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Title: Prioritizing the most needed paediatric antiretroviral formulations: The PADO4 list

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Abstract

Despite significant progress in paediatric HIV treatment, optimal antiretroviral formulations for infants, children and adolescents remain limited. The paediatric antiretroviral drug optimization group regularly reviews medium- and long-term priorities for antiretroviral drug development, to guide industry and other stakeholders on formulations most needed for low- and middle-income countries. Ongoing medium-term priorities include a scored dispersible dolutegravir tablet (10mg), a dolutegravir-containing fixed-dose combination, and fixed-dose combinations containing tenofovir alafenamide. Darunavir/ritonavir combination tablet remain a priority for second-line treatment. Future treatment options of potential interest for paediatrics include broadly neutralizing antibodies, long acting/extended release formulations, and novel technologies. Issues specific to neonatal prophylaxis and treatment, and to the investigation of novel antiretrovirals in adolescents and pregnant and lactating women are also discussed. Continued focus on identifying, prioritizing and ensuring access to optimal formulations suitable for infants, children and adolescents is key to ensuring that global HIV treatment targets can be met.

Introduction

Despite significant progress in scaling up HIV services for children, we are still far from reaching global treatment targets. In 2017, only 52% of children living with HIV received antiretroviral therapy (ART), and more than a third of those on treatment received suboptimal regimens and formulations[1,2]. Rates of HIV viral suppression in infants, children and adolescents on ART are consistently lower than in treated adults[3]. World Health Organization (WHO) guidelines[4] recently recommended more potent and tolerable ART regimens for treatment of infants and children, but optimal formulations to deliver those regimens across the entire age spectrum from birth through adolescence are still lacking. In addition, there are significant gaps in the investigation and use of existing and novel antiretroviral drugs (ARVs) for treating and preventing HIV in adolescents, and pregnant and lactating women[5].

Over the past few years, global stakeholders have come together to enable more focused and coordinated actions to accelerate the availability of optimal age-appropriate formulations for infants, children and adolescents living with HIV[6]. Several new initiatives have been launched and diverse work streams have now been gathered under the collaborative platform of the Global Accelerator for Paediatric formulations (GAP-f)[7]. The work of GAP-f takes identified priority products through the entire product life-cycle by facilitating key steps to investigate, develop and introduce the most needed paediatric medicines. The WHO-led Paediatric Antiretroviral Drug Optimization (PADO) group establishes and reviews medium- and long-term priorities for drug development and sets the foundation for GAP-f in the areas of paediatric HIV treatment and prevention[7]. Since its inception in 2013[8], PADO has provided an evidence-based list of priority products and a clear and consistent message to guide industry and interested stakeholders on the formulations most needed to be developed for use in low- and middle-income countries (LMIC). This list has eliminated a number of unnecessary formulations and continues to be a critical tool to focus efforts and resources[9,10].

WHO recently convened a fourth meeting on paediatric drug optimization, PADO4, to assess the progress made, evaluate current and future needs, and further advance the paediatric and adolescent ARV optimization agenda[11]. This meeting review and revise the list of medium- and long-term priorities for paediatric ARV drug and formulation development and identify research gaps for HIV, as well as for prevention and treatment of HIV-associated infections. In this edition, the PADO group paid special attention to adolescents with the goal of addressing their needs in the context of the care continuum. While treatment recommendations for adolescents now fully align with those for adults, delays and gaps remain in the investigation of new ARVs[12] in this population. For this reason, the group discussed how to develop better mechanisms to facilitate enrolment of adolescents in adult drug development studies and to accelerate access to suitable novel treatment strategies.

Due to the important intersection between maternal and child health when considering use of ARVs in pregnant and lactating women, PADO4 also provided the opportunity to review gaps and challenges in investigating ARVs in this population. The goal was to identify key principles to guide more targeted and accelerated generation of critical data to increase access to safe and efficacious ARVs for pregnant and lactating women, in alignment with the treatment optimization research agenda that has been established for adults[13].

Here we summarize the updates reviewed by the PADO4 group and describe the key considerations made in updating the list of priority products for prevention and treatment of HIV in infants, children and adolescents. We also summarize existing research gaps and highlight important principles for future work to accelerate investigation of new ARVs for pregnant and lactating women as well as of medicines to prevent and treat HIV-associated infections in children and adolescents.

Methods

Paediatric HIV researchers, clinicians, programme managers, regulators and other stakeholders involved in developing and introducing paediatric ARVs in LMICs were invited by WHO to the fourth

edition of the PADO meeting[8,9,10]. The meeting was held on 10-12 December 2018 in Geneva, Switzerland, with participants representing more than 15 countries. PADO4 particpants were identified from existing WHO expert advisory groups (i.e., Paediatric ARV Working Group, Adult ARV working group, HIV Drug Resistance Network-Resnet) and from established partnerships in the area of ARV drug optimization (i.e., GAP-f, Paediatric HIV Treatment Initiative, ARV Procurement Working Group) as well as from HIV programmes in countries with a high burden of paediatric HIV such as South Africa, Zimbabwe, Mozambique, Kenya and Malawi. The PADO4 group included internationally recognized experts with published expertise in the populations of interest (infants, children, adolescents, pregnant and lactating women) and detailed understanding of the programmatic challenges.

During plenary sessions the group reviewed key updates supported by a summary of the literature gathered prior to the meeting. Workgroup sessions (n=4) were organized to allow review of the PADO list and in depth discussions of specific issues to be considered. Separate sessions (n=3) were dedicated to discussing pregnant and lactating women and adolescents as well as HIV-associated infections. Recommendations were formulated after discussion in breakout sessions and with the support of a prioritization tool developed by the Clinton Health Access Initiative[14]. Consensus was reached in plenary discussion.

Current reality and ongoing developments in paediatric antiretroviral treatment for HIV

In contrast with enormous progress made in optimizing treatment regimens for adults, children remain underserved in most treatment programmes, where far too many children continue to receive suboptimal treatment with a fixed dose combination (FDC) of nevirapine (NVP)/zidovudine (AZT) /lamivudine (3TC) due to its low cost and ease of administration. Documentation of high levels of pre-treatment nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in several sub-Saharan African countries[15], with up to 60% of children resistant to NVP, continues to raise important concerns about the efficacy of NNRTI-based regimens in children. These data find

important correlates with the poor level of viral suppression consistently documented in population-based surveys[3]. Moreover, despite WHO recommending ritonavir-boosted lopinavir (LPVr)-based ART regimens since 2013 for infants and young children, implementation of this recommendation has faced multiple challenges including unpalatability and cold chain requirements for LVPr syrup as well as inadequate supplies of heat-stable LPVr pellets or challenges with administration and palatablity when available. In study settings, implementation of LPVr pellets has been associated with good viral suppression in children switching from LPVr syrup- or NVP-based regimens[16]. Of note, viral suppression rates have been somewhat lower in younger children initiating ART, for whom administration of and adherence to LPVr pellets appears to be more challenging. Sites using the formulation as part of routine care programs report similar viral suppression rates as with LPVr syrup, due to persisting administration and palatability issues[17].

The newly developed "4-in-1" abacavir (ABC)/3TC/LPV/r taste-masked granule formulation, with approval expected down to 4 weeks of age, holds promise, particularly for very young children, due to better palatability and easier administration[18]. This formulation is expected to receive regulatory approval and be available in countries in early 2020.

Since the last PADO meeting in 2016, dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), has been approved for children age 6 years and above (weighing at least 30 kg (US Food and Drug administration - FDA) or 15 kg (European Medicines Agency - EMA)) using paediatric 10 mg and 25 mg oral film coated tablets (FCT) and adult 50 mg oral FCT. DTG dosing is not yet available for infants and young children: it is currently being studied across the paediatric age and weight spectrum down to 4 weeks in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1093 trial using novel paediatric dispersible 5 mg tablets. The ODYSSEY trial is investigating a simplified dosing approach including the extended use of adult 50 mg tablets for older children and has informed the dosing currently recommended by WHO for children weighing above 20 kg[19]. Finally, with full approval for use of raltegravir (RAL) down to birth in term newborns, an INSTI option is now available for use in the first 4 weeks for life[20]. RAL for neonatal treatment is

being considered in countries implementing birth testing with assisted introduction to document feasibility and to develop appropriate tools to support scale-up of treatment for newborns, in light of the complexity associated with rapid dose escalation over the first weeks of life, and multistep administration.

A number of other ARVs already introduced in adult HIV treatment practice are currently under investigation in adolescents and children. Several tenofovir alafenamide (TAF)-containing FDCs are approved for adolescents weighing ≥25 kg at adult doses and are also being investigated in Phase II/III studies in children. Approval of TAF dosing in children weighing 15-25 kg and < 15 kg is expected by 2020 and 2021 respectively. Finally, doravirine, a novel NNRTI, has recently been approved in adults, and a trial in adolescents is underway[21].

Despite challenges with implementing the treatment regimens newly-recommended by WHO, several countries are taking concrete steps to enable optimization of their national formularies and increase access to optimal formulations for children. As of December 2018, 10 countries had already agreed to introduce DTG for children above 25 kg and to actively phase out NVP-based regimens by increasing use of LPVr-solid formulations. Supply issues around existing LPVr pellets and recently approved LPVr granules (40/10 mg sachet) are expected to be resolved following increased generic production capacity over the next 12-18 months. In addition, approval and full commercialization of DTG 10 mg scored dispersible tablets to administer DTG in younger children is expected to occur by the end of 2020 with an FDC containing DTG, ABC and 3TC becoming available shortly thereafter.

In this context progressive consolidation of demand for a limited number of regimens containing either LPVr (below 20 kg) or DTG (above 20 kg) in combination with an ABC/3TC dispersible FDC will likely characterize paediatric treatment programmes over the next several years. This will enable infants, children, and adolescents to access the most effective regimens available to them and dramatically simplify programmatic scenarios resulting in more predictable demand and more reliable supply of paediatric formulations. However, we anticipate a future where children failing DTG + ABC/3TC will require a new line of treatment that may need to optimize available ARVs

without requiring knowledge of previous treatment history. Whether a combination of DTG and ritonavir boosted darunavir (DRVr) with or without NRTI or DRVr in combination with an NRTI backbone (potentially recycled) would be appropriate in such scenarios needs to be evaluated.

Focusing immediate efforts on priority products with highest impact

The PADO4 meeting reviewed and updated the list of priority ARV formulations most needed in the short- to medium-term for treatment of infants and children living with HIV in LMICs (Figure 2). While overall, these priority formulations are broadly in line with those outlined in the PADO3 meeting[10], several formulations were modified or removed considering recent developments in paediatric and neonatal treatment. For example, co-formulation of AZT/NVP for use in neonatal HIV prophylaxis, not yet developed despite its presence in the PADO list since 2014, was removed due to the anticipated future transition toward presumptive antiretroviral treatment with a three-drug regimen for high-risk infants in lieu of enhanced prophylaxis with a dual regimen. In addition to removing AZT/NVP FDC from PADO3 list, PADO4 has streamlined the list of paediatric ARVs needed for treating HIV in infants and children according to the most current optimal therapeutic approaches, emerging drug resistance data and target product profiles for paediatric drug formulations. With DTG introduction in LMICs, high value continues to be placed on the DTG 10 mg scored dispersible tablet already in development, which will enable administration of the minimum dosage strength (5 mg) while reducing pill burden. At the same time, a single-tablet once-daily regimen of a DTG-based FDC – DTG/3TC/TAF or DTG/emtricitabine (FTC)/TAF (called DTG/XTC/TAF), and DTG/3TC/ABC dispersible tablets – were confirmed as a priority to promote use of FDCs in line with previous PADO3 recommendations. Specifically, a DTG/3TC/ABC dispersible tablet at already confirmed dosing ratio represents a critical formulation to provide the currently preferred first-line ART, while DTG/XTC/TAF represents an important future option for full harmonization with adult ART once dosing and ratios are confirmed. Moreover, with anticipated approval of DTG dosing for infants and younger children in the coming 12-24 months and emerging concerns about the

selection of INSTI resistance with RAL use potentially compromising the subsequent use of DTG, the need for a 50 or 5 mg dispersible tablet of RAL was considered of limited added value for future treatment strategies.

Following expected advancement in the development of paediatric TAF dosing and TAF-based FDC formulations, and accounting for smaller tablet size and target product profile of TAF-based products, PADO4 retained XTC/TAF dispersible tablets on the high priority list to preserve flexibility and provide a dual NRTI FDC to supplement and possibly replace current NRTI therapeutic options.

A potent ritonavir-boosted protease inhibitor (PI) FDC of DRV at paediatric dose of 120/20 mg DRVr remained high on the priority list. This formulation, which unfortunately, has made little progress in its development to date, represents the preferred choice in managing DTG-based ART failure in children. Being a robust PI combination with a high threshold for resistance and with an option for once-daily dosing in children without prior PI exposure, DRVr also represents a potent alternative to other currently available paediatric PI formulations for second-line use (LPVr and atazanavir (ATV) plus RTV) as we transition to an era of first-line INSTI-based ART.

Furthermore, after consideration of the most recent evidence for dual regimens such as DTG/DRVr or DTG/3TC, the PADO4 group decided to deprioritize the development of FDCs to deliver such regimens due to concerns for hepatitis B virus coinfections and limited data on safety benefit and long-term outcomes. This area has been identified as a research gap (e.g., DTG/TAF, DTG/3TC, DRVr/3TC, DRVr/DTG) for treatment-naïve and -experienced children and adolescents along with other simplification strategies currently investigated by ongoing trials such as SMILE[22] and 3D[23]. Additional areas for further investigation are summarized in Table 1 and add granularity to the paediatric and adolescent HIV research priorities identified by WHO and CIPHER in 2017[24].

Finally, the PADO4 group has identified several unmet needs in paediatric formulations for treating HIV-associated infections, such as tuberculosis, severe bacterial infections and cryptococcal meningitis in infants, children and adolescents (see Box 1). While these products are not formally

included in the PADO list they will be considered in other prioritization processes being planned for 2019 under the GAP-f scope of work.

Looking ahead: the future of paediatric HIV treatment

A number of potentially promising products and technologies are currently under investigation and have been deemed of interest for future paediatric treatment or prophylaxis by the PADO4 group (Figure 2).

Long acting/extended release (LA/ER) ARV products have the potential for use in both treatment and prevention of HIV. Broadly speaking, LA/ER products include parenteral formulations (such as intramuscular or subcutaneous injectables, intravenous infusions, and biodegradable or non-degradable implants) and oral formulations[25]. Cabotegravir combined with long-acting injectable rilpivirpine are in Phase I/II studies as monthly or bimonthly maintenance therapy for adolescents (IMPAACT 2017) [26] and adults who have become virologically suppressed with ART.

LA/ER formulations have multiple advantages over daily oral therapy, including the potential for improving adherence, avoiding pill-fatigue and avoiding stigma[27]. These characteristics suggest a promising role for LA/ER formulations in neonatal prophylaxis and in the prevention and treatment of adolescents with HIV[28]. However, current LA/ER formulations in advanced clinical development may find limited application for children, partly due to the requirement for frequent intramuscular injections with relatively large injection volumes. In the case of RPV-LAI, the reliance on cold chain storage could make it unsuitable for use on a public health scale in LMICs. Furthermore, it is likely that dose determination in LA/ER formulations across the age spectrum will be challenging in children, given changes in weight and muscle mass, as well as metabolic systems from infancy to adolescence.

Broadly neutralizing antibodies (bNAbs), potent and long-acting in nature, could play an important role in both paediatric HIV treatment and prevention. Apart from the potential for preventing HIV infection in neonates, animal studies suggest the exciting potential of bNAbs to eradicate very early

newborn infection[29]. The IMPAACT P1112 trial is currently investigating the safety and pharmacokinetics (PK) of VRC01, VRC01-LS (a modified VRC01 with longer half-life), and VRC07-523LS when given subcutaneously to HIV-1 exposed infants alongside ARV prophylaxis[30]. To date, VRCO1 has been shown to have favourable PK, and preliminary results indicated that serial subcutaneous doses of VRC01 administered over the first 6 months of life were safe and well tolerated[31]. There remain a number of unanswered questions around bNAbs, for instance, the likely need for cold chain and higher cost of production relative to small molecules; the protective titers and optimal route of injection, as well as optimal combination(s) remain to be determined; and further safety data and risk of resistance transmission are also needed. Nevertheless, the research community sees great potential in bNAbs for postnatal prophylaxis. Future generations of bNAbs combining multiple epitopes (e.g. a single tri-specific antibody) may offer broad coverage of circulating strains while reducing volume of injection[32].

Other LA/ER technologies involving alternative delivery systems are also under development for HIV, albeit at earlier stages of development. Examples of such technologies include microneedle patches (or microarray patches)[33,34,35] and ultra-long-acting oral formulations (such as gastroretentive dosage forms[36]).

Among other ARVs that could hold potential for paediatric treatment in LMIC, PADO4 highlighted ARVs characterised by high genetic barrier to resistance and/or high potency. One example is doravirine , a new NNRTI with a higher resistance threshold compared to existing NNRTIs[37], which is being studied in adolescents aged 12-17 years (with weight over 35 kg)[21]. Its exact role in LMIC is yet unclear, given that there are no safety data in pregnancy, and no efficacy data on potential second-line use; it is also contraindicated for use in TB co-treatment. However, its role in paediatric treatment should be reviewed as further data emerge, particularly if it is prioritized within the adult treatment agenda.

Another example of interest to both adult and paediatric research communities is the novel reverse transcriptase translocation inhibitor (NRTTI), MK-8591 (EfdA), which is currently in development.

MK-8591 is known to have long half-life and high potency, and such characteristics provide the potential for very low and/or less frequent oral doses[38], which in turn could lower treatment costs. Further, MK-8591 may be compatible with versatile long-acting formulation technologies, with the potential of further decreasing dosing frequencies[39]. As no paediatric investigation plan (PIP) has yet been identified for MK-8591, its further development should take into consideration the need for appropriate formulations and clinical data for infants, children and adolescents. Clinical validation of high efficacy against notable resistance-associated RT mutations is also warranted.

Treating and preventing HIV in neonates and infants

The PADO4 meeting once again focused attention on the special issues of neonates and young infants. Availability of optimal ARVs for prevention and treatment in the very youngest children has been especially delayed, and AZT, 3TC, and NVP have, until recently, been the only ARVs available for treatment of neonates. RAL is now approved for use in full-term neonates and is being considered for early treatment in settings where HIV infection can be diagnosed at birth. In addition, approval of the long-awaited '4-in-1' ABC/3TC/LPVr granule formulation for infants < 4 weeks of age is expected imminently and has the potential, as an FDC regimen of currently recommended first-line ARVs in an 'infant-friendly' formulation, to transform treatment outcomes for this vulnerable age group. The meeting participants prioritized the study of PK and safety of this FDC product down to birth, especially as dosing data on abacavir (ABC) in neonates are lacking. The importance of studying the PK and safety of DTG down to birth was also highlighted, since current studies of DTG begin at 4 weeks of age. The paucity of products that have been studied in low birth weight (LBW) and premature infants was also noted, and the study of key ARVs in LBW infants was identified as a research priority.

The group members endorsed a shift from the current infant prophylaxis approaches to a simplified framework harmonized with early treatment. They considered the multiple advantages of using the same regimen for prophylaxis of high-risk neonates that is recommended for neonatal treatment,

including reducing the PADO product list by eliminating AZT/NVP, using a potent combination regimen for those at highest risk of infection, and initiating early treatment in those determined to be infected. This approach would simplify the supply chain and increase demand for a single product. Determination of safety and PK among newborns, including LBW infants, through 4 weeks of age of the '4-in-1' LPVr granule formulation was highlighted as a priority research question. The potential for bNAbs for neonatal and infant prophylaxis has generated much interest and the study of LA/ER formulations in this population also received high priority. Other critical research questions are included in Table 3.

Challenges in optimizing HIV treatment for adolescents

Research, treatment and care of adolescents living with HIV pose several unique considerations including issues around disclosure, confidentiality, autonomy and consent. Other considerations include potential PK challenges (e.g. use of contraceptive drugs), and low rates of care and treatment adherence and associated viral suppression compared to adults. Transitioning from paediatric to adult management is challenging for the individual as well as health systems, and drug harmonization across the life course from childhood through adolescence and adulthood is critical to ensure successful treatment. In the context of lifelong HIV treatment, careful sequencing of ART regimens between childhood, adolescence and adulthood is needed to preserve and protect future treatment options.

Drug-reduction strategies using regimens containing DRVr plus DTG dual ART have been considered in adults, and now being investigated in children or adolescents[22] . A number of other alternative strategies for simplifying ART are being investigated and are of particular interest for adolescents. Such strategies may improve quality of life by reducing toxicity, preserving future treatment options, facilitating uptake and decreasing costs. Simplification and other innovative approaches including using dual oral ARV regimens or long-acting injectables, decreasing number of days on treatment (short-cycle therapy), are attractive considerations for adolescent populations. It was noted,

however, that several of these strategies may be difficult to implement in LMICs where frequent virological monitoring may not be feasible. Critical gaps in research regarding optimal treatment strategies in adolescent populations remain and studies including adolescents are needed before they can be considered on a public health level.

To ensure that information on ARV formulations and treatment approaches are optimized for adolescents, adolescents need to be included early in the product development cycle. In particular, PK studies in adolescents should be carried out as soon as a dose is proposed and being studied in adults and should include adolescents as young as possible based on weight rather than age limits. PADO4 recommends that adolescents should be included in adult Phase II/III studies, unless specific concerns exist. However, including adolescents in adult clinical trials can be challenging, and better collaboration in the trial design with paediatric research networks could help address barriers to recruitment and retention.

Healthy mothers, healthy children: improving treatment options for pregnant and lactating women

In 2017 there were 18.2 million women living with HIV worldwide, with 1000 new infections occurring daily among young women aged 15-24 years. An estimated 80% of the 1.4 million pregnant women living with HIV received ARVs in 2017. Despite the public health need for ARVs that are safe and effective for use in women of childbearing potential, pregnant and breastfeeding women are generally excluded from clinical trials. This has resulted in a paucity of data on the use of these drugs during pregnancy and breastfeeding, putting women and their children at risk for potentially harmful or ineffective interventions.

PADO4 strongly emphasized that current approaches to studying drugs in pregnant and lactating women should be re-examined, with appropriate consideration of the risks of *not* including pregnant women in treatment and prevention research. These risks should be weighed against any preclinical data on risk in pregnancy, PK and dosing data, and whether the drug would offer direct benefit to

the mother and/or fetus. The group supported the premise that PLW need to be included in clinical trials of antiretroviral drugs and agreed that there is a compelling need to accelerate the investigation of new ARVs in PLW to closely follow the timeline of development in non-pregnant adults.

Approaches to support an accelerated timescale for investigation of antiretrovirals in PLW were discussed, and key principles to 1) assess PK and safety in this population and 2) include this population in clinical trials with non-pregnant adults were deliberated. In collaboration with the Conference on ARV Drug Optimization (CADO) group, these principles will be fully delineated in 2019. Furthermore, the Pediatric Antiretroviral Working Group (PAWG) will continue to work to address relevant questions around ARVs in PLW and advocate with regulatory, industry and research partners to create an enabling environment to study ARVs in this population. PADO4 also recognized the critical importance of the other stakeholders working in this space[40,41] and places high value on early and consistent involvement of the community, particularly of informed and vocal participation of women, to inform this agenda.

Community engagement

Throughout the process of drug development, including during design and conduct of clinical trials, ongoing community engagement remains key to ensuring that the needs of children, adolescents and their parents and carers, as well as pregnant and lactating women are understood and factored into decisions relating to the development and optimization of ARV regimens and formulations. Furthermore, enabling meaningful involvement of adolescents as advisors and peer-representatives at all stages of trial design and planning, along with the establishment of Youth Trial Boards[42], as has been done for the ODYSSEY trial, are likely to benefit the implementation and successful recruitment and retention in the trials.

Conclusion

The outcomes of the PADO4 meeting renew the commitment of key stakeholders to better target global efforts and accelerate research and development of the most critical formulations. The PADO4 group reviewed the ARV landscape, the expected timelines for introducing and rolling out new ARVs in countries and confirmed the critical role of DRVr FDC as well as of formulations containing DTG and TAF. These priority products will be the core HIV component of the product portfolio that the Global Accelrator for paediatric formulations will focus on to ensure that every step is taken to investigate, develop and introduce better formulations in the shortest possible time.

As innovative strategies to simplify and better sequence ARV regimens over time are being tested, more efforts should be put into exploring the value of long acting and extended release formulations. It is important that the development plans include consideration of potential use in infants, children, and adolescents, as well as in pregnant and lactating women. Manufacturers are encouraged to consult with PADO for guidance on paediatric requirements for specific novel products.

PADO4 has retained a strong focus on adolescents and promoted stronger collaboration of innovators and adult researchers with existing paediatric and adolescent HIV research networks spped up approval of optimal ART options for youth globally. Urgent need to better and more rapidly investigate new ARVs in pregnant and lactating women was also clearly endorsed by the group which acknowledged that optimal child health outcomes cannot be ensured without supporting mother to be virologically suppressed and clinically stable.

Without continued focus on identifying, prioritizing and ensuring access to optimal formulations suitable for infants, children and adolescents global HIV treatment targets will not be met.

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Tables and figures

Figure 1 Anticipated timelines for approval, introduction and roll out of new ARVs (2019-2021). [DTG = Dolutegravir, TLD = Tenofovir/Lamivudine/Dolutegravir, RAL = Raltegravir, LPV/r = Lopinavir/ritonavir, SRA = stringent regulatory authorities, disp = dispersible].

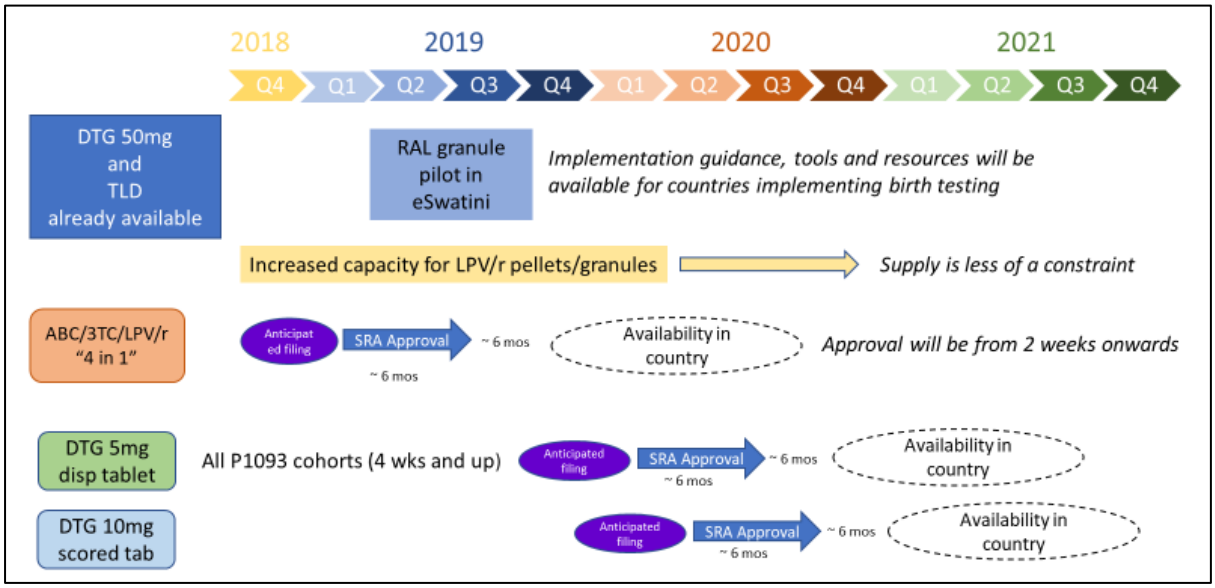

Figure 2: PADO4 priority list (medium-term 3-5 years) and watch list (products of potential interest for paediatric treatment in the longer term)

PADO 4 Priority list

- DTG/3TC/ABC (5/30/60 mg dispersible)*
- DTG (10 mg scored dispersible)
- DRV/r (120/20 mg)*
- DTG/XTC/TAF
- XTC/TAF

PADO 4 Watch list

- Broadly neutralizing antibodies
- Long-acting/extended release parenteral formulations
- Novel delivery technologies
- Doravirine
- MK-8591

* Dosing and ratio are endorsed/recommended by the Pediatric Antiretroviral Working Group (PAWG) if feasible a scored double strength tablet would also be appropriate (DTG/3TC/ABC 10/60/120 mg)

Table 1 – PADO research priorities

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Box 1. Management of HIV-associated infections in children

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Figure 1

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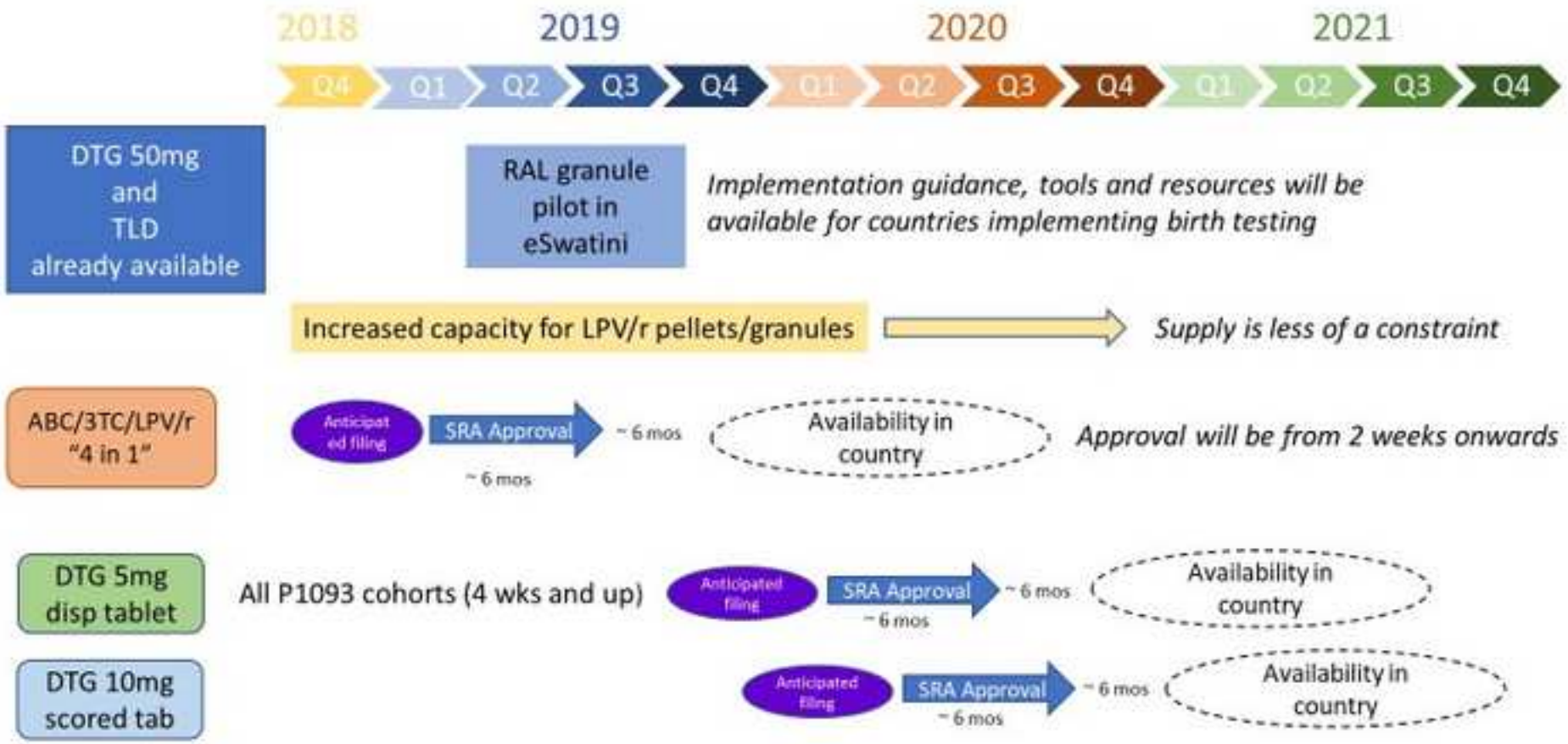

Figure 2
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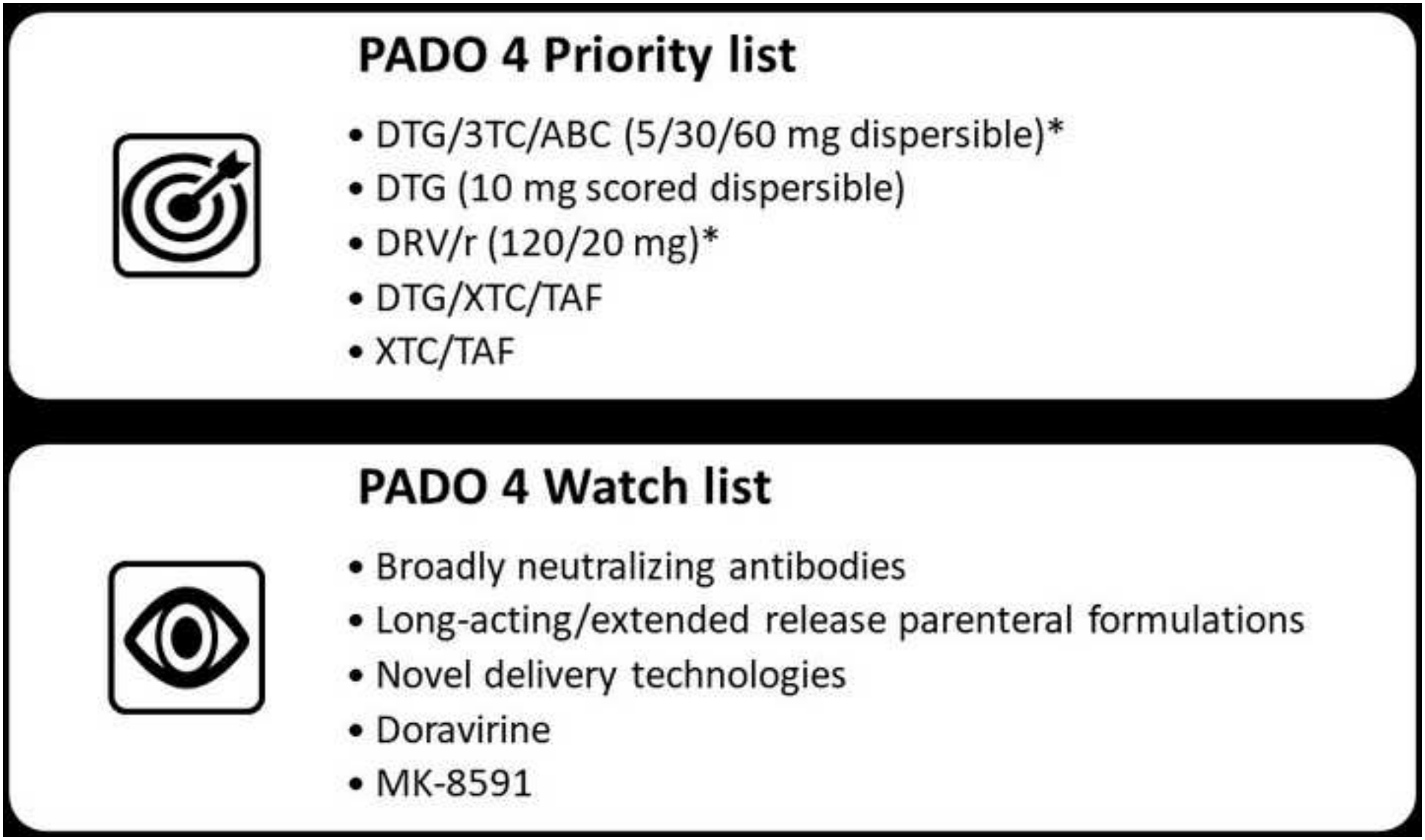

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