Paediatric ARV Drug Optimization 3 Review

Summary report

The Paediatric ARV Drug Optimization (PADO) group re-convened at the end of 2017 to review the implementation of the PADO3 list and discuss key technical elements to advance drug optimization for infants, children and adolescents in the context of future antiretroviral (ARV) guidelines revision. This is a summary of the outcomes of the discussion that took place via teleconference on December 12th 2017.

Background

The PADO3, held on 12 December 2016, issued a revised list of priority paediatric antiretroviral products (http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en/). A number of important events have occurred since this meeting, including: 1) introduction of new products in different countries; 2) new evidence to inform safe use of novel drugs in children; 3) new information to assess feasibility and timing of paediatric formulations development and; 4) renewed momentum to jointly address the challenges that prevent scale up of treatment for children and adolescents. For these reasons the WHO convened a PADO virtual meeting to review the PADO3 priority list proposed in 2016 and reflect on its implementation through 2017.

This review was also held to consider alignment with the agenda of the drug optimization priority list for adults following the outcomes of the Third Conference on Antiretroviral Drug Optimization (CADO 3) meeting held in November 2017 in South Africa. In anticipation of the next WHO Guidelines review process (planned for Q2 2018) this PADO meeting offered a strategic opportunity to review how the "PADO vision" translates into potential changes to the WHO recommendations for paediatric first and second line antiretroviral treatment (ART).

In this context, the overall objectives of the meeting were:

1. Review the PADO3 list and develop key considerations for its implementation

2. Identify remaining research gaps to inform implementation of the PADO 3 list

3. Provide formal advice to the 2018 WHO Guidelines review process on the use of ARVs in paediatrics

See agenda and list of participants in Annexes.

PADO3 implementation: progress and remaining hurdles in a fast-changing environment

Policies to start ART as early as possible are in place globally, but less than half of all children living with HIV are receiving treatment (43% vs 54% adults). Despite major advances in antiretroviral drug development for adults, paediatric treatment is often provided with suboptimal drug regimens and formulations. More than 50% of the children globally on ART are still receiving nevirapine (NVP)-based regimens despite the high level of HIV drug resistance (HIVDR) reported in many countries in Sub-Saharan Africa, particularly among the youngest children[i]. Poor adherence, as a result of lack of child-friendly formulations, and the continued use of NVP-based regimens in the face of high levels of HIV resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) are likely to be the major contributors to the lower virologic suppression in children compared to adults, as recently reported by the Population-Based HIV Impact Assessments (PHIAs) undertaken in several African countries, which suggest that virologic suppression is lowest in children under 5 years of age[ii]. This reminds us that better drugs in age appropriate formulations are urgently needed and that the

market for such drugs will continue to increase in the foreseeable future as a result of accelerated efforts to scale-up diagnosis and treatment for children and adolescents.

Significant progress has been made by better coordinating and aligning different work streams from prioritization of products all the way to product development, selection and introduction. However, efforts to support paediatric drug optimization need to be faster, more efficient and more sustainable. With this in mind, a new framework was developed over the past year: The Global Accelerator for Paediatric Formulations (GAP-f). This framework has the objective of better connecting and streamlining an array of existing efforts and actions to accelerate research, development, introduction and procurement of new products. The GAP-f will rely on using innovative financing mechanisms to ensure that each step in the cascade is adequately funded in a timely manner[iii]. As part of this, members of the PAWG have identified innovative approaches to ensure that the research that is undertaken will inform a faster drug and formulation development[iv]. Adoption of these innovative approaches will be increasingly facilitated by a closer interaction between the Paediatric ARV Working Group (PAWG), industry and regulators. Over the past year, the PAWG has initiated an active review of existing antiretroviral drug Paediatric Investigation Plans (PIPs) with the goal of providing input to PIP development and revision at earlier stages.

Meanwhile, through coordinated partner work, progress was also made in the proportion of optimal formulations being selected and procured by countries. However, more effective action is needed to phase out the use of NVP based regimens such as zidovudine/lamivudine/NVP (AZT/3TC/NVP) in favour of regimens containing lopinavir/ritonavir (LPVr) as a heat stable child-friendly oral solid formulation is now available for children under 3 years. Unfortunately, limited manufacturing capacity by the single generic drug supplier for LPVr pellets has resulted in delays in introduction and procurement of LPVr pellets by countries. While, capacity is expected to improve in the next year and other similar ARV products are anticipated to come to market, this need to be urgently addressed.

Other key updates for 2017 include:

- Rapid introduction of dolutegravir (DTG) in a co-formulated fixed-dose combination (FDC) tenofovir/lamivudine/DTG (TLD) product for adults and adolescents, which has been accelerated by a reduced price agreement: TLD is now available at $6.25 for 30 day supply[v].
- CADO 3 clarified direction in adult treatment optimization (Nov 2017).
- Approval of DTG by the European Medicines Agency (EMA) for children >6 years and weighing at least 15 kg (Dec 2016)[vi].
- Raltegravir (RAL) granules approved in neonates >37 week of gestation and weighing > 2 kg (Nov 2017)[vii].
- Emtricitabine/tenofovir alafenamide (F/TAF) and elvitegravir/cobicistat/F/TAF (E/C/F/TAF) now approved for children 6-12y ≥ 25 kg (U.S. Food and Drug Administration [FDA] & EMA).
- LIVING study results confirm the tolerability and efficacy LPVr oral pellets (by DNDi/Unitaid, ICASA)[viii].
- 4-in-1 co-formulation of Abacavir/3TC/LPVr (ABC/3TC/LPVr): The Pathfinder study showed bioequivalence between the 4-in-1 FDC granules vs the AbbVie LPV/r tablets, and ViiV ABC/3TC tablets (two additional pivotal bioequivalence studies in fed and fasted status will be conducted in early 2018) (by DNDi/Unitaid).
- Paediatric ABC/3TC/efavirenz (ABC/3TC/EFV): two companies plan to submit regulatory files in 2018 and a plan for country uptake being discussed with countries with high volume of paediatric patients in need of ART (by MPP/Unitaid).
- A request for proposal to support development of DTG 10 mg dispersible scored tablet launched (by CHAI/Unitaid) [ix].

All this progress will benefit from a renewed political momentum which was catalysed by a high-level consultation co-convened by PEPFAR, UNAIDS and the Holy See held in Rome on Nov 17, 2017.

This consultation resulted in concrete commitments by UN agencies, regulators, industry, implementing partners and donors to FOCUS, ACCELERATE and COLLABORATE to expedite development and introduction of paediatric ARVs. An action plan[x] was launched on Dec 1, 2017 and WHO and the Elizabeth Glazer Pediatric AIDS Foundation (EGPAF) will monitor its implementation under the AIDS FREE initiative.

Key actions include:

- Focus development efforts on PADO priorities;
- Revise paediatric development plans to investigate WHO weight bands and enrol different weight bands/age groups into PK studies simultaneously;
- Include adolescents in adult trials or investigate them separately but at the same time as adults;
- Waive WHO prequalification fees for paediatric products and accelerate in country registration via collaborative procedures or regional regulatory network;
- RAL and DTG to be provided by innovators at access price until generic production has been initiated and generic drugs are available;
- Accelerate in-country introduction of new drugs and formulations by supporting uptake and procurement.

CADO3 outcomes and key messages

CADO 3 was held in November 2017, with the objective to define the critical research necessary to optimize second- and third-line treatment regimens for adults, the sequencing and recycling of key drugs (e.g. tenofovir prodrugs, DTG, and ritonavir-boosted darunavir [DRVr]) in the context of a public health approach. The discussion was undertaken in light of what will likely be the first-line standard of care in five years' time (i.e. transition to DTG and TAF). The workshop also addressed the needs to ensure products that are safe and effective in some sub-populations (pregnant and breastfeeding women, patients with comorbidities), patients infected with HIV drug-resistant strains, and under conditions where disease monitoring is insufficient and/or contact with health services is infrequent.

The growing evidence provided by programme data on safety of DTG in 1st line, particularly from Botswana, Brazil and some small European cohorts was discussed and supports further expansion of DTG as a preferred first-line ART option. This drug however should not be viewed as a "magic bullet" to solve adherence problems, and its role in second-line ART and as a substitution in stable patients on use of EFV-based ART regimens, is still debatable. Low-dose EFV was viewed as an alternative first-line ART option for those who cannot tolerate DTG or where DTG cannot be accessed because of cost/patent issues. There was insufficient evidence to fully support two drug combination strategies for adults (e.g. DTG/rilpivirine (RIL), DTG/DRVr, DTG/3TC, DRVr/3TC) given current clinical trial data, as the recent/ongoing simplification studies with this approach have not been designed considering the low and middle-income country (LMIC) context, and are missing important subpopulations (e.g. pregnant women, TB and HBV co-infections). Significant additional clinical research with focus on LMIC reality would be needed if current studies of two-drug regimens in adults prove to be promising.

A prioritized list of research questions was established (Fig. 1). Clinical studies, on sequencing and recycling of tenofovir disoproxil fumarate (TDF) and TAF as well as on the role of DTG in patients who previously failed NNRTI-based ART regimens, were defined as key priorities. The availability of DRVr as a heat stable formulation and at a price similar to LPVr (expected by end of 2018), was viewed as an opportunity to transition to this protease inhibitors (PI) as the preferred option for second-line in the near future. Dose optimization studies on use of low dose DRVr in second-line patients were also identified as a key priority. Use of orally and parenteral administered long-acting drugs as well as nanoformulations and implantable devices were viewed as the optimal approach for future treatment options, and the need to continue their development was considered a priority.

Furthermore, CADO3 recommended that all these studies should be designed to reflect the realities of populations currently enrolled in treatment programs (including pregnant and breastfeeding women, women of child-bearing age, patients with TB coinfection and with other co-morbidities). These studies need to expand community participation and consider regulatory/intellectual property incentives.

CADO 3: Remaining research questions

Clinical studies on sequencing and recycling of TDF and TAF

- Switching from TDF to AZT (SoC) versus maintaining TDF in 2L after failing a TDF regimen in 1L
- Retrospective resistance testing

Clinical studies on use of DTG in 2L patients who failed to EFV vs 2 NRTI + PI (SoC)

- Consider factorial on NRTIs use
- Clinical data to support whether DTG boosting is necessary for rifampicin containing co-administration (in HIV/TB patients)
- If programmes implementation before RCT results : enhanced monitoring protocol and only proceed if good access to VL monitoring; organize result monitoring to gather real data

Dose optimization study on use of low dose DRVr in 2L patients

- DRV/r 400/100mg OD versus DRV 800/100mg OD (SoC)
- Consider factorial on NRTIs used

All studies should reflect real characteristics of people in treatment programs (eg: pregnant & women of child-bearing age, TB co-infection and other co-morbidities)

- Consider to include community participation and regulatory/IP incentives

Figure 1 Main recommendations of the CADO 3 meeting

Based on the trends in ARV optimization discussed at the meeting, a list of priority optimized products and formulations to be developed by drug manufacturers were defined for the short-term, medium term and long-term (Fig.2). Products listed as lower priority can be considered if new data become available in the future.

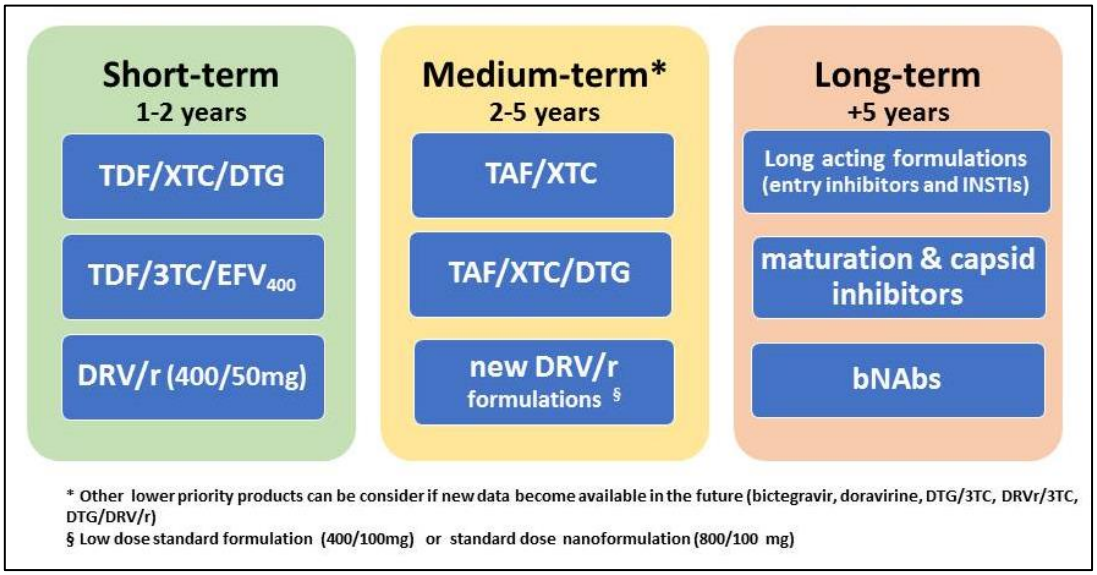

Figure 2 Key priority products for use in adults living with HIV

PADO 3 Implementation: Internal prioritization to maximize impact

In order to further support suppliers and focus their resources in developing products that are most needed and more age- and weight-appropriate, a small group of the PAWG convened to identify the

best way to approach the PADO list of priority products, with the aim to provide manufacturers with a clearer and more concise direction.

Based on a Pugh decision matrix which scores a list of options (in this case ARV products) according to a set of weighted criteria, a technique was developed to further refine the prioritised list of PADO products. This approach combines a critical set of draft criteria, defined by the group, integrating additional time-based parameters that are constantly evolving (e.g. time for collecting clinical data sufficient to launch at-risk product development with generic suppliers, product development and regulatory reviews). Each product was then ranked against the criteria and the time-based parameters were incorporated.

This algorithm was tested by comparing a real-time setting in which some products are far along the development process (for example, 4-in-1 pellets) to a setting assuming no work has been done on any product yet. This exercise provided useful information that might help manufacturers to further focus their efforts in the product development process, staging the prioritised PADO3 list with a more realistic timeframe and targeting products identified as higher priority according to their score and level of importance.

The group believes that this structured approach would provide further level of clarity on priority products and accelerate the time-to-market for all products by staging efforts across suppliers. However, more work needs to be done with a larger group of stakeholders (e.g. Paediatric HIV Treatment Initiative [PHTI], additional clinicians from PAWG, etc) in order to agree and finalise the list of criteria and scoring system, at CROI or on future PAWG calls. The goal is to present the finalised tool and staging of the PADO3 list at AIDS 2018 in July 2018.

PADO 3 key considerations for implementation

The group proceeded with reviewing the key principles for target product profile and implementation of each mid-term product included in the PADO3 list. The product review was undertaken to check on the status of development, review dosing and ratio recommendations and provide prioritization level relative to other PADO3 priorities in light of current feasibility and potential information gaps.

1. Target product profile

The group agreed to maintain the general principles defined in PADO 3: 1) triple FDC to be preferred but not required, since such a requirement could prevent rapid introduction of new drugs while waiting for the ideal triple FDC; 2) crushable, chewable or dispersible solid oral dosage forms to be considered the most desirable (exceptions to be defined on a case by case basis).

Emphasis was placed on the first principle and the need to highlight the urgency for new drugs to rapidly become accessible for children (even if not immediately in the ideal FDC). This is particularly relevant for desired formulations that would combine drugs developed by different innovators, which may not be possible in the short-term. This conversation highlighted also the importance of discussing formulations on a case by case basis with the goal of maximizing the speed of introduction of any new drug and potentially acknowledging the advantage of a staged approach (from using single-drug products as developed by the innovator to single-drug generic products to the development of the ideal generic FDC).

2. Review of mid-term priorities

Dolutegravir-containing formulations: DTG and DTG/ABC/3TC

DTG single strength and an FDC of DTG/ABC/3TC were reviewed in parallel to ensure alignment with dosing assumptions. The group reviewed the dosing currently approved by US FDA and EMA, as well as the dosing under investigation by two key paediatric clinical trials IMPAACT P1093 and ODYSSEY/PENTA-20. Since some uncertainty about dosing still exists for children below 30 kg (and particularly for children below 15 kg), the group discussed future options based on a hypothetical scenario, which represents slightly revised dosing by WHO-weight bands compared to the one identified by PAWG in 2016 (figure 3). This hypothetical scenario is supported by the well-established notion that for many drugs a higher mg per body weight is required in small children to reach same exposure levels as observed in adolescents and adults. Additional support for this approach comes from increased confidence in the safety and tolerability of higher doses of DTG based on adult twice daily dosing.

WHO Weight (kg)	Hypothetical future scenario	Branded DTG	Generic ABC/3TC 120/60 mg	Generic DTG	Branded (initially) and Generic Triple FDCs
Neonates	n/a				n/a
3 to <6	10 mg	2 DT5*	1 (120/60)	**1 DT10**	2 ALD (120/60/10)
6 to <10	15 mg	3 DT5*	1.5 (180/90)	**1.5 DT10**	3 ALD (180/90/15)
10 to <14	20 mg	4 DT5*	2 (240/120)	**2 DT10**	4 ALD (240/120/20)
14 to <20	25 mg	1 FCT25	2.5 (300/150)	**0.5 ST50**	5 ALD (300/150/25)
20 to <25	25 mg	1 FCT25	3 (360/180)	**0.5 ST50**	6 ALD (360/180/30)
25 to <35	50 mg	1 FCT50	600/300 mg	**1 ST50**	TLD (TDF?)
>=35	50 mg	1 FCT50	TDF/XTC	**1 ST50**	**TLD**
>=40	50 mg	1 FCT50	TDF/XTC	**1 ST50**	**TLD**

5 mg dispersible tablets = DT5* (to be approved)
25 mg film coated tablets = FCT25
50 mg film coated tablets = FCT50
300/300/50 mg film coated tablets = TLD

10 mg scored dispersible tablets = DT10
50 mg scored tablets = ST50
60/30/5 mg dispersible tablets = ALD
300/300/50 mg film coated tablets = TLD

Figure 3 Illustration of dosing schedule using existing and future formulations based on hypothetical dosing scenario to be confirmed by P1093 and ODYSSEY trial results. (ALD= Abacavir/lamivudine/dolutegravir).

The group agreed that, should the hypothetical dosing scenario be confirmed, **DTG 10 mg scored dispersible tablets would be the best dosage form to be developed**, pending demonstration that the scored tablets can adequately meet standard regulatory requirements (in terms of uniformity of dosing and product stability). A minimum dose of 5 mg DTG could be considered for administration of DTG in neonates; studies are currently being planned to investigate dosing in this difficult-to-dose age group. The group noted that if WHO guidelines are revised in March 2018 to extend use of DTG to children older than 6 years and weighting at least 15 kg this **will initially require use of DTG 25 mg film coated tablets which are currently produced by the innovator but that these should be replaced by generic 50 mg scored tablets as soon as possible.** Barriers to the existing regulatory pathway for this product (scored generic 50 mg tablets) are expected to be rapidly resolved as soon as a 25 mg dose is approved by the US FDA. **It should be noted however that the WHO prequalification programme has invited submission from generic companies for development of DTG 50 mg scored tablet through inclusion of this product in their Expression of Interest (EOI) list, therefore this alternative regulatory pathway could be already considered.**

It was also agreed that the current recommendation for development of ABC/3TC/DTG 60/30/5 mg fixed-dose dispersible tablets remain the most likely appropriate dosage form based on the best available information; however, the group strongly emphasized the importance of validating this

dosing and ratio as soon as final dosing for DTG is approved down to 4 weeks of age, and of the need to communicate to generic manufacturers the need for this validation. Scored tablets with doubled-strength of each component drug (ABC/3TC/DTG 120/60/10 mg) would enable reduction of the pill burden for children, but difficulties with assuring accuracy of dosing when scoring a triple-drug FDC will need to be addressed. **Importantly, manufacturers interested in developing ABC/3TC/DTG could start development of a prototype, but will need to delay advancing their development plans until the dosing and the ratio are confirmed (expected in Q4 2018).**

Members of the group discussed the possibility of extending the use of the currently available TLD fixed-dose formulation down to 25 kg, in light of the dosing currently investigated in ODYSSEY, that would support use of DTG 50 mg in children weighing down to 25 kg. However, the group felt there is **insufficient evidence to support the use of 300 mg TDF in children and adolescents weighting 25 to 30 kg, and recommended use of separate DTG 50 mg tablets plus ABC/3TC 600/300 mg FDC tablets in these patients. Generation of safety data on the use of 300 mg TDF in this weight-band, with a focus on renal toxicity, may in the future allow use of TLD at these lower weights.**

Tenofovir Alafenamide -containing formulations: F/TAF and DTG/F/TAF

TAF paediatric development programme remains incomplete. TAF is only approved for children at least 6 years old and weighing more than 25 kg (TAF 10mg is approved as part of Genvoya® for children above 25 kg and TAF 2 5mg is approved as F/TAF as part of Descovy® for children above 35kg; Descovy® is also approved for 25-35 kg kids taking ARVs without boosted PI), but approved dosing for children under 6 years old is not available yet and investigation of a formulation for these younger children has only recently been started due to delays resulting from the challenges with taste–masking of the current formulation. While the originator has committed to completing their studies by late 2018/early 2019, there are concerns that these timelines will need to be extended further. **The PADO group agreed on the urgent need to re-discuss this with the originator to explore ways for accelerating the work. In the meantime, the group encouraged preliminary feasibility work to be undertaken by generic manufacturers for paediatric DTG/XTC/TAF development. This should happen in close communication with WHO, PAWG and other PHTI partners.**

Boosted Darunavir-containing formulations: DRVr 120/20 mg tablets and DRVr/DTG

Dosing and ratio recommendations for the development of a DRVr FDC have existed since 2015, when the PAWG reviewed the modelling information shared by the innovators and confirmed 120/20 mg to be appropriate dosage form to be developed (a double-strength scored tablet was expected to be unfeasible due to inability to score/cut tablets manufactured using hot melt extrusion technology). Unfortunately, despite inclusion in the PADO and EOI lists, this formulation has not generated any interest among manufacturers so **CHAI is currently exploring options for incentivizing this development as part of their Unitaid supported Optimal ARV project.**

The DTG/DRVr formulation is a recent inclusion to the PADO 3 list that was justified by the potential use of this regimen in third-line ART, based on current WHO guidelines, and possible future indication for this regimen in second-line ART or simplification strategies (currently investigated in the PENTA 17 trial). Recent preliminary interaction with manufacturers suggested that this FDC may be difficult to develop. For this reason, the **group agreed to de-prioritize for now the development of DTG/DRVr** and to gather more information in order to re-assess its inclusion in the PADO list in 2018. This may include exploring opportunities for co-packaging instead of co-formulation.

Raltegravir: 50 mg scored

Dispersible paediatric tablets of RAL are at very early stages of development by one generic manufacturer. There is therefore the opportunity to re-evaluate whether the 50 mg scored dosage form that PADO previously recommended is the appropriate form for the expected use of the drug in the near future. With the introduction of DTG in older children, the most strategic use of RAL moving forward is likely to be for treatment of neonates since studies with DTG in neonates have not started yet and it may take 3-5 years before dosing for neonates is approved and an appropriate formulation available. RAL could be used for treatment in this population but may also have use for postnatal prophylaxis (PNP) as well. In this context of envisioned future use of RAL primarily in the youngest age, **the group agreed that development of a 5 mg scored dispersible/crushable tablet formulation would be more appropriate.**

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing †	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily
*The dosing recommendations are based on approximately 1.5 mg/kg/dose. †The dosing recommendations are based on approximately 3 mg/kg/dose.	

Figure 4 Approved and simplified RAL dosing schedule as considered by the group

The group discussed whether re-packaging of the existing granule formulation might be an interim solution that could more rapidly enable the use of this drug for neonates, infants and young children until DTG becomes available. This approach is currently being discussed with the innovator, who is also willing to share additional information on the feasibility of mixing the drug with breastmilk and to discuss a packaging that is more user-friendly. This information, together with more clarity on timelines, market size and potential availability of incentives, will be critical to **re-assess the inclusion of the 5 mg scored RAL tablets formulation in the PADO list at the next revision.**

Enhanced postnatal prophylaxis formulation: AZT/NVP (7.5mg/15mg)

This formulation is included in the PADO list to deliver enhanced PNP for high-risk HIV-exposed infants. No generic development of this product has been initiated, but several discussions have taken place in the PAWG. The PAWG has identified the best dosing and ratio as AZT/NVP 7.5mg/15mg. Countries are currently delivering PNP by combining oral solution formulations or by using ¼ of a FDC AZT/3TC/NVP dispersible tablet formulation. The main barrier to developing this product is identifying a regulatory pathway to be used when no reference product is available and neither NVP nor AZT/NVP have an stringent regulatory authority (SRA)-approved indication for prophylaxis as opposed to treatment. Re-packaging with the use of the Pratt pouch has been excluded due to the limited volume of the pouch and challenges of mixing the drugs.

The group recognized that **the AZT/NVP 7.5/15 mg formulation is a priority, but probably less urgently needed than other products such as DTG single-strength tablet and DRVr formulations**. Concerns also remain with continuing to use NVP in the longer-term, given that use of NVP for treatment is decreasing rapidly and hence the drug will become less available. Some of the related questions and barriers will need to be reviewed carefully and re-discussed in PADO 4 for a final decision.

World Health Organization

Informing WHO guidelines revision

Use of Dolutegravir in first-line ART

The group reviewed current approvals for DTG in children and ongoing WHO-weight band dosing investigated in the ODYSSEY/PENTA-20 trial (PK data available by May). The principle that efficacy data should be extrapolated from adults and that availability of dosing and safety data from studies in infants and children is sufficient for inclusion in treatment guidelines was reconfirmed. The group also noted that rapid access to DTG may be enabled by existing commitments by innovators and other key stakeholders (CHAI, Unitaid, PEPFAR). In this context, the **PADO group agreed to advise the WHO Guidelines Development Group (GDG) (meeting in May 2018) to extend the use of DTG as preferred first line regimen for children older than 6 years and weighing more than 15 kg.** This potential recommendation should be conditional to availability and review of DTG PK data from the ODYSSEY trial in support of WHO-weight-bands dosing for this group of children. Further expansion of DTG use in even lower weight-bands will depend on completion of IMPAACT P1093 and ODYSSEY PK sub-studies, these data will be important to review in Q1 2019.

The group reconfirmed preference for combining DTG with an ABC/3TC NRTI backbone and acknowledged the importance of ensuring **that rapid introduction of DTG is coupled with robust national systems for enhanced monitoring of toxicity in children** (WHO is currently working with partners to set up those systems, but it will be critical to use data from observational cohorts as these systems are being strengthened). The group also discussed the use of DTG in children requiring **TB-co treatment and agreed that, DTG double-dosing, which has been tested in adults with TB co-infection, should also be appropriate for children, but review of paediatric-specific data on co-administration will be important** (ODYSSEY trial will provide that data-likely available in 2018). Until more data is available, children should switch from DTG-based to EFV-based ART while receiving rifampicin-containing TB treatment.

The PADO group discussed the possibility of switching children that are currently stable on other regimens to a DTG-based regimen. For adults, WHO currently sees viral load (VL) monitoring prior to switch as a good practice. However, this is still a matter of debate in light of the potential barrier that this may pose to optimal use of DTG in populations that don't have access to routine VL monitoring but may well be by and large well suppressed virologically, as demonstrated by data from PHIAs from several African countries. **The PADO group was in favour of enabling a switch to DTG-based ART for those children who are stable (as defined by national standards to assess treatment failure) on EFV, NVP or LPVr-based first-line regimens and considers VL monitoring prior to switching as a good practice but not a pre-requisite to avoid delays with switching where VL monitoring is not routinely available**. The group was also comfortable with the vision of the CADO3 group and agreed that it would **be important to advocate for implementation studies to assess how this may work in clinics in low and middle income countries.**

Use of RAL in first-line ART for neonates and children less than 6 years

Use of RAL from birth has recently been approved by the US FDA. Low birth weight and premature babies are not included in most recent approvals but are currently under study by the IMPAACT network, and data will become available in the next one to two years. The limited ARV drug options available for the first 4 weeks of life are well known, as are the challenges of using LPVr oral solution (which can only be used after 2 weeks of age). Use of RAL in neonates would provide a more potent regimen (particularly compared to NVP in the context of increasing rates of NNRTI resistance observed in newly-infected infants) and potentially a more practical option (compared to LPVr oral solution) for programmes that are currently able to undertake nucleic acid amplification test (NAT) at birth and can initiate treatment in the first 4 weeks of life. Of note, WHO already recommends

RAL as an alternative option for first-line use in children younger than 3 months where LPVr pellets cannot be used.

The group acknowledged remaining concerns on the challenging administration of RAL granules in LMIC, the limited access and cost of RAL (even though there is now commitment by the innovator to provide RAL paediatric formulations "at cost"), the current limited access to LPVr pellets as well as the timeline required for introduction of new FDCs such as 4-in-1 granules (ABC/3TC/LPVr) and ABC/3TC/EFV.

The PADO group agreed that, despite lack of comparative efficacy data and the challenges with using RAL granules, the WHO Guidelines Development Group should consider recommending RAL for first–line ART in neonates (0 to 4 weeks of age) upon careful consideration of its feasibility in LMIC. In this infants use of RAL could continue beyond 4 weeks until LPVr pellets can be easily used (3-6 months of age).

This recommendation could be extended to infants starting ART after 4 weeks of age, if RAL chewable crushable tablets are available. However, the group was concerned that because data on DTG dosing in young children and infants will be available in the near future, issuing a time-limited recommendation for RAL use in infants >4 weeks could have a negative impact on paediatric ARV procurement, supply management, and program implementation. Feasibility of this option will also depend on in-country registration of RAL. Members of the group also expressed concerns on the lack of data for dosing RAL in children on TB co-treatment and on whether potential selection of integrase inhibitors resistance (given the low genetic barrier of RAL for resistance development) could compromise or complicate (i.e. require twice daily dosing) subsequent use of DTG for second-line ART. For these reasons **PADO advises the GDG to consider RAL only as an alternative option but not as a preferred first line regimen for children starting ART between 4 weeks to 6 years of age.**

Use of Dolutegravir in second-line ART

While definitive evidence on the efficacy and safety of DTG use as second-line ART for children will become available from the completion of the ODYSSEY trial (estimated 2020), data from the DAWNING trial suggests that DTG is superior to LPVr when combined with an optimized background regimen (OBR). **The group agreed that, once appropriate DTG dosing is confirmed, DTG in combination with OBR should be considered by the GDG as the preferred second-line ART regimen for all children failing LPV/r or NNRTI-based in first-line ART for whom DTG dose is approved.** Use of DTG-based second–line ART following failure of RAL-based first-line ART should be further discussed based on available evidence in adults.

Previous PADO recommendations to use DRVr-based second-line ART following failure on DTG-based first-line ART is still reasonable but more discussion may be required as more data is generated in adults and children. Overall alignment of paediatric ART approaches with those defined for adults will remain desirable.

Enhanced postnatal prophylaxis

The currently recommended enhanced PNP regimen of AZT/NVP for prevention of mother to child HIV transmission in high risk infants has been difficult to implement; simplified approaches include use of the triple FDC AZT/3TC/NVP or extension of enhanced prophylaxis to all infants irrespective of risk stratification. These strategies may have potential impact on the limit of detection of NAT assays at different time points and various scenarios will need to be carefully considered. WHO is planning to convene a technical consultation in April 2018 that will shed light on these complex issues and better inform future strategies to deliver efficacious, safe and practical PNP in LMIC.

Research gaps and next steps

Although research to address the key gaps highlighted in PADO3 is ongoing, many questions remain unanswered. The PADO3 research priorities were broadly confirmed by the WHO/CIPHER research prioritization exercise[xi], which reached a broad set of stakeholders in many countries. The WHO/CIPHER process emphasized the need to explore new drug delivery systems for children and adolescents as well as to better investigate pharmacokinetics of the priority ARV drugs to inform paediatric formulations development. **Additional questions that emerged from the virtual discussion include:**

- Need to better define renal toxicity of TDF 300 mg in children 25-30 kg;
- PK data for dose reduction of DRVr;
- Efficacy of DTG in second line for failures on RAL-based first-line ART;
- PK data to support the use of TAF and DRVr in children on TB treatment;
- Efficacy and safety of alternative regimens for PNP.

A list of research priorities will be reviewed by the PADO group for more detailed considerations.

The key messages from the virtual discussion will be disseminated in early 2018 **to industry and relevant stakeholders**, particularly in the context of the broader follow up to the high level meeting held in Rome. WHO will collaborate with the International AIDS Society (IAS) Industry Liaison Forum (ILF) to convene **webinars to further disseminate the PADO 3 implementation considerations** agreed in this virtual meeting and will share the PADO recommendation with the GDG members that will revise ARV guidelines in May 2018. The **PADO prioritization tool will be further discussed** in dedicated meetings around CROI 2018 and AMDS 2018 to enable finalization by July 2018 and used during the next PADO revision.

PADO 4 is expected to be held in Q4 2018 and until then the PAWG will continue to refine dosing recommendations, interact with industry and regulators to accelerate ongoing paediatric investigation plans, and follow up on specific issues with bimonthly calls. These efforts will all contribute to further refine the concept of GAP-f and enable its implementation to accelerate research, development and introduction of priority paediatric ARV formulations.

Annex 1. Agenda of the teleconference held on December 12th, 2017.

12 December 2017		
13:45-14:00	Connection	
14:00-14:10	Welcome and overview of meeting objectives and agenda	Meg Doherty
Session 1: Updates and critical review (chair George Siberry)		
14:10-14:20	PADO 3 Implementation: Progress and remaining hurdles in a changing environment	Martina Penazzato
14:20-14:40	CADO 3 outcomes: What's on the horizon for adult drug optimization?	Marco Vitoria
	Q&A	All
14:40-14:50	PADO 3 Implementation: Internal prioritization to maximize impact	Melynda Watkins
14:50-16:00	Structured discussion – Target product profile review – PADO3 review (Pending issue? What next?) o DTG containing formulations o TAF containing formulations o DRVr o RAL o NVP/AZT	
16:00-16:20	***Break***	
Session 2: Informing WHO Guidelines revision (chair Elaine Abrams)		
16:20-16:30	Preparing the ground for the next Guidelines revision – DTG for children – RAL for neonates – Second line options – Postnatal prophylaxis	Martina Penazzato
16:30-18:00	Discussion	
Session 3: Next steps		
18:00-18:10	Remaining evidence gaps: the PADO research agenda	Marissa Vicari
18:10-18:30	Next steps and Closing remarks	Martina Penazzato and Meg Doherty

Annex 2. List of Participants.

Elaine Abrams Columbia University, School of Public Health New York, USA eja1@columbia.edu	**Gloria Anyalechi** U.S Centers for Diseases Control and Prevention Atlanta, USA iyo8@cdc.gov
Isabelle Andrieux-Meyer DNDi Geneva, Switzerland landrieux-meyer@dndi.org	**Moherndran Archary** University of KwaZulu-Natal. Durban, South Africa archery@ukzn.ac.za
Yodit Belew US Food and Drug Administration Washington DC, USA Yodit.Belew@fda.hhs.gov	**Carolyn Bolton-Moore** Centre for infectious Disease Research Lusaka, Zambia Carolyn.Bolton@cidrz.org
David Burger Radboud University Nijmegen Medical Centre Nijmegen, Netherlands David.Burger@radboudumc.nl	**Edmund Capparelli** University of California San Diego, USA ecapparelli@ucsd.edu
Deborah Carpenter U.S. Centers for Diseases Control and Prevention Atlanta, USA vgp7@cdc.gov	**Diana Clarke** Boston Medical Center Boston, USA diana.clarke@bmc.org
Polly Clayden HIV i-Base London, United Kingdom Polly.clayden@i-base.org.uk	**Ray Corrin** WHO Prequalification Team Geneva, Switzerland ray.corrin@gmail.com
Mark Cotton Stellenbosch University, Tygerberg, South Africa MCOT@sun.ac.za	**Timothy R. Cressey** Program for HIV Prevention and Treatment (PHPT-IRD-174), Harvard T.H. Chan School of Public Health & Chiang Mai University, Thailand Tim.cressey@phpt.org
Mutsa Dangarembizi University of Zimbabwe Harare, Zimbabwe dangas@zol.co.zw	**Paolo Denti** University of Cape Town Cape Town, South Africa paolo.denti@uct.ac.za
Nonhlanhla Dlamini National Department of Health Pretoria, South Africa Nonhlanhla.Dlamini@health.gov.za	**Andrea Ecker** European Medicines Agency London, UK Andrea.Ecker@ema.europa.eu
Shaffiq Essajee UNICEF New York, USA sessajee@unicef.org	**Carlo Giaquinto** Pediatrics AIDS and Clinical Research Unit. University of Padova, Italy carlog@pediatria.unipd.it
Diana Gibb MRC Clinical Trials Unit London, United Kingdom D.Gibb@ctu.mrc.ac.uk	**Rohan Hazra** National Institute of Child Health and Human development Bethesda, USA hazrar@mail.nih.gov
Mansoor Khan Texas A&M University Rangel College of Pharmacy Texas, USA Mkhan@pharmacy.tamhsc.uk	**Maria Grazia Lain** Fundação Ariel Glaser Maputo, Mozambique liongr@yahoo.it
Marc Lallemant Chiang Mai, UMI 174 PHPT, Chiang Mai University Chiang Mai, Thailand	**Lana Lee** U.S. Agency for International Development Arlington, USA

mlallemant@dndi.org	llee@usaid.gov
Linda Lewis Clinton Health Access Initiative Boston, USA llewis.ic@clintonhealthaccess.org	**Christine Malati** U.S. Agency for International Development Arlington, United States cmalati@usaid.gov
Helen McIlleron University of cape Town Cape Town, South Africa Helen.mcilleron@uct.ac.za	**Anita Mesic** Medecins Sans Frontieres Amsterdam, Netherlands Anita.Mesic@amsterdam.msf.org
Sebastien Morin International Aids Society Geneva, Switzerland sebastien.morin@iasociety.org	**Mark H. Mirochnick** Boston Medical Center. Boston, US. Mark.Mirochnick@bmc.org
Lynne Mofenson Elizabeth Glaser Pediatric AIDS Foundation Washington DC, USA mofensol@gmail.com	**Mireille Muhimpundu** The Global fund Geneva, Switzerland Mireille.Muhimpundu@theglobalfund.org
Victor Musiime Joint Clinical Research Centre Kampala, Uganda vmusiime@jcrc.org.ug	**Eleni Nastouli** University College London London, UK e.nastouli@ucl.ac.uk
Elizabeth Maleche Obimbo University of Nairobi Nairobi, Kenya eobimbo@yahoo.com	**Atieno Ojoo** UNICEF Copenhagen, Denmark aojoo@unicef.org
Fernando Pascual Medicine Patent Pool Madrid, Spain fpascual@medicinespatentpool.org	**Carmen Perez Casas** UNITAID Geneva, Switzerland perezcasasc@who.int
Jorge Pinto Federal University of Minas Gerais, Belo Horizonte, Brazil jorgeandradepinto@gmail.com	**Natella Rakhmanina** Elizabeth Glazer Paediatric AIDS Foundation Washington DC, United States nrakhmanina@pedaids.org
Pablo Rojo Hospital de 12 Octubre Madrid, Spain pablorojoconejo@netscape.net	**Theodore Ruel** University of California San Francisco California, USA Theodore.Ruel@ucsf.edu
Agnes Saint-Raymond European Medicines Agency London, United Kingdom Agnes.Saint-Raymond@ema.europa.eu	**George Siberry** OGAC, US Department of State Washington DC, United States SiberryGK@state.gov
Nandita Sugandhi ICAP at Columbia UniversityNew York, USAnss14@cumc.columbia.edu	**Cheick Tidiane Tall** Le réseau EVA Dakar, Senegal cttall@reseaueva.net
Anna Turkova MRC Clinical Trials Unit at UCL, University College London, London, United Kingdom a.turkova@ucl.ac.uk	**Marissa Vicari** International AIDS Society Geneva, Switzerland Marissa.vicari@iasociety.org
Melynda Watkins Clinton Health Access Initiative Raleigh-Durham, USA mwatkins@clintonhealthaccess.org	**Jacque Wambui** **ICW** Nairobi, Kenya jcqwambui@gmail.com

World Health Organization (WHO) Staff	
Meg Doherty Coordinator, Treatment and Care Unit HIV/AIDS and Hepatitis Department dohertym@who.int	**Martina Penazzato** Medical Officer, Treatment and Care Unit HIV/AIDS and Hepatitis Department penazzatom@who.int
Silvia Bertagnolio Medical Officer, Treatment and Care Unit HIV/AIDS and Hepatitis Department bertagnolios@who.int	**Marco Vitoria** Medical Officer, Treatment and Care Unit HIV/AIDS and Hepatitis Department vitoriam@who.int

[i] Jordan et al CID 2017 https://www.ncbi.nlm.nih.gov/pubmed/29020335

[ii] http://phia.icap.columbia.edu

[iii] Penazzato M, Lewis L, Watkins M, Prabhu V, Pascual F, Auton M, Kreft W, Morin S, Vicari M, Lee J, Jamieson D, Siberry G. Shortening the decade-long gap between adult and paediatric drug formulations: a new framework based on the HIV experience in low- and middle-income countries. Journal of the International AIDS Society 2017, 21(S1):e25049 http://onlinelibrary.wiley.com/doi/10.1002/jia2.25049/full (in press)

[iv] Penazzato M, Gnanashanmugam D, Rojo P, Lallemant M, Lewis LL, Rocchi F, Saint Raymond A, Ford N, Hazra R, Giaquinto C, Belew Y, Gibb DM, Abrams EJ; Paediatric Antiretroviral Working Group (PAWG).Optimizing Research to Speed Up Availability of Pediatric Antiretroviral Drugs and Formulations. Clin Infect Dis. 2017 Jun 1;64(11):1597-1603. doi: 10.1093/cid/cix194. https://www.ncbi.nlm.nih.gov/pubmed/29190337

[v] http://www.who.int/hiv/mediacentre/news/high-quality-arv-reduced-price/en/

[vi] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002753/WC500237910.pdf

[vii] http://s2027422842.t.en25.com/e/es?s=2027422842&e=23012&elqTrackId=B1F0B909CCF90C71B9C490C37BFE6647&elq=0a0540c9394140bd920d2e1417e1d90a&elqaid=1486&elqat=1

[viii] https://www.dndi.org/2017/media-centre/events/icasa-2017/

[ix] https://clintonhealthaccess.org/request-proposal-rfp-selection-generic-manufacturer-development-pediatric-dolutegravir-dtg/

[x] http://www.pedaids.org/page/-/Rome_Action_Plan_2017.pdf.

[xi] WHO cipher