

The Pediatric Antiretroviral Pipeline

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Introduction

The big news since the *2014 Pipeline Report* is that there is finally a solid form of lopinavir/ritonavir (LPV/r) suitable for infants and young children.

On 21 May 2015, the United States Food and Drug Administration (FDA) tentatively approved LPV/r pellets, manufactured by Cipla, for infants and young children less than three years old.^{1, 2}

A few months before, in December 2014, the Medicine Patent Pool (MPP) signed a licensing agreement with AbbVie – that holds the patent for LPV/r. This agreement will help to make the new formulation available for children in low- and middle-income countries. The next hurdles will be getting it approved by regulatory agencies and used in programs in these countries.³

There has not been a lot of activity in the pediatric pipeline over the last year. This year's chapter confirms (again) the need for priority generic products and highlights the ones to watch in the originator pipeline. It also includes a few new ones: the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine, and long acting formulations cabotegravir and rilpivirine.

Lopinavir/Ritonavir Pellets Tentatively Approved

The World Health Organization (WHO) recommends LPV/r-based regimens as preferred for infants and young children.⁴ Compliance with the recommendation has been hard as this boosted protease inhibitor was previously only available as syrups, which are too complicated to use for most programs in low- and middle-income countries. The new formulation consists of a finite number of LPV/r 40/10 mg pellets in a capsule, which is opened and sprinkled on soft food.

Although it is quite a step forward from syrup, the new formulation of LPV/r is still not ideal. The pellets are much easier to transport and store (no cold chain), and for this reason programs are keen to start using them. But acceptability data from the CHAPAS-2 trial⁵ – that showed similar LPV/r exposure with pellets and syrups – revealed that pellets were not more acceptable than syrups by 48 weeks.⁶ For infants and young children overall, the trial found pellets were more acceptable than syrups at week 12 but not by week 48. The main problem was taste.

Infants less than three months old have not yet been treated with the pellets. As they cannot be stirred, dissolved/dispersed or crushed in liquids it is important to make sure that infants can swallow them. For the youngest infants (three to six months old) in CHAPAS-2, the pellets were either added to a small amount of expressed breast milk in a spoon and given to the infant, or put on the infant's tongue before breastfeeding.

DNDi is waiting for the production of the clinical batch of the pellets to begin the LIVING study (implementation study using the new formulation) in Kenya.⁷ All the necessary local regulatory approvals are in place to start the study.

DNDi is also working on an improved taste masked granule formulation of LPV/r (as part of a fixed dose combination [FDC] 4-in-1 regimen).

WHO Recommendations and Current Priority Formulations

WHO 2013 guideline recommendations for adults are simple: two preferred first line regimens and two alternatives. Recommendations for children are more complicated (see Table 1). Only one regimen, AZT plus 3TC plus nevirapine (NVP) is currently available as an FDC. There is still some way to go with formulations and regimens appropriate to children. Despite some advances in the last few years, innovation and access in antiretrovirals for children still lags behind that for adults.

Table 1: 2013 WHO Guidelines Pediatric Recommendations

First-line	<3 years old	<p>LPV/r-based regimens regardless of previous NNRTI exposure. If LPV/r is not feasible, NVP-based.</p> <p>Consider substituting LPV/r with an NNRTI after sustained virological suppression (defined as viral load less than 400 copies/mL at six months, confirmed at 12 months from starting treatment).</p> <p>Children who develop active TB while on LPV/r- or NVP-based regimens should be switched to ABC + 3TC + AZT during TB treatment. They should switch back to the original regimen when their treatment for TB is completed.</p> <p>The NRTI backbone should be one of the following (in order of preference): ABC or AZT + 3TC; d4T + 3TC.</p>
	>3 years	<p>EFV preferred and NVP alternative.</p> <p>< 12 years or weighing less than 35 kg, backbone (in order of preference): ABC+3TC; AZT or TDF + 3TC or FTC.</p>
	>12 years	<p>Adolescents 12 years (weighing more than 35 kg) should align with adults, the backbone: TDF+ 3TC or FTC; ABC or AZT + 3TC.</p>
Second-line		<p>After first-line NNRTI failure, a LPV/r regimen is preferred.</p> <p>After LPV/r failure, children <3 years should remain on the regimen with improved adherence support.</p> <p>After failure of first-line regimen containing ABC or TDF + 3TC or FTC, the preferred backbone is AZT + 3TC.</p> <p>After failure of first-line regimen containing AZT or d4T + 3TC or FTC, the preferred backbone is ABC or TDF + 3TC or FTC.</p>

ABC, abacavir; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate, 3TC, lamivudine.

NNRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TB, tuberculosis

Missing Pediatric Formulations

Several gaps remain in available products for children that need to be filled before the 2013 WHO guidelines (and the 2015 ones that are on the way) can be implemented in most low- and middle-income settings.

Where possible these should be FDC dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules) granules are preferable to liquids. Liquid formulations are expensive, have short shelf lives, and often require a cold chain, making them hard to store and transport and inappropriate for most low- and middle-income countries.⁸

The WHO 2014 supplement to the 2013 guidelines include a pediatric chapter: *Optimizing Antiretroviral Drugs for Children: Medium- and Long-Term Priorities*.⁹ WHO highlights two priority formulations needed to treat children according to the 2013 guidelines:

AZT or abacavir (ABC) plus 3TC plus LPV/r. These formulations are in development and are needed to make it possible to give FDCs to children younger than three. Better solid forms could overcome palatability issues with the currently available nasty tasting LPV/r syrup (although taste masking is complicated and can limit drug absorption and the recently approved solid form still needs improving). Many barriers with supply chain – transport, storage and distribution – could be addressed by these formulations.

Supported by UNITAID, DNDi is working on a more palatable version of LPV/r – which will be produced in combined 4-in-1 granule formulations (finer than the newly approved 0.8mm pellets and more sand-like in texture).¹⁰ The plan is to have the optimized 4-in-1 LPV/r-based FDCs by 2016.

ABC plus 3TC plus efavirenz (EFV). Currently this regimen can only be given by using ABC/3TC co-formulated tablets with EFV tablets. A one-pill, once-daily regimen for children aged three to 10 years (less than 35 kg) would be useful. There is some discussion as to what dosing ratios for the FDC best facilitate recommendations for the individual agents across weight bands. Optimal doses need to avoid under- and overdosing of children at either end of each weight band, as far as possible, and be most suitable from a regulatory standpoint.

These two formulations have been a priority for some time now and are still unavailable.

Recommendations From the Second Pediatric Drug Optimization Meeting

The first Pediatric Antiretroviral Drug Optimization (PADO1) meeting, held in Dakar in 2013, brought together researchers, clinicians, activists and other experts to identify medium- and long-term priority drugs and formulations for children. The recommendations from this meeting were summarized in the WHO 2014 supplement,¹¹ and continue to inform formulation development.

The Second Pediatric Antiretroviral Drug Optimization (PADO2) meeting,¹² held in December 2014 was conducted to build on the PADO1 agenda and provide technical advice to the WHO 2015 guidelines development group. Among the topics discussed at the meeting were the needs for children at both ends of the age spectrum: newborns and adolescents.

For newborns, less than four weeks, the participants noted that there was currently no alternative to NVP plus 3TC plus AZT. Although very early treatment is being explored for infants, data for this very young age group are scarce. See Table 2. Some missing data will be provided by ongoing International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) trials:

- P1026s – phase IV, prospective, pharmacokinetic study in pregnancy and post partum, that obtains infant antiretroviral washout data.¹³
- P1093 – phase I/II, open label, non-comparative, intensive pharmacokinetics and safety study of dolutegravir (DTG) down to four weeks.¹⁴
- P1097 – washout pharmacokinetic study of raltegravir (RAL) including in low birth weight (<2500 g) infants.¹⁵
- P1106 – phase IV prospective pharmacokinetic study in low birth weight infants receiving NVP prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or LPV/r-containing ART.¹⁶
- P1110 – phase I open label, non-comparative pharmacokinetic dose-finding study of RAL in high risk, HIV-exposed neonates.¹⁷
- P1115 – phase I/II proof of concept study of very early intensive antiretroviral therapy (ART) in infants to achieve HIV remission.¹⁸

Table 2: Newborn Treatment Options
(including ongoing and planned IMPAACT trials)

Compound	Preterm	Term	2 weeks
Nucleos(t)ide Reverse Transcriptase Inhibitor			
ABC	P1106 < 2500 g		
AZT	✓	✓	✓
ddl			✓
d4T	P1106 < 2500 g	✓	✓
FTC		✓	✓
TAF	P1026s washout	P1026s washout	
3TC	P1106 < 2500 g	✓	✓
Non-nucleoside Reverse Transcriptase Inhibitor			
Doravirine	P1026s washout	P1026s washout	
EFV	P1026s washout	P1026s washout	
ETR	P1026s washout	P1026s washout	
NVP	P1106 < 2500 g	P1115 >34 weeks GA	✓
RPV			
Protease Inhibitors			
ATV			
DRV	P1026s washout	P1026s washout	
LPV	P1026s washout P1106 <2500 g	P1026s washout	✓
Integrase Inhibitors			
DTG	P1026s washout	P1026s washout P1093 dosing (in development)	P1093 dosing (in development)
EVG	P1026s washout	P1026s washout	
RAL	P1097 washout	P1097 washout P1110 dosing	
CCR5 Receptor Antagonist			
Maraviroc		In development	

Adapted from Ruel T. IMPAACT 2015.

ABC, abacavir; ATV, atazanavir; AZT, zidovudine; ddl, didanosine; DTG, dolutegravir; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; ETR, etravirine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; 3TC, lamivudine. GA, gestational age.

For infants two weeks and above, the immediate priority first-line is still LPV/r-based regimens and for older children EFV-based FDCs. An alternative to the liquid formulation of ritonavir (RTV) is needed to make double boosting (adding extra RTV to overcome pharmacokinetic interactions with TB drugs during co-treatment) easier with LPV/r.

For second-line treatment a generic, co-formulated, heat stable version of darunavir/ritonavir (DRV/r) was prioritized. Children who fail on LPV/r-based first-line regimens particularly need a robust option second-line.

Current dosing recommendations for DRV/r (approved by regulators in the United States and Europe) need to be simplified to reduce the number of different formulations and minimize pill burden for children in low- and middle-income countries. A 240/40 mg DRV/r tablet for twice daily dosing is a priority for children in weight bands 10 kg and above. DRV/r is not approved for children less than three years old and will not be investigated in this age group due to toxic levels in pre-clinical studies.

Discussion about adolescents focused on adherence and more tolerable alternatives to EFV.

The priority antiretrovirals in the medium-term (five years) are: DTG, RAL and tenofovir alafenamide fumarate (TAF). Although the PADO2 participants did not expect RAL to be used widely when DTG comes to the market (and it has not been identified as a priority for adults) a better formulation of RAL might offer an alternative for infants.

The Pipeline

Pediatric investigation plans (PIPs) will be in place or under discussion for all compounds in early phases of development by originator manufacturers (described in the adult antiretroviral chapter). Although a generic company and DNDi are developing the LPV/r-based 4-in-1 FDC, the list of pipeline pediatric drugs and combinations also includes this.

There are considerable incentives and/or penalties from regulatory agencies to ensure that any new drug that might benefit children must be studied in this population. Pediatric research and development of new drugs is mandatory. The European Medicines Agency (EMA) enforces penalties for companies that do not provide a PIP as part of their application (or request a waiver). The FDA also extends six month patent protection to companies that perform the requested pediatric studies – though companies are not required to do this.

A PIP can be waived for specific drugs or classes of drugs that are likely to be ineffective or unsafe in all or some pediatric age groups. A waiver can also be obtained for products that are intended for conditions that only occur in adults, or that do not represent a benefit over existing pediatric treatments. In some cases, studies can be deferred until after the adult studies have been conducted.

Manufacturers must include pharmacokinetic data for all age groups of children, efficacy, tolerability, and differences in side effects. They must have stability and palatability data for formulations and demonstrate that they are able to achieve pharmacokinetic targets associated with efficacy in adults.

Studies are conducted in children as soon as there are sufficient data from those in adults. Most pediatric development programs take a staggered approach, starting with the older cohorts of children and working in de-escalated age bands: 12 to 18 years; six to 12 years; two to six years; six months to two years and less than six months. Data are required in the youngest age groups – down to newborns – unless a regulatory waiver is obtained. As the youngest age group is last to be studied and approved there are considerable delays in availability of new drugs for this population.

Whether this process could be accelerated and age groups studied simultaneously, where possible, has been discussed for some time. It would be interesting to see if doses for younger children have changed dramatically from predicted milligrams per kilogram ones due to pharmacokinetic data from older cohorts.

The current pediatric antiretroviral pipeline is shown in Table 3.

Table 3. The Pediatric Antiretroviral Pipeline

Compound	Sponsor	Formulation/s and dose	Status and comments
Nucleotide reverse transcriptase inhibitor and combinations			
Tenofovir alafenamide fumarate (TAF)/ emtricitabine (FTC) elvitegravir (EVG)/ cobicistat (COBI) (E/C/F/TAF)	Gilead	Reduced dose FDC tablets in development	Phase II/III single arm, open label E/C/F/TAF treatment-naive children and adolescents 6 to <18 years PK within adult range at 24 weeks in 12 to <18 years Waiver <6 years
FTC/TAF (F/TAF)	Gilead	Reduced dose, co- formulated tablets and non-solid formulation in development	Switch study in children and adolescents stable on FTC/TDF plus 3 rd agent Study in infants and children 4 weeks to <6 years planned
Rilpivirine (RPV)/FTC/TAF	Gilead/Janssen	Reduced dose, FDC tablets planned	Dependent on development of RPV and F/TAF Initial indication adolescents >12 years
Non-nucleoside reverse transcriptase inhibitors			
Etravirine (ETR)	Janssen	Dispersible tablets 25 (scored), 100 mg	FDA/EMA approval for children and adolescents 6 to <18 years Phase I /II treatment-experienced infants and children 2 months to <6 years and treatment-naive 2 months to <2 years enrolling Waiver <2 months
Rilpivirine (RPV)	Janssen	Tablet 25mg Granules 2.5 mg /g	Submitted to FDA and EMA for adolescents 12 and above with viral load < 100,000 copies/mL 2 to <12 years planned
Doravirine	Merck	Single agent and FDC with TDF/3TC planned	Pediatric plans under discussion with EMA and FDA
Protease inhibitor and combinations			
Lopinavir/ritonavir/lamivudine/ abacavir or zidovudine (LPV/r/3TC/ABC or AZT)	DNDi/Cipla	4-in-1 FDC granules	Formulation work ongoing
Booster			
Cobicistat (COBI)	Gilead	75 mg tablets 20 mg dispersible tablets for oral suspension	Booster with ATV, DRV and as part of E/C/F/TDF and E/C/F/TAF
Atazanavir/cobicistat (ATV/c)	Gilead/BMS	Reduced dose and dispersible tablets planned	Phase II/III treatment experienced children 3 months to <18 years (ATV/c)
Darunavir/cobicistat (DRV/c)	Gilead/ Janssen		3 to < 18 years (DRV/c)

Compound	Sponsor	Formulation/s and dose	Status and comments
Integrase inhibitors and combinations			
Raltegravir (RAL)	Merck	Granules for suspension 6mg/kg (100 mg sachet)	FDA-approval for use in children 4 weeks and older Passive PK study ongoing: neonates born to women who received RAL in pregnancy and during labor Neonates PK and safety study for prophylaxis ongoing in high-risk HIV-exposed neonates from birth to six weeks
Elvitegravir (EVG)	Gilead	Reduced dose tablets and suspension in development	EVG PK completed, RTV boosted 12 to <18 years RTV-boosted EVG to be studied in all age groups
E/C/F/TDF (Stribild)	Gilead	Reduced dose tablets in development	Studies underway in treatment-naive 12 to <18 years 6 to <12 years planned Waiver <6 years
E/C/F/TAF See TAF above	Gilead	Reduced dose tablets in development	Studies underway in treatment naive 12 to <18 years 6 to <12 years planned Waiver <6 years
Dolutegravir (DTG)	ViiV Healthcare	Granule formulation (for studies) Dispersible tablets in development 10 mg and 25 mg tablets	Approved for adolescents 12 to <18 years weighing ≥ 40 kg in US and EU Phase I/II study, 6 weeks to <18 years treatment-naive and -experienced children, ongoing In a PK study, exposures from granules were moderately higher than with tablets and highest with formula milk
DTG/ABC/3TC (572-Trii)	ViiV	Pediatric formulation development planned	FDA/EMA approval for adolescents >12 years and >40 kg Dependent on ongoing studies confirming DTG dose in children and ability to establish appropriate dosing ratios for components
DTG/RPV	ViiV/Jansen	Reduced dose co-formulation	PIP in development Studies planned in children and adolescents 6 to <18 years
Cabotegravir/RPV long acting (LA)	ViiV/Janssen	Age appropriate liquid formulation for induction Intramuscular nanosuspension as for adults	PIP approved October 2014 (to be completed by 2018) Waiver <2 years Deferral 2 to <18 years
CCR5 Receptor Antagonist			
Maraviroc (MVC)	ViiV	Suspension 20 mg/mL	Phase IV Treatment-experienced CCR5 tropic 2 to <18 years

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

Tenofovir Alafenamide Fumarate

TAF is considered to be a priority for future generic FDCs for children. Early data in adults suggests that it might have a better safety profile than TDF. This has yet to be confirmed in children. TAF also has a low milligram dose: 25 mg without a boosting agent and 10 mg boosted.

For children TAF might be an alternative to ABC. It could help to harmonize pediatric and adult ART regimens, particularly if it could be co-formulated with DTG and 3TC or FTC.

The originator company Gilead Sciences is not developing TAF as a single agent for adults or children. The development of an FDC of elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (E/C/F/TAF) is the company's priority.

As with adults, Gilead is also investigating a co-formulation with FTC (F/TAF), which hopefully will provide data to inform the dose of TAF as part of future un-boosted generic regimens.

E/C/F/TAF and F/TAF are currently under regulatory review for adults.^{19, 20, 21}

F/TAF

TAF is being investigated co-formulated with FTC in a phase II/III switch study will enroll children down to six years of age.²²

Adolescents aged 12 to 18 years will switch their current two nucleoside reverse transcriptase inhibitor (NRTI) containing regimen to F/TAF (while continuing on their third antiretroviral agent) for 96 weeks. After review of the pharmacokinetic and safety data from the older cohort, children aged six to 12 years will be randomized to receive either F/TAF or FTC/TDF (continuing on their third agent) for 96 weeks.

A study in infants and children aged four weeks to six years is planned. Reduced dose tablets and a non-solid formulation are in development. As with the pediatric formulation of TDF, the taste of TAF is bitter and will need masking. Because of TAF's low milligram dose, taste masking might be easier than it was for TDF.

E/C/F/TAF

A phase II/III, single arm, open label study of once-daily E/C/F/TAF in treatment-naive children and adolescents aged six to 18 years is ongoing.²³ There is a waiver for children less than six years old.

Data were recently presented from the phase II/III for 48 treatment-naive 12 to 18 year olds with a median age of 15 years receiving E/C/F/TAF for 24 weeks.²⁴

Steady-state pharmacokinetic parameters of EVG, COBI, FTC, TAF and tenofovir (TFV) were compared to adult exposures. The study found TAF (as well as TFV, EVG, COBI, and FTC) pharmacokinetic parameters in adolescents to be consistent with those associated with safety and efficacy in adults.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Etravirine

A scored 25 mg etravirine (ETR) tablet with dosing recommendations for treatment-experienced children and adolescents aged six to 18 years and weighing at least 16 kg is currently approved.²⁵ The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naïve and -experienced children aged two months to six years.²⁶ Phase I/II studies in the younger age groups are currently enrolling treatment-experienced children. There is a waiver for infants less than two months.

Rilpivirine

Rilpivirine (RPV) is approved for treatment of adults 18 years old and above with viral load less than 100,000 copies/mL. The originator company Janssen has submitted applications for an adolescent indication (12 to 18 years) to the FDA and EMA.

PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278), is an ongoing, open label, 48-week phase II trial looking at RPV pharmacokinetics, safety and efficacy in treatment-naïve adolescents aged 12 to 18 years.²⁷

Based on pharmacokinetics, tolerability and efficacy data at four weeks, a dose of 25mg RPV once daily with food was selected²⁸ – providing comparable exposure to that in adults. This dose was effective and generally well tolerated over 24 weeks for the treatment of ART-naïve adolescents with viral load less than 100,000 copies/mL.²⁹ PAINT is ongoing.

IMPAACT P1111 is planned in children from two weeks to less than 12 years of age.³⁰ A granule formulation of RPV is in development.

RPV is also being developed as an intramuscular long acting formulation for treatment and prevention (see cabotegravir below).

Doravirine

Once-daily 100 mg doravirine looks promising in adults (see antiretroviral pipeline chapter).

The originator company Merck has submitted pediatric plans to FDA and EMA for doravirine as a single agent and as an FDC: doravirine plus TDF plus 3TC. The plans are being discussed with the regulatory agencies. The current aim is to enroll populations similar to those in adult phase III studies: treatment-naïve and stable experienced patients for switch studies.

PROTEASE INHIBITOR

Lopinavir/ritonavir

As described above, the FDA has recently tentatively approved LPV/r pellets for young children. DNDi and Cipla are now developing a more palatable version of LPV/r granules in 4-in-1 FDCs with two NRTIs, ABC or AZT, plus 3TC. The granule formulation of LPV/r will be tested in HIV-negative adults very soon. The plan is to have the 4-in-1 by 2016.

INTEGRASE INHIBITORS

Raltegravir

RAL is approved for infants and children from four weeks of age.³¹ For the youngest age group (four weeks to less than two year olds, weighing 3 kg to 20 kg) it is formulated as an oral suspension. This comes in single-use packets of banana-flavored granules containing 100 mg of RAL, which is suspended in 5 mL of water giving a final concentration of 20 mg/mL.

For older children there is an orange-banana flavored, chewable pediatric formulation. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and have specific guidance.

The pediatric program is ongoing including in neonates below four weeks of age (both HIV-infected and exposed) infants.^{32,33, 34, 35, 36, 37}

Elvitegravir

Elvitegravir (EVG) is an integrase inhibitor given with a booster and mostly used for adults in the FDC containing EVG/COBI/FTC/TDF (E/C/F/TDF). It is also being developed as part of E/C/F/TAF.

Exposures in adolescents 12 to 18 years old receiving 150 mg once daily EVG plus a RTV-boosted protease inhibitor-optimized background regimen, showed comparable exposures to those seen in adults.³⁸

Two pediatric formulations are in development: a 50 mg tablet and a 5 mg/mL suspension. Single-dose pharmacokinetics evaluations compared two formulations to the 150 mg adult formulation (all boosted by RTV) in a crossover study in HIV-negative adults.³⁹

In this study, both pediatric formulations were bioequivalent to the adult formulation. The RTV-boosted formulations are being evaluated in children in an ongoing phase II/III study in children aged 4 weeks to 18 years of age.⁴⁰

PENTA 17 will evaluate EVG with DRV/r in stable, virologically suppressed children.

E/C/F/TDF

EVG is also being studied in treatment-naive adolescents aged 12 to 18 years as part of the adult FDC, E/C/F/TDF containing EVG 150 mg, COBI150 mg, FTC 200 mg and TDF 300 mg.⁴¹ Early data has shown similar exposures of all the individual agents to adults and good virologic suppression.⁴² Study of E/C/F/TDF in adolescents and children continues.

Dolutegravir

DTG is manufactured by ViiV and is approved for adults and children aged 12 years and above. It is currently under investigation for use in all age groups from birth. DTG has shown good safety, efficacy and tolerability so far, does not require boosting and has a low milligram dose. There is a lot of interest in this drug as an option for adults and children for first- and second-line regimens.

It is being evaluated for children in IMPAACT P1093 – an ongoing, phase I/II, open label pharmacokinetic, safety and efficacy study in children and adolescents in age de-escalated cohorts.⁴³ Preliminary (24 week) data from the first cohort of the study were included with the adult regulatory submissions and led to the recent approvals.

Twenty-four week data have been presented for children aged 6 to 12 years and 48-week data for children and adolescents aged 12 to 18 years.

Treatment-experienced but integrase inhibitor-naïve children (n=11) with viral load greater than 1000 copies/mL were enrolled in an intensive pharmacokinetic evaluation.⁴⁴

Participants received DTG tablets (10, 25, 50mg) dosed at 1 mg/kg once daily (based on weight bands) added to a stable, failing ART regimen, with optimized background therapy added after the pharmacokinetic evaluation performed between days 5 and 10.

Children were a median age of 10 years, had received prior ART for a median duration of about nine years, and just over half were triple-class experienced.

The dose of 1 mg/kg once a day achieved adequate DTG exposure. Adolescents aged 12 to 18 had also previously achieved exposures comparable to those in adults with the pediatric weight band dose.⁴⁵ Both age groups showed good short-term safety and tolerability.

In a safety and efficacy evaluation of the older age group, at 48 weeks, 74% of adolescents (n=23), a median of 15 years, achieved virologic suppression to less than 400 copies/mL and 61% less than 50 copies/mL. There were no serious adverse events.⁴⁶

Reduced-strength 10 mg and 25 mg tablets have been developed for children.

A granule formulation is being used for early studies. In a phase I pharmacokinetic study in healthy adult volunteers the granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water.⁴⁷

Participants received a single dose of DTG as a 50 mg tablet (adult formulation) and as 10 g of granule given: with no liquid; with purified water; with mineral water; or with infant-formula milk.

DTG exposures of the granule formulation were all moderately higher than those of the tablet formulation, with or without liquids. Exposure was highest when the granule formulation was given with formula milk.

The granule formulation is currently being evaluated in the six to 12 years of age cohort of IMPAACT P1093. It will be used in the two to six years of age cohort that has begun screening.

The company is developing a dispersible tablet formulation that will be used in future studies and marketed. The granules will not be available commercially.

A treatment strategy trial ODYSSEY (PENTA 20) of DTG in all age groups of children is also planned.

Dolutegravir timeline:

Dispersible tablet formulation end 2015

Pharmacokinetic data from IMPAACT P1093

- from 2 to 6 years mid 2017
- from 4 weeks to 2 years mid 2019

Comparative efficacy

- ODYSSEY (PENTA 20) opens early 2016

DTG/ABC/3TC

Development of a pediatric formulation of the FDC of DTG/ABC/3TC, – currently approved for adults and adolescents aged 12 years and above^{48, 49} - is also planned.

The DTG/ABC/3TC PIP requires data from IMPAACT P1093 in two to 12 year old children to inform DTG dosing. Results from the ARROW trial⁵⁰ (that found once-daily dosing of ABC and 3TC non-inferior to twice-daily in children) will provide data for ABC/3TC once-daily dosing.

The investigation plan also requires the completion of a DTG/ABC/3TC FDC pediatric study in two to 12 year olds. This will be an open-label, switch design and enroll children who are fully suppressed on ART and integrase inhibitor-naive.

DTG/RPV

The current plan for a pediatric DTG/RPV FDC is as a maintenance regimen in children and adolescents aged six to 18 years and virologically suppressed.

Data from planned adult phase III studies and existing adolescent data from single agents will be used for the 12 to 18 years age group. Providing the adult data supports the maintenance strategy, dosing studies and pediatric FDC development will then go ahead in the 6 to 12 age group.

Cabotegravir and Rilpivirine Long-Acting

Cabotegravir is under investigation as a long-acting formulation with RPV. An age appropriate formulation will be developed for induction and the intramuscular nanosuspension will be the same as for adults.

The final PIP was approved October 2014 and includes pharmacokinetics, safety, tolerability, durability, acceptability and maintenance of cabotegravir and rilpivirine in two to 18 year olds.

There is a waiver for children less than two and a deferral for two to 18 year olds. The PIP will be completed by 2018, so although the idea of long acting formulations might be appealing for children and adolescents, it is some way off.

PHARMACOKINETIC BOOSTER

Cobicistat

COBI is a CYP3A inhibitor with no antiretroviral activity. COBI 150 mg is approved for adults as a booster of atazanavir (ATV) 300 mg or DRV 800 mg, including in co-formulated tablets.^{51, 52} It is also under investigation for children and adolescents aged at least six years as a part of the FDCs: E/C/F/TDF and E/C/F/TAF.

A 50 mg pediatric immediate-release tablet and a 20 mg pediatric dispersible tablet are in development.

COBI is being studied in treatment-experienced children aged three months to 18 years who are suppressed and on RTV boosted ATV- or DRV-containing regimens.⁵³ The study will switch children from RTV to COBI and look at steady state pharmacokinetics and confirm the dose. It will also evaluate the safety, tolerability, and efficacy of ATV/COBI or DRV/COBI. Reduced dose co-formulations are planned.

CCR5 RECEPTOR ANTAGONIST

Maraviroc

The pediatric maraviroc (MVC) study is still ongoing in children aged two to 18 years who are infected with CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.⁵⁴

Dosing of MVC is complex and determined by body surface area and concomitant medications.⁵⁵ Wide use of MVC is not expected.

What Needs to be Done?

With a few modifications, most of the recommendations from previous years remain:

Implement WHO recommendations. As simpler formulations identified to implement the guidelines become available (most topically this year LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

Ensure that patents are not an obstacle. The MPP is putting a lot of emphasis on pediatric antiretrovirals and has now negotiated patent sharing agreements with ViiV, Gilead, Bristol-Myers Squibb, Merck/MSD and Abbvie – which takes care of the priority products in most low- and middle-income countries with large pediatric HIV epidemics. Licenses for the drugs in development need to make it easy to transfer patent agreements from one age band to another as approval is gained.

Speed up approval. The gap needs to be narrowed between approval of new drugs for adults, children, and neonates. An evidence base to support not always taking a de-escalated age band approach when studying new drugs is needed. Harmonization of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is needed to help speed up approval.

Coordinate procurement. Guidance on optimal formulations needs to be easily available to countries and updated as better ones become available. Companies need to be informed of the priority formulations. Donors need to ensure the availability of low volume products in a diminishing market.

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