The Pediatric Antiretroviral Pipeline

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INTRODUCTION

The development of new antiretroviral drugs and appropriate formulations for children continues to be far too slow. There are now 2.6 million children in need of antiretroviral treatment (ART) globally. Of those treated, more than 40% are on a suboptimal regimen.[1] What is on offer to treat them has been described as: "too much of what we don't need".

This means limited options for newborns, still too few appropriate fixed dose combinations (FDCs), and pediatric regimens that cannot harmonize with those recommended for adults.

Since the 2015 *Pipeline Report*, there has been little change. But a few steps in the past year are noteworthy:

- World Health Organization (WHO), The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) and UNICEF published and policy brief and factsheet on the lopinavir/ritonavir (LPV/r) oral pellets, that provide program managers, implementers, procurement and supply chain managers, important points to consider before and during the introduction of the new formulation.[2]
- The updated WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection now include integrase inhibitors – a new antiretroviral class for children.[3]
- The US Food and Drug Administration (FDA) approved dolutegravir (DTG) 25 mg and 10 mg tablets for children weighing at least 30 kg in ages six to less than 12 years old.[4]

This commentary gives an update on the pediatric antiretroviral pipeline, with a focus on low- and middle-income countries (LMIC). Sharp-eyed regular readers will note that not much has moved on from last year's report (so some of the summaries remain the same) as unfortunately recent developments have not been very speedy.

WHO 2015 Guidelines

In line with adult first-line recommendations, there are two new alternative regimens for adolescents: DTG or efavirenz (EFV) 400 mg based. Raltegravir (RAL) is now recommended second-line for younger children and DTG and darunavir/ritonavir (DRV/r) is recommended for third-line.

As with the 2013 recommendations, there are no suitable generic formulations yet to support this guidance (although for adolescents DTG and EFV 400 mg based ones are on the way for adults. See Fit for Purpose: antiretroviral treatment optimization chapter).

Only one regimen (that is not preferred), zidovudine (AZT) plus lamivudine (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: WHO recommended first-line ART for children and adolescents

First line ART	Preferred regimens	Alternative regimens
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV 400 mg TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LVP/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

Table 2. WHO recommended second- and third-line ART for children and adolescents

First line ART	Preferred regimens	2nd-line regimens	3rd-line regimens
Children	2 NRTIs + LPV/r	Less than 3 years: 2 NRTIs + RAL	DTG + 2 NRTIs DRV/r + 2 NRTIs DRV/r + DTG + 1-2 NRTIs
		Older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTIs + EFV	2 NRTIs +ATV/r or LPV/r	

Key: ATV/r, atazanavir/ritonavir; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LVP/r, lopinavir/ritonavir; NVP, nevirapine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir

Lopinavir/ritonavir pellets

In 2015 the big news for pediatric HIV in LMIC was that there is finally a solid form of LPV/r suitable for infants and young children. On 21 May 2015, the US FDA tentatively approved LPV/r pellets, manufactured by Cipla (working in collaboration with the Drugs for Neglected Diseases Initiative [DNDi]) for infants and young children less than three years old.[5, 6]

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.[7] The agreement should help to make the new formulation available for children in LMIC. The next hurdles are getting it approved by regulatory agencies and used in programs in these countries.

WHO has recommended LPV/r-based regimens as preferred for infants and young children since the 2013 guidelines.[8] Following this 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 LMIC. The solid 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 trial[9] – that showed similar LPV/r exposure with pellets and syrups – revealed that pellets were not more acceptable than syrups by 48 weeks.[10] 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.

The LIVING study is an implementation study using the new formulation ongoing in Kenya and starting soon in several other sub-Saharan African countries.[11] 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).

Missing pediatric formulations

Several gaps remain in available products for children that need to be filled before even the 2013 WHO guidelines (you read that right) can be implemented in most LMIC.

Where possible these should be FDC dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules like LPV/r) pellets 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 LMIC. [12]

The two priority formulations needed to treat children according to the 2013 guidelines remain notable by their absence: [13]

AZT or abacavir (ABC) plus 3TC plus LPV/r. These formulations are still 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 LPV/r pellets still need 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 0.8mm pellets and more sand-like in texture). [14]

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 quite some time now and are still unavailable.

Recommendations from PADO2: more missing formulations

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 a WHO 2014 supplement,[15] and the priority formulations are still missing.

The Second Pediatric Antiretroviral Drug Optimization (PADO2) meeting,[16] 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.

Newborns

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 3. Data from population modelling can help to predict dosing regimens in this age group.

NVP clearance is low immediately after birth and increases dramatically over the first months of life. Since PADO2 the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) have presented population modelling and pharmacokinetic simulations predicting dosing regimens to achieve target NVP treatment concentrations in term and late preterm infants.[17]

NVP clearance is low in term neonates, and lower still in preterm ones, because of immaturity in CYP2B6 and CYP3A4 activity. Clearance is also autoinduced in proportion to the size of the NVP dose in the first years of life.

Pharmacokinetic data are available to guide NVP dosing for treatment of HIV in infants after one month of life: trough concentration target 3.0 ug/mL. But NVP pharmacokinetic studies in infants less than one month old are limited to evaluations of dosing regimens for prevention of vertical transmission: trough concentration target 0.1 ug/mL.

Increasing evidence for early treatment and trends on early infant diagnosis – as well as a paucity of other antiretroviral options in this age group – has led to considerable interest in the use of NVP as part of ART regimens for neonates.

IMPAACT used population modelling to evaluate proposed NVP dosing regimens to meet target concentrations in term and late preterm infants (34-37 weeks gestation) from birth to 6 months old. The model included data from 192 infants (1121 plasma NVP concentrations) from US, Africa and Brazil.

CYP286 metaboliser status, rate of autoinduction, and preterm effects were estimated from published literature. Dosing regimens from birth through 6 months of age were evaluated using simulations. Simulations were used to evaluate proposed NVP doses of 6 mg/kg twice daily for term infants and 4mg/kg twice daily for one week followed by 6 mg/kg twice daily for late preterm infants. The target was to meet trough concentrations of > 3.0 ug/mL.

Clearance was scaled allometrically and volume of distribution scaled linearly for weight. It was modelled to mature with age and autoinduction as a linear function of dose. Effects of prematurity and maturation of CYP2B6 and CYP3A4 activity on NVP clearance from published data were included.

The model revealed that typical NVP clearance (L/hr/kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and by an additional 79% due to induction. The final simulations used term infant doses of 6 mg/kg twice daily and late preterm infant doses of 4mg/kg twice daily for one week followed by 6 mg/kg twice daily. In these simulations, the dosing regimens achieved NVP targets.

The study concluded that NVP dosing regimens in neonates must take into account the impact of maturation, auto-induction and prematurity on NVP clearance.

More missing data for priority antiretrovirals will be provided by ongoing IMPAACT trials:

P1026s – phase IV, prospective, pharmacokinetic study in pregnancy and post partum, that obtains infant antiretroviral washout data.[18]

P1093 – phase I/II, open label, non-comparative, intensive pharmacokinetics and safety study of DTG down to four weeks.[19]

P1097 – washout pharmacokinetic study of RAL including in low birth weight (<2500 g) infants.[20]

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.[21]

P1110 – phase I open label, non-comparative pharmacokinetic dose-finding study of RAL in high risk, HIV-exposed neonates.[22]

P1115 – phase I/II proof of concept study of very early intensive antiretroviral therapy (ART) in infants to achieve HIV remission.[23]

Table 3: Newborn treatment options (or lack of options to date): including ongoing and planned IMPAACT trials

Compound	Preterm	Term	2 weeks
Nucleos(t)ide Reverse Transcriptase Inhibitor			
ABC	P1106 < 2500 g		
AZT	√	√	√
ddI			√
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	√

Compound	Preterm	Term	2 weeks
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.

Key: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; ddI, 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.

Infants and children

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.

Adolescents

Discussion about adolescents at PADO2 focused on adherence and more tolerable alternatives to EFV.

Priority antiretrovirals

For second-line treatment a generic, co-formulated, heat stable version of darunavir/ritonavir (DRV/r) is a priority. 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 FDA and EMA) need to be simplified to reduce the number of different formulations and minimize pill burden for children in LMIC. 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.

Approved pediatric dosing regimens for DRV/r are different from WHO-recommended ones because different weight bands have been used. When considering a co-formulation for children, generic manufacturers will likely use a darunavir:ritonavir (DRV:RTV) fixed ratio and the WHO pediatric weight bands.

To simplify administration, WHO recommends five weight bands from 10 kg to > 35 kg and a 6:1 ratio of DRV:RTV. US approved dosing uses eight weight bands from 10 kg to >40 kg, and varying DRV:RTV ratios that range from 7.5:1 to 5.8:1.

Janssen, the originator manufacturer of DRV, conducted a pharmacokinetic simulation to look at a regimen that conforms with the WHO weight bands and 6:1 ratio, and reaches DRV exposures comparable to

those in adults. [24] These simulations suggest that DRV dosing according to current WHO weight band recommendations might lead to either under-dosing in a lower weight band or over-dosing in a higher weight one. The study suggested that simple changes to the current WHO dosing schedule could improve DRV exposure in children while still keeping to the number of weight bands and a standard DRV/r dosing ratio.

The priority antiretrovirals identified by PADO2 participants in the medium-term (five years) are: DTG, RAL and tenofovir alafenamide (TAF), which are discussed below. The meeting 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. A pediatric first-line regimen of DTG/TAF/3TC has the potential to harmonize with that planned for adults.

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, and the list of pipeline pediatric drugs and regimens 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 an age 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.

The problems with the age-staggered approach that results in delays in approval and availability of new drugs, particularly in the youngest age group where options are lacking, have been much discussed. WHO uses a weight band dosing approach and it would make sense to investigate weight band dosing in pediatric antiretroviral development from the beginning, optimizing the use of pharmacokinetic data and modelling. The DTG development program, IMPAACT P1093 (see below), will try to capture enough data to inform weight band dosing, with the dispersible tablet in the younger cohorts.

Moving away from the age-staggered approached to weight bands could also make it possible to open multiple cohorts simultaneously, if formulations are available, which would speed up availability of new drugs for infants and children considerably.

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.

If work on aligning age bands with WHO weight bands could be done as originator manufacturers conduct their pediatric development programs, this would help generic manufacturers develop co-formulations and FDCs that allow dosing aligned with recommendations across the weight bands. It could help close the gap between when new drugs and regimens are available in LMIC for adults and children.

The current pediatric antiretroviral pipeline is shown in Table 4.

Table 4. The pediatric antiretroviral pipeline

Compound	Sponsor	Formulation/s and dose	Status and comments
Nucleotide reverse transcriptase inhibitor and combinations			
Tenofovir alafenamide f (TAF)/ emtricitabine (FTC) elvitegravir (EVG)/cobicistat (COBI) (E/C/F/TAF)	Gilead	Reduced dose FDC tablets in development	Phase II/III singlearm, 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 3rd 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

Compound	Sponsor	Formulation/s and dose	Status and comments
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) 3 to < 18 years (DRV/c)
Darunavir/cobicistat (DRV/c)	Gilead/Janssen		
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	10 and 25 mg tablets approved for children and adolescents 6 years and above weighing >30kg in US Phase I/II study, 6 weeks to <18 years treatment-naive and -experienced children, ongoing
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

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 adult 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 development of an FDC of elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (E/C/F/TAF) is the originator company, Gilead Science's priority. Gilead is also investigating a co-formulation with FTC (F/TAF) – recently approved for adults. [25, 26]

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.[27]

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 to18 years is ongoing.[28] There is a waiver for children less than six years old.

In the phase II/III study in 12 to 18 year olds with a median age of 15 years receiving E/C/F/TAF, 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.[29]

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.[30] The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naive and -experienced children aged two months to six years.[31] 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-naive adolescents aged 12 to 18 years.[32]

Based on pharmacokinetics, tolerability and efficacy data at four weeks, a dose of 25mg RPV once daily with food was selected[33] – providing comparable exposure to that in adults. This dose was effective and generally well tolerated over 24 weeks for the treatment of ART-naive adolescents with viral load less than 100,000 copies/mL.[34] PAINT is ongoing.

IMPAACT P1111 is planned in children from two weeks to less than 12 years of age.[35] 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 studies will enroll populations similar to those in adult phase III studies: treatment-naive and stable experienced patients for switch studies.

PROTEASE INHIBITOR

Lopinavir/ritonavir

As described above, the FDA has tentatively approved LPV/r pellets for young children. DNDi and Cipla are continuing to develop 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 soon.

INTEGRASE INHIBITORS

Raltegravir

RAL is approved for infants and children from four weeks of age.[36] For the youngest age group (four weeks to less than two year olds, weighing 3 kg to 20 kg) it is formulated as granules for oral suspension. The formulation 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. Giving RAL to neonates currently requires a complex dosing regimen.

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. There have been discussions about the possibility of using the chewable formulation in younger age groups, as the granules for oral suspension are complicated to use.

A comprehensive development plan is ongoing with the IMPAACT Network including in neonates less than four weeks of age (both HIV-infected and exposed) infants. [37,38, 39, 40, 41, 42] This development plan is excellent and deserves detailed review. It will provide comprehensive data to inform dosing of young infants for both treatment and prophylaxis. IMPAACT are following a similar plan with DTG.

IMPAACT P1097 was conducted to look at washout PK in neonates born to mothers receiving RAL in late pregnancy. This study showed that RAL crosses the placenta well. There was variable and prolonged elimination of RAL in the first days of life compared with older infants and children. P1097 is now assessing washout PK in a cohort of low birth weight (including preterm) neonates.

IMPAACT P1110 is an ongoing two-part PK and safety study of RAL in term neonates at high risk of vertical HIV infection, informed by P1097 results.

RAL has the potential for use in prophylaxis and treatment of neonates at high risk of vertical HIV infection. The drug is primarily metabolized by UGT1A1, which has low activity at birth but increases over the first weeks of life and will influence neonatal dosing.

IMPAACT P1110 aims to evaluate the phamacokinetics and safety of RAL and find an appropriate dose for neonates and infants up to six weeks of age. The study has a two cohort adaptive design: pharmacokinetic data from cohort 1 are included in pharmacokinetic modelling to inform dosing in cohort 2. It is a phase I multicentre pharmacokinetic study of in full-term, HIV-exposed, high-risk neonates.

Data from P1110 were presented last year. [43] Cohort 1 participants received a single oral dose of RAL within 48 hours of birth added to standard of care antiretrovirals for PMTCT prophylaxis, and a second dose at 7-10 days old. The initial dose was 3 mg/kg and doses were adjusted as the study progressed. RAL-exposed infants born to mothers receiving the drug during pregnancy and delivery were excluded at the beginning of the study. Later their enrollment was permitted with a lower initial dose.

An intensive pharmacokinetic sampling was performed around the initial dose: pre-dose and 1-2 hours, 4-8 hours, 12 hours, 24 hours post-dose and a random sample at 3-4 days old. Sampling was at three time points around the second dose: pre-dose and 1-2 hours and 24 hours post-dose. A validated HPLC-MS-MS method with a lower limit of quantification of 22.5 nM was used to analyse the samples. Protocol specified exposure limits from non-compartmental analysis for each participant were: Cmax $<$ 19.6 uM and AUC12 $<$63 uMxhr.

Cohort 1 comprised 13 neonates: 10 were born to mothers who did not receive RAL before delivery (RAL-naive) and 3 to mothers who received RAL before and during delivery (RAL-exposed). Neonates were 54% female with a median gestational age of 39.0 weeks (range 36.0 to 39.6) and birth weight of 3.02 kg (2.39 to 4.20). Evaluable initial dose and week 1 dose concentration data were available for 12/13 neonates.

The interim analysis of pharmacokinetic data from the first six RAL-naive neonates who received 3 mg/kg initial doses found none exceeded the Cmax upper limit but two exceeded the AUC12 upper limit. Following this analysis, the initial dose was reduced to 2 mg/kg for RAL-naive and 1.5 mg/kg for RAL-exposed neonates.

All neonates received 3 mg/kg for the second dose at 7-10 days old. All 12 evaluable neonates had a Cmax $<$19.6 uM. But, 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose exceeded AUC12 $<$ 63 uMxhr.

A population pharmacokinetic model including the initial cohort 1 pharmacokinetic data from 6 neonates and

RAL concentration data from 24 infants and children ages 4 weeks to <2 years from IMPAACT P1066 – a phase 1/2, multi- centre, open-label, non-comparative intensive pharmacokinetic study in infants and children – was developed. And population modelling of the combined data was performed.

This revealed a change in absorption rate from 16% of maximum at birth to 90% within 2 weeks. Clearance changed from almost nil to a maximum at approximately 6 months of age.

Pharmacokinetic parameters including absorption and clearance were estimated using this population model, and simulations of various dosing regimens in the first 6 weeks of life were run.

In the final model the dosing regimen through 6 weeks of age that best met the following revised PK exposure targets (defined for safety and efficacy from recent studies in older infants, children and adults) was selected for use in cohort 2: Cmax <19.63 uM, Cmin>75nM, AUC12 (twice a day) <45 uM*hr and AUC24 (one a day) < 90 uM*hr.

Cohort 2 will begin enrolling RAL-naive neonates with the dose selected from the pharmacokinetic modelling and simulations: 1.5 mg/ kg once a day from birth to day 7, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day to age 6 weeks.

Additional pharmacokinetic data need to be obtained before RAL-exposed neonates are enrolled. Pharmacokinetic results for cohort 2 will be evaluated on a rolling basis and dosing adjusted based on these results.

Neonates exposed to RAL in utero might require a different dosing strategy and are also being studied in P1110.

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.[44]

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.[45]

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.[46]

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.47 Early data has shown similar exposures of all the individual agents to adults and good virologic suppression. [48] Study of E/C/F/TDF in adolescents and children continues.

Dolutegravir

DTG 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.

DTG is being studied in infants (down to 4 weeks of age), children and adolescents in IMPAACT P1093. [49] The estimated primary completion date for the whole study is May 2018.

Expert groups have identified DTG as a priority for children (as well as adults) in LMIC. The development of generic formulations of DTG for children should follow as swiftly as the originator company ViiV Healthcare and regulators allow.

The US FDA recently approved a supplemental new drug application (sNDA) for DTG 10 mg and 25 mg oral tablets, reducing the weight limit from at least 40 kg to at least 30 kg in ages 6 to less than 12 years old.[50] The indication is for treatment naive and experienced but not INSTI experienced children and based on 24-week data from IMPAACT P1093.

IMPAACT P1093 is an ongoing, phase I/II, open label pharmacokinetic, safety and efficacy study in children and adolescents in age de-escalated cohorts of DTG plus optimized background regimen. [51]

The dose is 1 mg/kg once daily (based on weight bands). Forty-eight week data have been presented for children aged 6 to 12 years and children and adolescents aged 12 to 18 years.[52, 53, 54, 55] Both age groups showed good short-term safety and tolerability. IMPAACT P1093 is continuing to evaluate infants and young children 4 weeks of age and above.

ViiV has developed a 5 mg dispersible tablet formulation of DTG as an alternative to the granule formulation (which was originally developed and used in early studies) for infants and young children. The dispersible tablet and granule formulations are bioequivalent.[56]

The oral bioavailability of DTG is affected by metal cation-containing supplements. The originator company has compared DTG pharmacokinetics when tablets are dispersed in either low mineral content or high mineral content water in a randomized, open-label, 5-way, single-dose crossover study in HIV negative adults with DTG administered at 20 mg.

ViiV have also evaluated whether or not consuming the dispersed in water tablet immediately or after the suspension had been standing for 30 minutes made a difference.

The study showed equivalent exposure with the two DTG formulations, so found the dispersible tablet to be bioequivalent to the granule formulation. DTG PK was not affected by water mineral content or 30-minute delay in dispersed tablet consumption. The dispersible tablet can be given under these conditions.

In the limited data collected on palatability, the majority of participants described the taste and mouth feel of the dispersible tablet as acceptable. But the granule formulation appeared to be more acceptable than the dispersible tablet.

The dispersible tablet is undergoing further development and the formulation is being adjusted to improve the taste. Taste masking work on the dispersible tablets is also ongoing. The tablets will be strawberry cream flavored.

The two cohorts in the youngest age groups (6 months-2 years and 4 weeks-6 months) started with the granules in suspension formulation but use of this will stop once the 5 mg dispersible tablet formulation is available on site. Only the dispersible tablets will be available commercially.

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

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 [57, 58] - 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 trial[59] (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 adults, 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.60, 61 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.62 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.[63]

Dosing of MVC is complex and determined by body surface area and concomitant medications. [64] Wide use of MVC is not expected.

WHAT NEEDS TO BE DONE?

Speed up development. 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. Optimize use of pharmacokinetic data and modelling.

Speed up approval. 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.

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

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. Plans need to be in place to phase out suboptimal formulations and phase in new ones. Donors need to ensure the availability of low volume products in a diminishing market.

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