Supporting Sustained Supply through the Coordinated Procurement of ARVs

ARV Procurement Working Group Newsletter

September 2017

Introduction

Through quarterly order cycles and business calls, the APWG continued to support the ARV market in low- and middle-income countries (LMICs) in the first part of 2017 via coordinated procurement, strategically managed demand, and reduced fragmentation.

Procurement Consortium Efforts and Successes to Date

In March 2017, the APWG met to review 2016's key performance indicators (KPIs) at an annual meeting in Geneva. Some highlights from the KPI analysis include:

- **More paediatric ARVs are being placed via 'well-planned' orders.** In 2016, 70% of total paediatric order volumes (packs) as seen through the APWG were deemed well-planned. This represents a notable increase as only 15% of APWG order volumes were well-planned in 2012.
- **Non-essential procurement continued to represent a small fraction of overall procurement.** Procurement of non-essential ARVs through the APWG decreased from 33% in 2010 to only 5% in 2016, when comparing the prevailing IATT list for the year in question. Over half of the non-essential APWG procurements in 2016 were attributable to 240ml bottles of NVP, AZT, and ABC.
- **The APWG successfully expanded to track adult formulations that are either low volume or in transition.** The inclusion of adult products, like DTG (50 mg) tablets, into the APWG's quarterly order cycles and work was seamless and the APWG will continue to track key products moving forward.

In addition to the KPI analysis, the APWG discussed opportunities to strengthen the group's work. One direct outcome from the meeting was to produce publicly available quarterly APWG Demand Forecasts. Since then, two forecasts have been shared (with the latest being the Q2 2017 APWG Anticipated Demand Forecast).

DTG Single Procurement Expands to Over a Dozen LMICs and TLD Receives First SRA Approval

DTG, an integrase strand transfer inhibitor (INSTI), has garnered a lot of excitement from national treatment programs and the ARV market. Many LMICs have formally included DTG in their national treatment guidelines, including Benin, Botswana, Cambodia, Kenya, Lesotho, Nigeria, Uganda, and Zimbabwe, with other nations at various stages of adoption. In addition, over a dozen countries have initiated procurement plans for DTG singles including, but not limited to, Armenia, Belarus, Botswana, Burkina Faso, Cambodia, Cameroon, Cote d'Ivoire, D R Congo, Egypt, Georgia, Jamaica, Kenya, Nigeria, Syria, Uganda, Ukraine, and Uzbekistan. Further, the Global Fund and PEPFAR have already seen demand for DTG quickly pick up through recent national forecasting and quantification exercises.

One highlight in the dolutegravir space is the recent catalytic procurement of DTG singles in Kenya, Nigeria, and Uganda. Under the leadership of Ministries of Health (MoH), CHAI and Unitaid have supported the roll-out of generic DTG 50 mg to be used with optimized two nucleosides in these three nations. In addition to offering DTG to thousands of HIV patients, the catalytic procurement is helping to understand the key requirements for national DTG roll-out as well as provide a platform for TDF/3TC/DTG (TLD) fixed-dose combination (FDC) introduction.

DTG was also a noteworthy topic at IAS 2017. CHAI hosted a satellite session titled "Accelerating Access to Dolutegravir and Other Optimal ARVs," which included highlights of the DTG implementation programs of Kenya and Botswana, an overview of South Africa's plan to fully scale-up to TLD through its next tender cycle, and anecdotes from AfroCAB's Kenly Sikwese, of his own experience of benefitting from DTG and how the broader patient community is demanding immediate access to the drug.

While there is still a need to monitor use in special populations, IAS 2017 revealed clear momentum and desire across partners to ensure that DTG is widely accessible to patients in LMICs as soon as possible.

Looking ahead, a handful of suppliers have already filed their generic TLD products to SRA bodies. In August 2017, Mylan and Aurobindo received tentative approval for TLD from USFDA. Reliable commercial supply of TLD is expected to be available by late Q4 2017 or early Q1 2018. While no supply constraints for DTG single and TLD products are anticipated, the APWG will continue to monitor the supply security of these products via routine order cycles and business calls.

Low-Dose Efavirenz Product (TLE400) Receives First SRA Approval

In March 2017, USFDA granted tentative approval of low-dose efavirenz FDC product (TDF/3TC/EFV 300/300/400mg) to Mylan. Several LMICs including Zambia and Zimbabwe have already included TLE400 in their national guidelines and a few orders have already been placed for the product.

Market Update on LPV/r Oral Pellets

Over the past year, the APWG has been working closely with key stakeholders from both the demand- and supply-sides of the ARV market to ensure the supply security of LPV/r oral pellets, an optimal, heat-stable pediatric formulation for children less than 3 years old.

LPV/r oral pellets are relatively new to the pediatric ARV market. Having received USFDA tentative approval in May 2015, Cipla initially began manufacturing the product solely for clinical trials and didn't start producing pellets for commercial use until May 2016. The first few quarters of commercial production (i.e., Q2 and Q3 2016) saw order volumes well below Cipla's production capacity.

Starting in late 2016, however, the APWG began to notice significant demand for the product that greatly exceeded Cipla's capacity. Given the supply security concerns, pellets were one of the primary topics of discussion at the face-to-face annual meeting of the APWG in March 2017. Cipla, in addition to Mylan, who is currently developing an LPV/r granule product similar to pellets, were invited to the meeting as well.

The APWG had open discussions with Cipla on the ability to meet demand, optimize capacity, ensure continued transparency, and get clear commitments on plans to increase capacity. With Mylan, the APWG was able to receive an update on their new LPV/r granules product and an updated timeline for filing and commercialization dates.

Beyond the successful coordination with partners and suppliers, there were two additional outcomes from the annual APWG meeting.

First, the APWG published and disseminated a memo advising national programs on the LPV/r pellet situation. The memo recommends programs to expect lead times of 6-8 months for orders, to stagger

larger quantities of orders, to share procurement plans with the APWG, to carefully quantify the need for pellets, and to slow (or hold-off on) the roll-out of pellets until the supply capacity was increased.

Additionally, the decision was made to set up monthly calls with Cipla to monitor the LPV/r oral pellet market to ensure supply is able to meet current and future demand. Since then, APWG procurement agent representatives have shared their latest order data and other demand-side updates to the working group on a monthly basis.

With the routine update calls with Cipla, the APWG has been able to successfully validate the known demand for pellets against Cipla's order set, determine the expected lead-times for orders, and mitigate any potential supply issues. Looking ahead, the APWG plans to continue the monthly calls with Cipla and monitor the LPV/r oral pellet space through coordinating with various partners.

ABC/3TC (120/60mg) Dispersible Tablets See Further Uptake

The uptake of ABC/3TC (120/60mg) dispersible tablets, which can reduce pill burden in children by at least 50% compared to the existing formulations of ABC has increased. To date, there are two SRA approved manufacturers for the product: Cipla (with its 60 tablet product) and Mylan (with its 30 tablet product). Over ten countries have initiated plans for procurement of ABC/3TC (120/60mg) dispersible tablets, including Cameroon, Cape Verde, Central African Republic, East Timor, Kenya, Laos, Myanmar, Syria, Tanzania, Uganda, and Vietnam.

Partner Publications and APWG Resources

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

- **2016 IATT Paediatric ARV Formulary and Limited-Use List**. The optimal and limited-use formulary list was revised by the IATT in 2016 following updates to the WHO Guidelines. The optimal list is designed to provide the minimum number of ARV formulations needed to provide all currently recommended WHO paediatric preferred 1st and 2nd line regimens across all paediatric weight bands (a summary of optimal and limited-use formulations can be found in the Appendix)

- **WHO's Transition to New Antiretrovirals in HIV Programmes.** The WHO recently published a policy brief that provides advice on how to phase-in some of the newer ARVs, such as DTG, TLE400, DRV/r, and RAL. The aim of the document is to help ensure continuous supply of ARVs, implement the 2016 WHO guidelines safely, rapidly, and efficiently, and enable a smooth transition to the newer regimens.

- **CHAI HIV Mid-Year Market Memo, 2017.** CHAI's recently published memo is an informational brief that covers the latest trends in the HIV space in LMICs since the publication of CHAI's annual ARV Market Report. The document has updates on the various markets within the HIV cascade, including prevention, diagnostics, and treatment.

- **MSF Access Campaign's HIV & Opportunistic Infection Treatment Issue Brief: Spotlight On Access Gaps.** Published in July 2017, MSF's issue brief provides information regarding the changing product landscape and updates on pricing and access to three critical medical interventions: optimal HIV therapy with dolutegravir, paediatric HIV therapy, and opportunities to improve treatment for two common opportunistic infections: cryptococcal meningitis and Kaposi's sarcoma.

Quarterly Order Cycle Coordination

The APWG Procurement Consortium consolidates the submissions 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 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 paediatric ARVs.

Deadline For Orders To Be Placed With Suppliers*	
Q3 2017	**29 September 2017**
Q4 2017	**29 December 2017**
Q1 2018	**30 March 2018**
Q2 2018	**29 June 2018**
*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 is provided:

Prioritised Paediatric ARVs (2016 IATT status)	
Optimal	ABC/3TC (120/60mg) dispersible
	LPV/r (80/20mg/ml) solution
	LPV/r (40/10mg) oral pellets
	NVP (50mg) dispersible
Limited-Use	3TC (50mg/5ml) solution (100ml)
	ABC (60mg) dispersible
	ATV (100mg)
	AZT (60mg) dispersible
	AZT (50mg/5ml) solution (100ml)
	RTV (25mg) tablets
Non-Essential	ATV 150mg
	AZT (50mg/5ml) solution (240ml)

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

New Product Availability

The following optimal and limited-use paediatric products as well as adult formulations have received SRA approval since the publication of the last APWG Newsletter:

Latest SRA Approvals			
Product	**Patient Type**	**Supplier**	**SRA Approval Body**
ABC/3TC (120/60mg) Tablet (Disp)	*Peds - Optimal*	Cipla	USFDA
ABC (60mg) Tablet (Disp)	*Peds – Lim. Use*	Micro Labs	WHO PQ
DRV (75mg) Tablet	*Peds – Lim. Use*	Cipla	USFDA
3TC (150mg) Tablet	Adult	Cipla	USFDA
3TC (300mg) Tablet	Adult	Cipla	USFDA
ATV/r (300/100mg) Tablet	Adult	Cipla	WHO PQ
ATV/r (300/100mg) Tablet	Adult	Cipla	ERP
DRV (400mg) Tablet	Adult	Cipla	USFDA
DRV (600mg) Tablet	Adult	Cipla	USFDA
DTG (50mg) Tablet	Adult	Hetero	ERP
EFV (600mg) Tablet	Adult	Aspen	USFDA
EFV (600mg) Tablet	Adult	Cipla	USFDA
RTV (100mg) Tablet	Adult	Aurobindo	USFDA
RTV (100mg) Tablet	Adult	Hetero	USFDA
TDF/3TC/DTG (300/300/50mg) Tablet	Adult	Aurobindo	USFDA
TDF/3TC/DTG (300/300/50mg) Tablet	Adult	Mylan	USFDA
TDF/3TC/EFV (300/300/400mg) Tablet	Adult	Mylan	USFDA
TDF/3TC/EFV (300/300/600mg) Tablet*	Adult	Hetero	USFDA
TDF/3TC/EFV (300/300/600mg) Tablet	Adult	Hetero	WHO PQ

*Hetero has received re-approval of their TLE600 product following a previous delisting of the product in 2016

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- Vineet Prabhu, Clinton Health Access Initiative

APPENDIX: The 2016 IATT Paediatric ARV Formulary and Limited-use List

2016 IATT Optimal Formulary			
Drug Class	**Drug**	**Formulation**	**Dose**
NNRTI	EFV	Tablet (scored)	200mg
NNRTI	NVP	Tablet (disp. scored)	50mg
NNRTI	NVP	Oral liquid	50mg/ml, 100ml
PI	LPV/r	Tablet (heat stable)	100/25mg
PI	LPV/r	Oral liquid	80/20mg/ml
PI	LPV/r	Oral pellets	40/10mg
FDC	AZT/3TC	Tablet (disp. scored)	60/30mg
FDC	ABC/3TC	Tablet (disp. Scored)	60/30mg, 120/60mg
INSTI	RAL	Chewable tablet	100mg

2016 IATT Limited-Use List				
Drug Class	**Drug**	**Formulation**	**Dose**	**Rationale For Use**
NRTI	AZT	Oral liquid	50mg/ml -100ml	Infant prophylaxis or as part of neonatal treatment regimen
NRTI	3TC	Oral liquid	50/5mg/ml	Neonatal treatment regimen
NRTI	ABC	Tablet (disp. scored)	60mg	Children <3 years undergoing TB treatment requirement triple nucleoside regimen
NRTI	AZT	Tablet (disp. scored)	60mg	Children <3 years undergoing TB treatment requirement triple nucleoside regimen
PI	DRV	Tablet	75mg	Third line
PI	RTV	Tablet	25mg	Boosting of noncoformulated PIs (DRV and ATV)
PI	RTV	Oral liquid	400/5mg/ml	Super boosting of LPV/r during TB treatment
PI	ATV	Solid oral dosage form	100mg	Alternative second line
INSTI	RAL	Tablet (chewable, scored)	25mg	Second line after LPV/r – containing first-line failure
FDC	AZT/3TC/NVP	Tablet (disp. scored)	60/30/50mg	Alternative first-line

For more details on the revised IATT list, please see the published report on the EMTCT-IATT website or contact Martina Penazatto (penazzatom@who.int), Nandita Sugandhi (nss14@cumc.columbia.edu), or Wesley Kreft (wkreft@nl.pfscm.org).