kg [v,xixxxi] Studies currently underway in children <6 y and <30 kg to establish dosing.[xx]
RAL	INSTI	25 (chewable product)	RAL serves as an option for first line preferred for neonate (granules) and first line alternative pediatric patients aged 4 weeks to 10 years.[vi]	High pill burden for patients in higher weight bands.

Table 1: PRIMARY PRIORITY ARVs (Abbreviations available in Annex 2)

DRUG or DRUG COMBINATION	DRUG CLASS	STRENGTH (mg)	RATIONALE	LIMITATIONS
LPV/r	PI	100/25 Heat Stable Tablet 40/10 Pellets or Granules	Preferred LPV/r formulations for children under 35 kg. LPV/r pellets and pediatric heat-stable formulations are more palatable than LPV/r solution.[vi,xxi,xxii]	
LPV/r/ABC/3TC	PI and NRTI	40/10/30/15 Granules or Powder	Convenience of all active ingredients co-formulated into a child-friendly formulation.	

Table 2: SECONDARY PRIORITY ARVs (Abbreviations available in Annex 2)

DRUG or DRUG COMBINATION	DRUG CLASS	STRENGTH (mg)	RATIONALE	LIMITATIONS
EFV/3TC/TDF	NNRTI and NRTI	400/300/300	Due to the data from the NAMSAL study showing that DTG is non-inferior to EFV400 when combined with TL and the need for an EFV based formulation for women of childbearing potential that are unable to take DTG based formulations.	

Table 3: WATCH PRIORITY ARVs

SPECIAL NOTE REGARDING BICTEGRAVIR: PEPFAR will continue to maintain vigilance of new information pertaining to bictegravir. PEPFAR did not include bictegravir on any of the lists based on information available at the time of last review. Bictegravir is comparable to dolutegravir in treatment efficacy and safety in treatment naive patients, treatment experienced patients that have previously had success with DRV/r or ATV/r and in treatment experienced patients that were previously suppressed on ABC/3TC/DTG (ALD). Similar to DTG, BIC when co-administered with rifampin resulted in a 75% reduction in exposure of BIC; therefore, theoretically, clinicians will need to administer an additional dose of BIC. Pediatric evidence is further along with DTG.[xxiii,xxiv,xxv]

Table 3: WATCH PRIORITY ARVs

DRUG OR DRUG COMBINATION	DRUG CLASS	STRENGTH (mg)	RATIONALE	LIMITATIONS
DTG/FTC/TAF	INSTI and NRTI	50/200/25	Improved safety profile of TAF vs. TDF for osteoporosis and osteopenia, decreased renal toxicity. TAF is also expected to be less expensive than TDF.[xxvi]	Potential drug-drug interactions of TAF with rifampin and with isoniazid. Additional studies in pregnancy and patients on TB medications are ongoing.
FTC/TAF	INSTI and NRTI	TBD	Improved safety profile of TAF vs. TDF for osteoporosis and osteopenia, decreased renal toxicity. TAF is also expected to be less expensive than TDF.[xxvii]	
DRV/r	PI	120/20 (pediatric friendly formulation)	Lower strength will enable dosing in children who are too small to take the adult DRV/r formulation.[vii]	DRV cannot be used in children <3 years old because of toxicity observed in juvenile animal studies.
DRV/r	PI	400/100	Once daily DRV/r for treatment experienced patients may potentially be an option because it would be reasonable to make an assessment of presence of PI mutations based on patient history in the absence of a genotype.	Current limitation is cost. DRV/r at 400/100mg once daily showed non-inferior efficacy to LPV/r as a switch option for patients with HIV RNA < 50 copies/mL, consistent with pilot studies showing no difference in efficacy versus standard 800/100 mg once daily dosing for PI-naïve patients. Results need to be confirmed in studies using DRV/r 400/100 mg once daily for PI naïve patients. If DRV/r 400/100 proves to be equivalent then it will cost less than the traditional dose of 800/100 (currently administered as two 400/50 tablets once daily).[xxv]
DRV/r	PI	400/50 or less. Solid drug nanoparticle formulation	400/50 or less. Solid drug nanoparticle formulation Work funded by PEPFAR through project OPTIMIZE has developed a solid drug nanoparticle formulation of DRV/r combination showing greater than 50% reduction in dose of DRV while maintaining	Final optimal dose in a nanoformulation presentation remains to be determined.

	key steady-state pharmacokinetic parameters in animals. These formulations are under GMP stability assessment for first-in-human clinical trials. Final optimal dose for the nanoformulation remains to be determined and the University of Liverpool, Clinton Health Access Initiative and Unitaid-funded Medicines Patent Pool are working to progress this FDC towards adult and pediatric treatment options.[xxviii]

ANNEX 1

Members of the PEPFAR ARV Prioritization Committee:

SGAC: J. Sean Cavanaugh
USAID: Rachel Golin, Lana Lee, Christine Malati (Secretariat), Thomas Minior, George Siberry
CDC: Deborah Carpenter, Bill Coggin, Rituparna Pati

Observers:

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HHS/OGA: Jin Park, Lisa Wagner

ANNEX 2

ABBREVIATION	NAME
NRTI	**Nucleoside reverse transcriptase inhibitor**
ABC	Abacavir
AZT	Zidovudine
3TC	Lamivudine
FTC	Emtricitabine
TDF	Tenofovir
TAF	Tenofovir alafenamide fumarate
NNRTI	**Non-nucleoside reverse transcriptase inhibitor**
EFV	Efavirenz
NVP	Nevirapine
PI	**Protease Inhibitor**
ATV	Atazanavir
DRV	Darunavir
LPV/r	Lopinavir/ritonavir
r	Ritonavir (as a low-dose booster)
INSTI	**Integrase Strand Transfer Inhibitor**
BIC	Bictegravir
DTG	Dolutegravir
RAL	Raltegravir

ANNEX 3: Record of UPDATES to ARV Formulation Priorities for PEPFAR					
Date	**Table**	**Drug or Drug Combination**	**Strength (mg)**	**Action Taken**	**Comment**
2017-AUG-21	Table 1: Primary Priority ARVs	EFV/3TC/TDF	400/300/300	Removed from PEPFAR priorities	PEPFAR is prioritizing a transition from TLE600 to formulations containing DTG.
2017-AUG-21	Table 1: Primary Priority ARVs	EFV/FTC/TDF	400/200/300	Removed from PEPFAR priorities	PEPFAR is prioritizing a transition from TLE600 to formulations containing DTG.
2018-JAN	Update to definition of Primary Priority ARVs, Secondary Priority ARVs, Watch Category to include the impact of an ARV formulation to the global ARV market.				
2018-JAN	Tale 1: Primary Priority ARVs	EFV/FTC/TDF	600/200/300	Moved to Secondary Priority	In reflecting on procurement data, the majority of countries are using TLE in lieu of TEE.
2018-JAN	Table 1: Primary Priority ARVs	DTG/FTC/TDF	50/200/300	Moved to Secondary Priority	PEPFAR is prioritizing a transition to TLD and countries are rapidly initiating procurement of this formulation.
2018-JAN	Table 1: Primary Priority ARVs	LPV/r	40/10	Addition of the word granules	
2018-JAN	Table 2: Secondary Priority ARVs	DTG	50	Moved to Primary Priority	This is to allow for additional doses during treatment for TB
2018-JAN	Table 2: Secondary Priority ARVs	DTG/3TC/ABC	5/30/60	Moved to Primary Priority	Pediatric formulation thus top priority
ANNEX 3: Record of UPDATES to ARV Formulation Priorities for PEPFAR					
Date	**Table**	**Drug or Drug Combination**	**Strength (mg)**	**Action Taken**	**Comment**
2018-JAN	Table 2: Secondary Priority ARVs	TDF/3TC	300/300	Removed from PEPFAR priorities	Ample manufacturers thus no need to continue to prioritize
2018-JAN	Table 2: Secondary Priority ARVs	TDF/FTC	300/200	Removed from PEPFAR priorities	To encourage countries to move to FTC over 3TC for the following reasons.

2018-JAN	Table 3: Watch Priority ARVs	DTG/TAF/3TC	50/TBD/300	Removed from PEPFAR priorities	1. TAF is not available as a reference product in the form of a single agent with the indication of HIV treatment. Therefore, establishing a reference standard for a bioequivalence study will be more costly than a bioequivalence study for TAF/FTC/DTG for the manufacturers. Moreover, TAF/FTC is available as reference standard and is currently being used by generic ARV manufacturers to develop DTG/TAF/FTC. Eight companies are now working on TafED, one company is working on TafED AND TafLD. 2. Recognizing that FTC can be interchanged with 3TC, this has not manifested at the clinic level. Countries will stock either one product or the other. Some countries may keep both products but fail to interchange in the event of a stockout of one product or the other. Therefore, promotion of both FTC and 3TC containing products will lead to management of more items in the warehouse and in the supply chain leading to inefficiency. 3. In analyzing the API market, the price of FTC will continue to decline, the API cost of 3TC has bottomed out. 4. By promoting only FTC, we aim to send a signal to decrease the number of applications that are submitted to the FDA, allowing FDA to focus on priority items of this document. 5. Countries may begin to use TafE and TE for PrEP. If we encourage countries to use a FTC based regimen for treatment, then we can continue to benefit from improved manufacturing processes of FTC. 6. Both FTC and 3TC based products are equivalent in price (TLE and TEE). By listing only FTC, we aim to avoid the misinterpretation that could arise from listing both products.
2018-MAR	Special Note	BIC		Will not be added to the Watch Priority List.	
2018-MAR	Table 1: Primary Priorities	EFV/3TC/TDF	300/300/600	Moved to Secondary Priority	Recognized continued need for this formulation in select populations (patients that do not tolerate DTG, some women of child-bearing potential)

2018-JUL	Table 3: Watch Priorities	DTG	10 and 50 scored	Moved to Primary Priority	Due to 2018 WHO Guideline revision
2018-JUL	Table 3: Watch Priorities	DRV/r	120/20	Added to Watch Priorities	Due to mention at PADO3 Conference Call 2017
2018-JUL	Table 1: Primary Priorities	LPV/r/AZT/3TC	40/10/30/15 Granules or pellets	Removed from Primary Priority	Due to need to streamline the list.
2018-JUL	Table 1: Secondary Priorities	ATV/r	300/100	Removed from Secondary Priority	Currently, there are three manufacturers are tentatively approved. Capacity is sufficient to meet demand for the near future.
2018-JUL	Table 2: Secondary Priorities	LVP/r	200/50	Removed from Secondary Priority	Currently, there are six manufacturers that are approved or tentatively approved. Capacity is sufficient to meet demand for the near future.
2018-NOV	Table 1: Primary Priorities	EFV/3TC/TDF	400/300/300	Added to Primary Priority	Due to the data from the NAMSAL study showing that DTG is non-inferior to EFV400 when combined with TL and the need for an EFV based formulation for women of childbearing potential that are unable to take DTG based formulations.
2018-NOV	Table 2: Secondary Priorities	EFV/3TC/TDF	600/300/300	Removed from Secondary Priority	Due to the need to prioritize TLE 400.

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