ARV PROCUREMENT WORKING GROUP (APWG) MEMORANDUM ON PAEDIATRIC LPV/r FORMULATIONS

To: Suppliers of paediatric LPV/r formulations, HIV program managers, and ARV logistics divisions
Date: January 10, 2019
Re: Coordinating supply and supporting scale up of paediatric LPV/r formulations

Due to the increasing uptake of paediatric LPV/r formulations, the ARV Procurement Working Group (APWG)[1] has developed the following memorandum to provide information on global coordination efforts to ensure paediatric LPV/r formulations are appropriately distributed and utilized.

Contents

I. INTRODUCTION OF LPV/r-BASED REGIMENS FOR PAEDIATRIC ART

Ritonavir-boosted lopinavir (LPV/r)-based antiretroviral therapy (ART) has been recommended by the WHO as a preferred first-line for all children under 3 years of age since 2013 due to its demonstrated superiority to NVP-containing regimens. Despite this longstanding recommendation, implementation has been slow and not wide-scale, due in part to the lack of availability of optimal formulations of LPV/r. In 2018, WHO guidelines were updated to include dolutegravir (DTG) as preferred for all children down to four weeks of age. However, as dosing and appropriate generic formulations for children below 25 kg are unavailable, LPV/r formulations continue to be an essential component of optimal treatment.

Heat-stable LPV/r oral pellets were tentatively approved by the US Food and Drug Administration (FDA) in May 2015 and became available for country procurement in mid-2016. Though early experiences have provided reassurance that LPV/r oral pellets offer a safe, effective, and acceptable alternative to LPV/r oral solution for infants and young children, multiple constraints have significantly limited uptake, including:

- Supply constraints which resulted in stockouts in early adopter countries and precluded introduction in other countries
- Lack of program readiness to introduce LPV/r oral pellets which resulted in reports of inappropriate usage, expiries, and wastage
- Country level stockpiling of LPV/r oral pellets which resulted in delays of fulfillment of other orders
- Concerns about cost, supply security, and programmatic complexity of LPV/r oral pellet introduction which resulted in ongoing use of inferior NVP-containing regimens by country programs

[1] Full list of members and observers can be found in the Annex.

Heat-stable LPV/r oral *granules* were tentatively approved by the FDA in August 2018, and are ready for country orders as of the time of publication.

II. INCREASED NEED AND DEMAND FOR PAEDIATRIC LPV/r FORMULATIONS

Based on two analyses developed by the APWG, across 17[2] low- and middle-income countries (LMICs) that have initiated pellet procurement, the estimated need for LPV/r pellet/granule formulations would be nearly 200,000 packs per month for children 3-13.9kg, and even greater when older children who cannot swallow tablets are considered. The Q1 2019 production capacity for LPV/r pellets and granules is able to accommodate less than 50% of the total need from the aforementioned 17 countries, not including high-volume countries that have yet to start pellet procurement such as South Africa, Tanzania, and Zambia.

The true global need is likely much greater than 200,000 packs per month as there are additional countries that have initiated pellet procurement, but there is insufficient data to make the same estimates. As mentioned above, high-volume countries that have not yet begun oral pellet or oral granule procurement must also be considered when estimating global need and demand.

With renewed commitments by international donors to discontinue inferior NVP-based treatment regimens (while concomitantly scaling up LPV/r use) in children, and new 2018 WHO recommendations expanding the use of LPV/r-based regimens to all CLHIV who are not yet able to receive DTG, the APWG anticipates a significantly increased demand beginning in 2019 for all paediatric LPV/r formulations, including:

- LPV/r oral solution for younger infants until they are able to take pellets or granules
- LPV/r oral pellets and granules for infants and younger children
- LPV/r 100 mg/25 mg heat-stable tablets for children 10kg and above and able to swallow whole tablets

Despite increased production of pellets/granules in 2019, and given past experiences with LPV/r oral pellets, there is a clear need for more intensive intervention and coordination to ensure paediatric LPV/r formulations, particularly **LPV/r oral pellets and oral granules, are rationally procured, distributed, and utilized to reach populations most in need.** An interagency team of major donors, procurers, and implementing agencies is available to provide guidance, support, and coordination in a way that is responsive to the needs of both the market and end users. This level of coordination will require open collaboration and transparency across all stakeholders in order to reach maximal impact.

III. COORDINATION STRATEGY AND RECOMMENDATIONS FOR SUPPLIERS OF PAEDIATRIC LPV/r FORMULATIONS

The APWG will continue to provide a platform for information sharing including regular calls with suppliers of paediatric LPV/r formulations. In addition, the APWG and partners will begin providing targeted support to country programs to ensure readiness for introduction of new LPV/r formulations. Donors such as USG

[2] Benin, Burkina Faso, Burundi, Cambodia, Cote d'Ivoire, Eswatini, Ethiopia, Kenya, Malawi, Mozambique, Myanmar, Nigeria, Papua New Guinea, Senegal, Togo, Uganda, Zimbabwe.

and the Global Fund will continue to provide support for countries that are adopting LPV/r-based regimens for paediatric patients, including advance procurement to mitigate financial risk for suppliers.

The APWG developed the following recommendations for suppliers of paediatric LPV/r formulations:

1. **Maintain close communication with the APWG** about changes in production capacity for paediatric LPV/r oral solution, oral pellet, and oral granule formulations

2. **Proactively share a list of countries that have placed orders for LPV/r oral pellets or granules** to enable APWG members to rapidly assess country program readiness to introduce pellets/granules to ensure that orders placed are in accordance with rational introduction and scale-up plans

3. For suppliers of LPV/r oral solution, oral granules, and oral pellets, **consider staggering the PEPFAR deliveries of large orders placed by country programs** or alternatively, **coordinate with USAID to make deliveries to Regional Distribution Centers (RDCs)** which can then distribute smaller volume deliveries to countries on a more frequent basis to match distribution with consumption and maintain a centralized buffer stock (rather than separate buffer stocks in each country)

IV. COORDINATION STRATEGY AND RECOMMENDATIONS FOR COUNTRY PROGRAMS

Donors such as USG through PEPFAR and the Global Fund will commit to providing support for countries that are adopting LPV/r-based regimens for paediatric populations. This includes advance procurement of LPV/r oral granules from USAID to maintain a centralized buffer stock of some quantities at RDCs that will be able to distribute smaller volumes on a more frequent basis to programs and ensure distribution of LPV/r granules closely matches consumption. This will enable more children globally to access LPV/r-based regimens, while mitigating risks for country programs if the rate of scale-up does not align with initial procurement plans which would result in shortages if scale-up happens too quickly or wastage if scale-up is slow.

Multiple resources are now available to support programs to plan and introduce LPV/r pellets including:

1. **PEPFAR's LPV/r Pellet Toolkit**: https://aidsfree.usaid.gov/resources/toolkits/lpvr-pellet-toolkit and
2. **CHAI's HIV New Product Introduction Toolkit**: https://www.newhivdrugs.org/national-level-planning

Additional resources will be available in early 2019 to support the introduction of LPV/r oral granules including guidance on administration as well as educational materials.

The APWG has also developed the following recommendations for country programs when planning to introduce and scale-up the use of LPV/r-based regimens for children:

1. **Countries should decide to primarily introduce either LPV/r oral pellets OR LPV/r oral granules, not BOTH.** Though dosing for the oral pellets and oral granules is interchangeable (1 capsule of pellets is equivalent to 1 sachet of granules), administration guidance and packaging differs considerably. To avoid confusion among healthcare workers and caregivers, it is recommended that programs that have already started to introduce pellets continue to scale-up use of pellets and countries that have not yet procured pellets consider the introduction of granules in lieu of oral pellets. Note: the pellets and granules are considered therapeutically equivalent

2. **Assess program readiness for introduction and scale-up of LPV/r-based regimens** including:

1. Updates to national policies and treatment recommendations
2. Development of transition plans at national, regional, and service delivery levels
3. Strategies for building capacity including mentorship and continuous supportive supervision at the service delivery level
4. Systems available or needed for transition monitoring

A tool for evaluating ARV transition readiness can be found at:
https://optimize.icap.columbia.edu/wp-content/uploads/2018/07/Readiness-Assessment_Finalv2.pdf

Further guidance on transitioning to new paediatric ARV formularies can be found at:
https://www.who.int/hiv/pub/paediatric/transition-paediatric-arv-formulary/en/

3. If not already doing so, **country programs should begin to procure LPV/r (100 mg/25 mg) heat-stable tablets for paediatric patients above 10kg and able to swallow tablets whole.** LPV/r (100 mg/25 mg) tablets are smaller than adult LPV/r (200 mg/50 mg) tablets, therefore children are able to swallow them more easily at a younger age. Transitioning younger children from pellets or granules to tablets as soon as possible is the best approach for patients and caregivers as it greatly simplifies administration and lowers pill burden, and is less expensive for programs as LPV/r heat-stable tablets are significantly less costly compared to oral pellets, oral granules, and oral solution. Additionally, as dosing of oral pellets or oral granules for larger weight bands requires multiple packs per month, transitioning those able to swallow tablets will enable prioritization of pellets or granules for younger children who have no other alternative.

   Please see below for a summary table estimating per patient per year (PPPY) costs of treatment with various LPV/r-based formulations:

	PPPY Costs (USD)			
Weightband	**ABC/3TC (120 mg/60 mg) Disp. Tablet - 30**	**LPV/r (40 mg /10 mg) Oral Granules - 120**	**LPV/r (40 mg/10 mg) Oral Pellets - 120**	**LPV/r (100 mg/25 mg) Tablets – 60**
	$3.30/pack	**$18.25/pack**	**$19.20/pack**	**$7.00/pack**
3-5.9kg	$42.90	$237.25	$249.60	-
6-9.9kg	$62.70	$346.75	$364.80	-
10-13.9kg	$82.50	$456.25	$480.00	$140.00
14-19.9kg	$102.30	$565.75	$595.20	$182.00
20-24.9kg	$122.10	$675.25	$710.40	$182.00

*Cost per pack comes from GHSC-PSM's December 2018 e-Catalog

**Dosing based on WHO interim guidelines released in Dec. 2018 (Annex 3)

   As the table above shows, there is a clear cost advantage to switching paediatric patients to LPV/r (100 mg/25 mg) heat-stable tablets (as soon as they are over 10kg and able to swallow tablets whole) compared to keeping them on pellets or granules.

4. **Develop clear eligibility criteria which prioritizes paediatric formulations for the appropriate populations,** and supports more accurate quantification for different formulations of LPV/r:
   1. Infants below 6 months should be prioritized for LPV/r oral solution
   2. Infants and young children between 6 months – 3 years should be prioritized for LPV/r oral pellets or granules

3. The age at which children are able to swallow LPV/r (100 mg/25 mg) tablets varies between 3-5 years of age. Therefore, estimate that 50% of children 3-5 years of age will continue to use LPV/r pellets or granules and 50% will be able to swallow LPV/r (100 mg/25) mg heat-stable tablets
4. Children 5 years and older should use LPV/r (100 mg/25 mg) heat-stable tablets until they can be transitioned to DTG-containing regimens

5. **Ensure training and dosing resources are prepared for healthcare workers** to prescribe and manage patients on LPV/r-containing regimens including:
    1. Eligibility and dosing guidance for all newly available paediatric LPV/r formulations
    2. Transitioning existing patients from NVP- or EFV-containing regimens to LPV/r
    3. Guidance, job aids, and standard operation procedures (SOP) on how to teach caregivers to administer LPV/r oral solution, pellets, or granules
    4. Guidance, job aids, and SOP on transitioning young children to LPV/r heat-stable tablets as soon as possible
    5. Guidance and job aids on teaching young children to swallow tablets

6. **Closely monitor the rate of LPV/r oral pellet or oral granule uptake and update forecasts on a frequent basis.** Forecasting should be shared with the APWG, which provides aggregated forecasts to suppliers to ensure that manufacturing matches anticipated demand.

7. **Countries are STRONGLY discouraged from stockpiling LPV/r oral pellets or oral granules** and instead advised to plan for more frequent, staggered small deliveries of large orders for pellets or granules to better match procurement with consumption. This mitigates the risk of wastage if scale-up plans occur more slowly than anticipated. USAID's RDCs will maintain buffer stocks of LPV/r oral granules to increase supply security. Country orders placed to the RDCs will decrease lead times to one to two months and enable more frequent deliveries as we study the rate of consumption.

V. CONTACT LIST

For further assistance or information, please contact:

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VI. ANNEX: DOSING TABLES AND APWG MEMBERS/OBSERVERS

	Daily Dosing			
Weightband	**LPV/r (80 mg/20 mL) Oral Solution**	**LPV/r (40 mg /10 mg) Oral Granules**	**LPV/r (40 mg/10 mg) Oral Pellets**	**LPV/r (100 mg/25 mg) Heat-Stable Tablets**
3-5.9kg	2 mL	4 sachets	4 caps	-
6-9.9kg	3 mL	6 sachets	6 caps	-
10-13.9kg	4 mL	8 sachets	8 caps	3 tabs
14-19.9kg	5 mL	10 sachets	10 caps	4 tabs

Source: Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.51). Licence: CC BY-NC-SA 3.0 IGO.

Full dosing guidelines can be found in the 2018 WHO updated treatment regimens in Annex 3 at: http://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?sequence=1&isAllowed=y

APWG Members
Centers for Disease Control and Prevention (CDC) (PEPFAR)
Clinton Health Access Initiative (CHAI)
Global Health Supply Chain - Procurement and Supply Management (GHSC-PSM)
The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM)
Kenya Medical Supplies Authority (KEMSA)
Pan American Health Organization (PAHO)
US Department of State/Global AIDS Coordinator (S/GAC) (PEPFAR)
Pharmaceuticals Fund and Supply Agency (PFSA)
Partnership for Supply Chain Management (PFSCM)
The Organization of Eastern Caribbean States (OECS)
Unitaid
United Nations Children's Fund (UNICEF)
United Nations Development Programme (UNDP)
United States Agency for International Development (USAID) (PEPFAR)

APWG Observers
AfroCAB
Drugs for Neglected Diseases Initiative (DNDi)
Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
Enfants et VIH en Afrique (EVA)
ICAP at Columbia University
International AIDS Society (IAS)
Médecins Sans Frontières (MSF)
Medicines Patent Pool (MPP)
World Health Organization (WHO) - HIV Department