Supporting Sustained Supply through the Coordinated Procurement of ARVs

ARV Procurement Working Group Newsletter

February 2020

Introduction

Through quarterly order cycles and monthly business calls, the APWG has continued to support the ARV market in low- and middle-income countries (LMICs) via coordinated procurement, strategically managed demand, and reduced fragmentation. As a supplement to our routine work, the APWG publishes a newsletter that provides an update on some of the key topics and issues facing the ARV market.

The APWG's website (https://www.arvprocurementworkinggroup.org/) continues to be a useful resource that hosts all relevant APWG documents including the quarterly demand forecast, product recommendations and memos, newsletters, and other resources. Please check back often for updates.

The February 2020 edition of the APWG newsletter includes:

- Updated WHO Guidelines
- Paediatric ARV Updates
- Advanced HIV Disease (AHD) Updates
- Partner Publications and APWG Resources

Updated WHO Guidelines

At IAS 2019 in Mexico City, the WHO released updated guidelines **recommending TLD for *all* patient populations (patients weighing at least 30 kg)**, including women of childbearing potential not on effective contraception. The strength of this recommendation was upgraded from "conditional" to "strong" in this update of the guidelines. The WHO also reaffirmed previous recommendations on the use of DTG in second-line for patients failing an NNRTI-based first-line regimen, and for paediatric patients with approved dosing.

Whereas previously the WHO guidelines listed both TLE600 *and* TLE400 as alternative first-line regimens to TLD, **TLE400 is now listed as the sole alternative regimen** due to lower rates of treatment discontinuation and severe treatment-related adverse events compared to TLE600.

Finally, **tenofovir alafenamide fumarate (TAF)** made its first appearance in the WHO guidelines for use in **special circumstances in adults** with established osteoporosis and/or impaired kidney function, and as an **alternative in pediatric patients over 25 kg**.[1,2] Key studies to inform broader TAF use in important populations, such as pregnant women, are ongoing.

See the full guidelines (linked above and in the *Partner Publications and APWG Resources* section) for more information.

[1] Please note that the Global Fund will only consider to fund TAF in *established* cases of osteoporosis and/or impaired kidney function.
[2] At the time of publication, USG was not permitted to procure any formulations containing TAF.

Paediatric ARV Updates

Paediatric DTG

The WHO recommends DTG for use in all children with age- and weight-approved dosing, pending availability of paediatric-friendly formulations of DTG for use in children below 20 kg.

In December 2019, ViiV Healthcare, the innovator of DTG, filed their Tivicay® DTG (5 mg) dispersible (disp.) tablet with the US FDA in December 2019 with an anticipated approval date in Q2 2020 (assuming priority review). Concurrently, Mylan and Macleods are developing a DTG (10 mg) disp. and scored tablet (with technical assistance from ViiV and a financial incentive from Unitaid via CHAI) and hope to file their products with the US FDA in Q2 2020. Barring potential issues with the filings and a priority review, the generic DTG (10 mg) disp. and scored tablets could be tentatively approved by the end of 2020 and available in-country in early 2021.

Potential US FDA Approval Timelines for Pipeline Paediatric DTG Products

	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020
ViiV DTG 5 mg disp.	Filed		Anticipated* approval date		
Mylan and Macleods DTG 10 mg disp. and scored			Anticipated file date		Anticipated* approval date

*Assuming priority reviews

If these products are approved, it would allow children below 20 kg to have access to WHO first-line preferred regimens and harmonize both paediatric and adult treatment.

Paediatric LPV/r Formulations

Cipla and Mylan have recently scaled up production capacity of their LPV/r (40 mg/10 mg) pellets and 2-in-1 granules (respectively) in order to improve the global supply. The APWG still maintains the **LPV/r Dashboard** hosted on the APWG website to provide information on supply availability for key paediatric LPV/r products over an 18-month period.

In addition to LPV/r pellets, Cipla has been developing their *Quadrimmune®* "4-in-1" ABC/3TC/LPV/r (30 mg/15 mg/40 mg/10 mg) heat-stable granules in a capsule (referred to as 4-in-1 capsule for the remainder of this newsletter), and filed with the US FDA in October 2019 with an expected approval date in April 2020. If approved, this would be the first paediatric fixed-dose combination that fulfills WHO recommendations. Cipla is offering the 4-in-1 at a price of US $15/pack of 120 capsules.

The WHO and other stakeholders are developing a memo to address the number of optimal paediatric products expected to enter the market over the course of 2020, and to assist countries with planning transitions. This memo will be broadly circulated soon.

Paediatric Ritonavir (RTV)

Two previously unavailable paediatric formulations of ritonavir (RTV) listed on the 2018 Optimal Formulary and Limited-Use List have recently been commercialized and may be procured by country programs.

Mylan has commercialized their film-coated **RTV (25 mg) tablets**, which have been prequalified by the WHO, and AbbVie has commercialized their **RTV (100 mg) powder**, which has been approved by the US FDA. Both of these products are recommended for use as superboosters of LPV/r during TB treatment and for boosting protease inhibitors that are not co-formulated with ritonavir.

Advanced HIV Disease (AHD) Updates

As discussed in the last APWG newsletter, the APWG recently expanded its scope to include products for the treatment of advanced HIV disease (AHD). The current products monitored are flucytosine, Amphotericin B (liposomal and deoxycholate), CTX/INH/B6 (Q-TIB), isoniazid, and rifapentine. The products have officially been included in the APWG's quarterly monitoring calls since Q3 2019, and are included in the APWG's quarterly demand forecast hosted on the website.

There have been a number of updates related to AHD treatment commodities in the preceding months.

- **Flucytosine.** The price of Mylan's flucytosine (5FC) has been **reduced** from US $110/pack **to US $75/pack**, representing a reduction of approximately one-third. Mylan also submitted a dossier to the WHO prequalification program.
- **Rifapentine.** In October 2019, a new public sector price was announced for Sanofi SA's 24-pack of Rifapentine (RPT) 150 mg tablets at **US $5.00/pack** (US $15 per 3-month treatment course for latent TB infection). The price deal was announced by Unitaid, the Global Fund, and Sanofi. However, given significant demand for RPT, the global supply will be limited through 2020 and early 2021.
- **Rifapentine/Isoniazid.** The RPT/INH (300 mg/300 mg) 36-pack is expected to be available for in-country delivery starting July 2020 from Macleods at a price of **US $15.00/pack**.

Finally, the Global Fund has published a new reference price list consolidating pricing data for advanced HIV disease products. The list includes medicines for TB preventive therapy, Kaposi Sarcoma, and Cryptococcal disease, as well as relevant diagnostic tests. The list also includes estimated regimen costs for treating Cryptococcal meningitis.

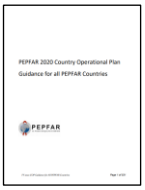
Partner Publications and APWG Resources

The APWG would like to highlight some key publications and resources that provide useful programmatic guidance:

Update of recommendations on first- and second-line antiretroviral regimens

At IAS 2019 in Mexico City, the WHO released updated guidelines on first- and second-line antiretroviral regimens, including the recommendation that TLD be the preferred first-line regimen for *all* patient populations.

PEPFAR 2020 Country Operating Plan Guidance for All PEPFAR Countries

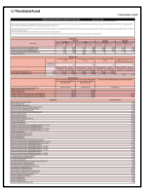


PEPFAR has released their latest country operating plan (COP) guidance for reference by all PEPFAR countries when developing their COP20 plans.

CHAI 2019 HIV Market Report

A clear understanding of the complex, ever-changing ARV and diagnostic markets in low- and middle-income countries is critical for all stakeholders in the HIV space. To address this need, CHAI publishes an annual HIV market report based on aggregated market intelligence from their programmatic work in over 30 countries.

Global Fund Pooled Procurement Mechanism (PPM) reference price lists



The Global Fund Pooled Procurement Mechanism (PPM) is a Global Fund strategic initiative that aggregates order volumes on behalf of participating grant recipients to negotiate prices and delivery conditions with manufacturers. The PPM produces reference price documents for global health commodities, including ARVs, other strategic medicines used in HIV programs, and a newly created list highlighting products used in the advanced HIV disease (AHD) package of care, for use when procuring health products.

Appendix

Quarterly Order Cycle Coordination

The APWG Procurement Consortium consolidates the orders of ARVs around fixed quarterly order cycle dates. These dates have been agreed upon by the AWPG and shared with suppliers and other stakeholders.

The aggregation of orders for at-risk ARVs (i.e., paediatric and low-volume adult products as well as those ARVs in transition) around this schedule allows manufacturers to plan production accordingly. Furthermore, consolidated product orders are more likely to meet the required minimum batch size and thus potentially avoid extended lead times associated with sub-batch orders.

Countries procuring ARVs independently or through non-APWG procurement agents are encouraged to use the quarterly order dates below to ensure a reliable supply of ARVs.

Deadline For Orders To Be Placed With Suppliers*	
Q1 2020	**27 March 2020**
Q2 2020	**26 June 2020**
Q3 2020	**25 September 2020**
Q4 2020	**25 December 2020**
*Orders should be submitted to procurement agents at least 6 weeks before these dates	

Scheduled ordering four times a year is especially recommended for low-volume paediatric and adult ARVs, a list of these prioritised products for coordinated procurement is provided below:

Prioritised Paediatric ARVs (2018 Optimal Formulary)	
Optimal	ABC/3TC (120 mg/60 mg) dispersible tablets
	AZT (50 mg/5 ml) oral solution *(100 ml)*
	LPV/r (40 mg /10 mg) pellets and granules
	LPV/r (100 mg/25 mg) heat-stable tablets
	NVP (50 mg) dispersible tablets
Limited-Use	3TC (50 mg/5 ml) oral solution (*100 ml*)
	ABC (60 mg) dispersible tablets
	DRV (75 mg) tablets
	LPV/r (80 mg + 20 mg/ml) oral solution
	RAL (100 mg) granules
	RTV (25 mg) tablets
	RTV (100 mg) powder
Non-Essential	3TC (50 mg/5 ml) oral solution (*240 ml*)
	ATV (150 mg) capsules
	AZT (50 mg/5 ml) oral solution *(240 ml)*

Prioritised Adult ARVS
3TC (150 mg)
ABC (300 mg)
ATV (300 mg)
AZT (300 mg)
DRV (400 mg)
DTG (50 mg) and FDCs
EFV (400 mg) FDCs
RAL (400 mg)
RTV (100 mg)
TDF (300 mg)

New Product Availability

The following products have been either tentatively approved by the US FDA, received WHO Prequalification (PQ), or have been reviewed and approved by the Global Fund Expert Review Panel (GF ERP) since the publication of the last APWG Newsletter.

Latest ARV Approvals for Key ARVs (Since June 2019 Newsletter)			
Product	**Patient Type**	**Supplier**	**Approval Body**
TAF/3TC/DTG (25/300/50 mg) Tablet	Adult	Mylan	US FDA
TAF/FTC/DTG (25/200/50 mg) Tablet	Adult	Mylan	US FDA
TDF/3TC/DTG (300 mg/300 mg/50 mg) Tablet	Adult	Hetero	WHO PQ
TDF/3TC/DTG (300 mg/300 mg/50 mg) Tablet	Adult	Laurus	WHO PQ
TDF/3TC/DTG (300 mg/300 mg/50 mg) Tablet	Adult	Sun Pharma	WHO PQ
TDF/3TC/EFV (300 mg/300 mg/400 mg) Tablet	Adult	Macleods	WHO PQ
TDF/3TC/EFV (300 mg/300 mg/400 mg) Tablet	Adult	Laurus	GF ERP (valid through 18 August 2020)
DRV/r (400 mg/50 mg) Tablet	Adult	Hetero	GF ERP (valid through 24 June 2020)

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The 2018 Optimal Formulary and Limited-Use List for Paediatric ARVs

2018 Optimal Formulary			
Drug	**Formulation**	**Dose**	**Rationale for Use**
AZT	Oral Solution – 100 mL	50 mg/5 ml	For postnatal prophylaxis or neonatal treatment
NVP	Tablet (Dispersible, Scored)	50 mg	For postnatal prophylaxis
NVP	Oral Solution – 100 mL	50 mg/5 mL	For postnatal prophylaxis or neonatal treatment
LPV/r	Tablet (Heat Stable)	100 mg/25 mg	For alternative first-line or second-line for children 10 kg and above and able to swallow tablets whole
LPV/r	Solid Oral Dosage Form	40 mg/10 mg	For alternative first-line or second-line for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole.
AZT/3TC	Tablet (Dispersible, Scored)	60 mg/30 mg	For first-line in special circumstances or second-line in infants and children 4-25 kg
ABC/3TC	Tablet (Dispersible, Scored)	120 mg/60 mg	For preferred first-line or second-line in infants and children 4-25 kg
RAL	Tablet (Chewable, Scored)	25 mg	To provide alternative first-line and second-line for infants and children between 3-25 kg

2018 Limited-Use List			
Drug	**Formulation**	**Dose**	**Rationale For Use**
LPV/r	Oral Solution	(80 mg + 20 mg) /mL	For alternative first-line or second-line for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole, until a suitable oral solid dosage form becomes widely available
3TC	Oral Solution – 100 mL	50 mg/5 mL	For neonatal treatment only
ABC	Tablet (Dispersible, Scored)	60 mg	For provision of a triple nucleoside regimen in combination with AZT/3TC dual FDC for the duration of TB treatment
DRV	Tablet	75 mg	For third-line regimens in children 3 years and above
RTV	Tablet	25 mg	For superboosting of LPV/r during TB treatment and boosting un-coformulated protease-inhibitors
RTV	Powder	100 mg	For superboosting of LPV/r during TB cotreatment and boosting non-coformulated protease-inhibitors
ATV	Capsule	200 mg	For alternative second-line in combination with RTV 100mg
AZT/3TC/NVP	Tablet (Dispersible, Scored)	60 mg/30 mg/50 mg	For first-line in special circumstances in children below three years until suitable bPI or INSTI dosage forms become widely available
EFV	Tablet (Scored)	200 mg	For first-line in special circumstances in children above three years until suitable bPI or INSTI dosage forms become widely available
RAL	Granules for suspension	100 mg	For neonatal treatment only

For more details on the 2018 revised WHO Optimal Formulary and Limited-Use List for Paediatric ARVs, please contact Martina Penazatto (penazzatom@who.int), Nandita Sugandhi (nss14@cumc.columbia.edu), Wesley Kreft (wkreft@iplussolutions.org), Mireille Muhimpundu (Mireille.Muhimpundu@theglobalfund.org), or Christine Malati (cmalati@usaid.gov).