The Pediatric Antiretroviral Pipeline

By Polly Clayden

The last Pipeline Report described a bumper year for pediatric antiretroviral approvals. This one reports after a year in which new approvals were fewer and far between.

Although the pipeline for children continues to look promising, pediatric investigational programs mostly sauntered along, with only two new United States Food and Drug Administration (FDA) approvals: an expanded indication for efavirenz to include children at least three months old, and once-daily dosing of darunavir in treatment-naive children three years and older.1,2

Two development programs—the granule formulation of ritonavir-boosted protease inhibitor lopinavir, and the integrase inhibitor dolutegravir—remained attention-worthy.3,4

This year’s headline-hogging news, of the Mississippi cure baby,5 was accompanied by a plague of bad journalism. Pipeline Report co-author Richard Jefferys provided a much-needed voice of reason on this case of a potential “functional cure” in an HIV-infected infant.6 The news would be good if the attention it grabbed helps to sharpen the focus of research and implementation of maternal/infant HIV programs in places where they are badly needed.

Finally the World Health Organization (WHO) has revised its HIV guidance—this time recommendations for adults (including pregnant women) and children are consolidated into one document.7 This chapter updates the pediatric antiretroviral pipeline in the context of the new recommendations.

Efavirenz

The FDA expanded indication for efavirenz to infants at least three months old and weighing at least 3.5 kg was approved on May 2, 2013. For children unable to swallow capsules, these can be broken and the contents (dispersible sprinkles) given with a small amount of soft food, or formula milk if they are too young for solids.

The updated labeling includes a table for dosing showing the number of capsules or tablets and strength by weight band. See Table 1.
Table 1. Efavirenz Weight Band Dosing for Children 3.5 to Less Than 40 kg

<table>
<thead>
<tr>
<th>Weight/kg</th>
<th>Daily Dose/mg</th>
<th>Number of Capsules a or Tablets b and Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 to less than 5</td>
<td>100</td>
<td>two 50 mg capsules</td>
</tr>
<tr>
<td>5 to less than 7.5</td>
<td>150</td>
<td>three 50 mg capsules</td>
</tr>
<tr>
<td>7.5 to less than 15</td>
<td>200</td>
<td>one 200 mg capsule</td>
</tr>
<tr>
<td>15 to less than 20</td>
<td>250</td>
<td>one 200 mg + one 50 mg capsule</td>
</tr>
<tr>
<td>20 to less than 25</td>
<td>300</td>
<td>one 200 mg + two 50 mg capsules</td>
</tr>
<tr>
<td>25 to less than 32.5</td>
<td>350</td>
<td>one 200 mg + three 50 mg capsules</td>
</tr>
<tr>
<td>32.5 to less than 40</td>
<td>400</td>
<td>two 200 mg capsules</td>
</tr>
<tr>
<td>at least 40</td>
<td>600</td>
<td>one 600 mg tablet OR three 200 mg capsules</td>
</tr>
</tbody>
</table>

aCapsules can be administered intact or as sprinkles. b Tablets must not be crushed.

Source: FDA. Sustiva (efavirenz) pediatric patients labeling update. 2013 May 2.

The update was based on three open-label trials to investigate the pharmacokinetics, safety, tolerability, and antiviral activity in antiretroviral-naive and experienced children age three months to 21 years.

Pharmacokinetic parameters at steady state were based on data predicted by a population pharmacokinetic model by weight ranges that correspond to the recommended doses.8

This approval came as a bit of a surprise as the pediatric formulations for efavirenz took some time to develop (adult approval was in 1998). An appropriate one for the youngest children has remained elusive for many years. The 2010 Pediatric Antiretroviral Pipeline described the hurdles:9

“Development of a liquid formulation of efavirenz has been besieged by setbacks for years. Efavirenz has potential for oral mucosa irritation; it also has poor aqueous solubility. Early development focused on palatable alternatives to the aqueous suspensions using oily vehicles that were known to mask irritation. The original oral solution, a suspended sugar solution, was found to have a low level of bacterial contamination; the culprit was confectioner’s sugar. A heating step was then incorporated into the process to destroy the bacteria, but this then led to clumping. The current liquid formulation is a sugar-free strawberry mint flavor 30mg/mL solution. It does not provide sufficient drug exposure for children less than three years of age.”

Formulation glitches aside, a strong influence of CYP2B6 genotype polymorphisms on efavirenz pharmacokinetics and safety has been shown in children less than three years old.10 In one study, using aggressive dosing (approximately 40 mg/kg) with the opened capsules, produced therapeutic efavirenz concentrations in most
(68 percent) children of the children in this age group (with GG or GT genotype), but this led to excessive exposure in the remainder (with TT genotype). This suggested that optimal use of efavirenz in children less than three years requires pretreatment genotyping. A related study, using modeling to predict the pharmacokinetics of efavirenz in children with different CYP2B6 genotypes, also indicated genotype-guided dose optimization might be used in young children.\textsuperscript{11}

Efavirenz could be important for use with concomitant tuberculosis (TB) treatment, but WHO has just recommended boosted lopinavir first-line for infants and children less than three, and triple nucleoside reverse transcriptase inhibitors (NRTIs) during treatment of TB.\textsuperscript{12} For older children, tentatively approved reduced strength (50 and 100 mg) and scored adult tablets (200 mg twice on one side and once on the other) are available.\textsuperscript{13,14}

Concerns about non-nucleoside reverse transcriptase (NNRTI) resistance acquired through in utero exposure, as well as comparative potency to protease inhibitors (PIs) that led to nevirapine being only recommended if boosted lopinavir is not available, could also apply to efavirenz.\textsuperscript{15,16}

It is unclear whether this new formulation and indication is an important breakthrough. But the tenacity of the sponsor to finally produce one—albeit without a clear role (including in rich countries)—is impressive.

**WHO Guidelines 2013**

The new guidelines include antiretroviral treatment recommendations for adults and children (including pregnant women). Guidance is also given on implementing the recommendations.

**When to Start?**

Infants and children should initiate antiretroviral therapy:

- Less than five years old regardless of CD4 count or WHO stage. Strong recommendation for children up to one year and conditional from one to five years.
- At five years and older with 500 CD4 cells/mm\textsuperscript{3}. Strong recommendation 350 cells/mm\textsuperscript{3} and below, and conditional 350 to 500 cells/mm\textsuperscript{3}.
- With severe or advanced symptomatic disease (WHO stage 3 or 4) regardless of age or CD4 count. Strong recommendation.
- With a presumptive HIV diagnosis below 18 months. Strong recommendation.
- With active TB. As soon as possible within eight weeks following the start of TB treatment regardless of CD4 or WHO clinical stage. Strong recommendation.
What to Start?

First-line for infants and children less than three years old:

- Lopinavir/ritonavir-based regimens regardless of previous NNRTI exposure. If lopinavir/ritonavir is not feasible, nevirapine-based. Strong recommendation.

- Consider substituting lopinavir/ritonavir 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). Conditional recommendation.

- Children who develop active TB while on boosted lopinavir- or nevirapine-based regimens should be switched to abacavir plus lamivudine plus zidovudine during TB treatment. They should switch back to the original regimen when their treatment for TB is completed. Strong recommendation.

- The NRTI backbone should be one of the following (in order of preference): abacavir or zidovudine plus lamivudine; stavudine plus lamivudine. Strong recommendation.

First-line for children three years and older:

- Efavirenz preferred and nevirapine alternative. Strong recommendation.

- Less than 12 years (or weighing less than 35 kg) the NRTI/nucleotide reverse transcriptase inhibitor [N(t)RTI] backbone should be (in order of preference): abacavir plus lamivudine; zidovudine or tenofovir disoproxil fumarate (DF) plus lamivudine or emtricitabine. Conditional recommendation.

- Adolescents 12 years (weighing more than 35 kg) should align with adults, the NRTI backbone should be: tenofovir DF plus lamivudine or emtricitabine; abacavir or zidovudine plus lamivudine. Strong recommendation.

Which Second-line?

- After first-line NNRTI failure, a boosted PI; lopinavir/ritonavir is preferred. Strong recommendation.

- After failure of first-line lopinavir/ritonavir, children less than three should remain on the regimen with improved adherence support. Conditional recommendation.

- After failure of first-line regimen containing abacavir or tenofovir DF plus lamivudine or emtricitabine, the preferred NRTI backbone is zidovudine plus lamivudine. Strong recommendation.
• After failure of first-line regimen containing zidovudine or stavudine plus lamivudine or emtricitabine, the preferred NRTI backbone is abacavir or tenofovir DF plus lamivudine or emtricitabine. Strong recommendation.

Missing Formulations

One of the goals of treatment optimization is to align pediatric antiretroviral regimens with recommendations for adults. With current options, the youngest children need to be considered differently, and there is some room for interpretation in the guidelines as to what age this harmonization should begin.

In order to implement the revised guidelines, child-sized solid dosing forms of recommended antiretrovirals, in appropriate strengths, are needed to facilitate dosages according to WHO simplified tables. Where possible these should be fixed-dose combination (FDC) dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules) granules are preferable to liquids. These formulations are expensive, have short shelf lives, and often require a cold chain, making them hard to store and transport.

Lopinavir/ritonavir

For the youngest infants and children, implementing lopinavir/ritonavir-based regimens with the currently available formulations is easier said than done. There is an 80/20 mg/mL liquid formulation, but it is unsuitable for most settings for the aforementioned reasons. It also tastes appalling. There are also scaled down 100/25 mg heat stable tablets available for children, but these are only suitable for those weighing 10 kg or more. The tablets are formulated with the active ingredient embedded in a matrix of insoluble substances, so cannot be split or crushed as they lose bioavailability.

Cipla and the Drugs for Neglected Diseases initiative (DNDi) are developing a more acceptable granule formulation of 40/10 mg lopinavir/ritonavir as part of a first-line regimen for infants and young children. They are also working on either abacavir or zidovudine plus lamivudine granules as backbone and aim to produce adapted 4-in-1 regimens for children under three.

In recognition of the urgency of a suitable formulation for this age group DNDi was awarded a substantial grant by UNITAID to expedite 4-in-1 development and delivery. The plan is to have the new formulation and regimen by 2015 and to help to consolidate rather than further fragment the market—that is, have this regimen replace many existing and not always very useful formulations currently available for infants and young children.
Tenofovir Disoproxil Fumarate

Last year a 40 mg/1 g oral powder formulation, and 150 mg, 200 mg, and 250 mg tablets of tenofovir DF, and dosing recommendations for children age two to less than 18 years were approved. The recommended dose is 8 mg/kg (up to a maximum of 300 mg).

Tenofovir DF for young children also took its time—the FDA approved it for adults in 2001. Like efavirenz, there were problems with the pediatric formulation—the original liquid-suspension formulation tasted too bitter for further development. The powder for younger children is an improvement, but its nasty taste is not well masked and it is hard to administer, making adherence problematic (sometimes called the “new nelfinavir”). The pediatric tablets appear to be more palatable, although exposure can be variable with the approved dose.

Also last year the WHO published a review of the current literature and unpublished data on the safety and efficacy of tenofovir DF in children. The review found it to be efficacious in children and adolescents at current FDA-approved doses, but further studies are needed to confirm the dose and investigate its side effects, particularly in combination with efavirenz.

The main toxicities are decreased bone mineral density, and glomerular and renal tubular dysfunction. Data in children are scant but suggest that the toxicities are similar to those seen in adults.

Bone turnover is higher in young children and adolescents because they are growing. Children’s bone mineral density increases over time whereas in adults it remains constant or decreases with age, so comparisons between adults and children are difficult. Plus children with HIV have lower bone mass than background population for their age and sex. The impact of lower bone mineral density on longer-term risk of fracture and osteoporosis is not known. This long-term risk is concerning.

Several studies have suggested significant glomerular and renal tubular toxicity in children on tenofovir DF, but the role of concomitantly used antiretrovirals, such as didanosine and ritonavir-boosted lopinavir is unclear.

At present there are still questions about its use in children and the guidelines are a bit ambiguous as to what age it should be recommended. It is introduced for the three to less than 12 age group third in order of preference after abacavir and zidovudine. For adolescents 12 years and older it takes first place in line with adult recommendations.

To facilitate simplified dosing with the current formulations, 2.5 scoops of the oral powder could be used for a child 10 to 13.9 kg and one 150 mg tablet for the next weight band, 14 to 19.9 kg etc. Triple FDCs, scaled down to a quarter of the
adult tablets, 75/75/150 mg tenofovir DF/lamivudine/efavirenz (or with 60 mg emtricitabine), as well as dual 75/75 mg and 75/60 mg with tenofovir and lamivudine or emtricitabine, respectively, are needed to make this a realistic option.

The WHO pediatric group considered the feasibility of scoring adult FDC tablets once on one side and twice on the other. The doses delivered by tablets divided into thirds and halves would be acceptable, but there is concern that in practice it might be difficult to manufacture, score and split large, multilayered FDC tablets in this way. If such tablets are possible, it will be important to establish feasibility, pharmacokinetic and bioavailability data to support this dosing strategy.

**Darunavir/ritonavir**

At the end of 2011, a 100 mg/mL oral suspension formulation of darunavir was approved, with dosing recommendations for children three to less than six years old. There is a waiver for children under three, due to very high darunavir concentrations in animals (of an analogous age) and, in turn, toxicities in preclinical studies.

Ritonavir-boosted darunavir is increasingly used in children and adolescents in rich countries, particularly in those with treatment experience. This could be a useful option for third-line regimens for children, and for second-line regimens where boosted lopinavir has been used as first-line.

The Pediatric Antiretroviral Group of the WHO considered darunavir to be of high priority and in the 2011 Updated List of Missing Drug Formulations listed a tablet or sprinkle formulation of darunavir/ritonavir as urgently needed.

Using boosted darunavir with the currently approved doses does not lend itself to harmonized, simplified weight-band dosing or to appropriate use in combined tablets to facilitate this. The establishment of a single ratio at best, or at least a simpler dosing range would make wider use of darunavir more feasible. As the varied ratios were because of the limits of ritonavir formulations, there seems no reason why a 6:1 ratio twice daily, as for adults, shouldn’t be possible.

For the 2013 guidelines, the WHO group lists a 240/40 mg darunavir/ritonavir tablet for twice-daily dosing as a priority for children weight bands 10 kg and above.

**Atazanavir/ritonavir**

The capsule formulation of atazanavir is approved in the United States and the European Union for children ages six years and older who are treatment-naive and -experienced children weighing 15 kg or more. Capsules are available in 100, 150, 200, and 300 mg atazanavir.
For boosting, the atazanavir/ritonavir ratio is 3:1 and, as with darunavir, this is complicated by the currently available formulations. A heat stable tablet once daily 100/33 mg atazanavir/ritonavir could help to align second-line treatment for children 10 kg and above, who received an NNRTI first-line, with adult recommendations.

Generic heat stable 300/100 mg atazanavir/ritonavir tablets for adults are already produced, including one that is tentatively approved. A reduced-strength tablet for children, scaled down to one third of the adult one, is another priority.

**The Pipeline**

Formulations for young children for all but one drug in the current pipeline are granules, dispersible tablets, or powder, some of which might be useful for resource-limited settings in the future.

**NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

**Etravirine**

A scored 25 mg etravirine tablet, and dosing recommendations for treatment-experienced children and adolescents ages six to less than 18 years of age and weighing at least 16 kg, are currently approved. The recommended dose is based on 5.2 mg/kg twice daily.

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

Etravirine might be a useful second-line NNRTI option for children as its resistance profile is different from those of nevirapine and efavirenz; it should not be co-administered with rifampicin.

**Rilpivirine**

The PAINT phase II trial is currently enrolling treatment-naive adolescents ages 12 to less than 18, weighing more than 32 kg, and receiving 25 mg once daily plus two NRTIs. The trial will evaluate steady-state pharmacokinetics and short-term antiviral activity in this age group.

IMPAACT 1111 is planned in children from neonates to less than 12 years. This trial
is also taking a staggered approach and will study the drug in de-escalated age
groups: six to twelve years, two to six years, six months to two years and less than
six months. A granule formulation is in development.

PROTEASE INHIBITORS

Atazanavir

Treatment-naive and -experienced children ages three months to eight years
receiving atazanavir boosted with ritonavir are being studied in PRINCE 1 and 2
and IMPAACT P1020A, phase II, IIB and I/II. PRINCE 1 is now fully enrolled,
and data are expected this year; PRINCE 2 is over half enrolled, and data are
expected at the end of 2013 and IMPAACT P1020A is ongoing.

For younger children a powder formulation is in development, which is boosted
with ritonavir liquid.

Lopinavir/ritonavir

The generic manufacturer Cipla is developing a pediatric formulation of lopinavir/
ritonavir in partnership with DNDi. The original sprinkle formulation (40/10 mg
lopinavir/ritonavir) consists of a finite number of mini-tablets in a capsule, which is
opened and sprinkled on soft food.

Data from a randomized crossover pharmacokinetic study in healthy adults
comparing a single dose of sprinkles from 10 capsules of lopinavir/ritonavir with a
single dose of 5 mL Kaletra oral solution found most pharmacokinetic parameters
fell within the conventional bioequivalence range of 80 to 125 percent in this study.
Where they fell outside, the differences were not large. Both formulations were
administered with about 150 g porridge and 240 mL water.

Initial data from CHAPAS-2—which compared twice-daily sprinkles to tablets in
children ages four to 13 years, and sprinkles with syrup in infants ages three to 12
months in a randomized cross-over pharmacokinetic study—found high variability
in the younger cohort with both sprinkles and syrup, with no significant differences
in sub-therapeutic concentrations between formulations. In the older children,
lopinavir/ritonavir concentrations were lower in children receiving the sprinkles than
in those who got the tablets.

The caregivers found the sprinkles were more acceptable for infants but not for
older children, mainly due to the taste. Acceptability data showed storage,
transport, and conspicuousness of treatment were less problematic for sprinkles
compared with syrups, but for older children, several caregivers commented about
the number of capsules needing to be used. At week eight, when they could chose which formulation to continue with, the majority of caregivers chose to continue sprinkles rather than syrups for the infants, but only a quarter of the older children chose sprinkles over tablet, and taste was particularly to blame.

When the investigators performed the same comparison in one to four year olds, lopinavir exposure with sprinkles was higher than with syrup and historical data for children aged six months to12 years. There was moderately high variability in with both formulations but neither gave subtherapeutic levels. Ritonavir pharmacokinetics were similar.

Poor taste was reported most frequently as a problem with both formulations, followed by swallowing difficulty. Although the majority of caregivers rated both formulations unpleasant, they reported easier storage and transportation with sprinkles compared to syrup.

The partnership is now working on further pharmacokinetic and acceptability investigations with an improved granule formulation (finer than the 0.8mm mini tablets and more sand-like in texture) with better taste masking. The new granules will be easier to mix with the NRTIs for the 4-in-1 regimens.

INTEGRASE INHIBITORS

Dolutegravir

The regulatory applications for dolutegravir have been submitted and include approval requests for adolescents ages 12 to less than18 years.

The ongoing IMPAACT P1093 phase I/II study is designed with de-escalated age bands of treatment naive and experienced children, from18 years down to four-week-old infants. The older children will receive tablets, and the younger ones the pediatric formulation.

A granule formulation is in development, and results from a phase I pharmacokinetic study in healthy adult volunteers shown. 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.

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

Dolutegravir 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.
Two reduced-strength 10 mg and 25 mg tablets have also been developed for children.

Preliminary data for dolutegravir from treatment-experienced adolescents, ages 12 to less than 18 years from IMPAACT P1093 showed good short-term safety and tolerability at four weeks. Concentrations were within the target range with approximately 1 mg/kg and pharmacokinetic data supports the selection of a 50 mg once daily for this age group weighing 40 kg or more. Enrollments for the next cohort in children ages six to less than 12 years is now ongoing evaluation, both tablets and granules.

A possible PENTA 20 trial of dolutegravir in all age groups of children is also under discussion.

A reduced strength pediatric FDC of dolutegravir plus abacavir plus lamivudine, (572-Trii)—currently under investigation for adults—is also planned. Following the results from the ARROW trial, which found once-daily dosing of abacavir and lamivudine non-inferior to twice-daily in children, ViiV is submitting data for this indication, which will support the once-daily pediatric FDC. The development of this formulation will depend on the dolutegravir dosages across the age groups and the dosing ratios of the regimen components.

Further along the adult pipeline, the follow-up integrase inhibitor S/GSK-1265744, under investigation as a long-acting formulation, has provoked interest as a potential treatment of adolescents (as has the long-acting formulation of rilpivirine).

The company is working in partnership with Clinton Health Access Initiative (CHAI), and Mylan on a dispersible tablet FDC of abacavir plus lamivudine. They will transfer the technology and resources to the generic company for production, registration, and distribution of this at the lowest possible cost for low-income countries. Any lessons learned with the collaboration should be used to ensure that dolutegravir—assuming it fulfils its early promise—is available, including in appropriate FDCs, for children in poor countries without delay.

**Elvitegravir/cobicistat**

GS-US-183-0152, a phase 1b open-label non-randomized trial, conducted in treatment-experienced adolescents 12 to less than 18 years receiving 150 mg once daily elvitegravir plus a ritonavir-boosted protease inhibitor-optimized background regimen, showed comparable exposures to that seen in adults.

GS-US-183-0160 will evaluate elvitegravir with ritonavir boosted protease inhibitors in non-suppressed children ages 4 weeks to less than 18 years old.
PENTA 17 will evaluate elvitegravir with darunavir/ritonavir in stable, virologically suppressed children.

Reduced strength tablets and dispersible tablets for suspension of the booster, cobi, are in development.

GS-US-216-0128 is planned to start enrolment this year and will switch children from ritonavir to cobicistat ages three months to less than 18 years, who are suppressed and on an atazanavir- or darunavir-containing regimen.

Cobicistat-boosted elvitegravir will be studied in de-escalated weight bands, and a suspension formulation is in development for the youngest children.

Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir DF) is being studied in treatment naive adolescents ages 12 to less than 18 years in GS-US-236-0112. Reduced strength tablets are planned for children ages six to less than 12 years.

An adolescent study of the FDC of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (AF), GS-US-292-0106, began in May 2013. Gilead plan to submit regulatory applications that include approval requests for adolescents ages 12 to less than 18 years for this FDC. As with adults, the plan for tenofovir AF as a standalone is unclear. As with adults the drug might be important in regimens other than those in development.

**Raltegravir**

The adult 400 mg film-coated raltegravir tablet is approved in the United States for use in children ages six to less than 18 years, weighing above 10 kg, and 100 mg and 25 mg chewable tablets are approved for children above two to less than 12 years at a maximum dose of 300 mg. The 100 mg tablet is scored so it can be divided in half.

Raltegravir’s approval was the first in a new therapeutic class—integrase inhibitors—for young children that might offer some advantages over the currently available drugs. Like darunavir, raltegravir has been suggested as a future option for third-line treatment for children. But like darunavir, it is currently very expensive, with no generic options yet—even for adults.

The pediatric program is ongoing in IMPAACT P1066, and a granule formulation for suspension is being studied in the youngest children and babies down to four weeks old. Children ages six months to less than two years old receiving a dose of approximately 6 mg/kg, twice daily showed similar exposure to that achieved in the two to 12 year old age group receiving chewable tablets. Preliminary 24-week safety and efficacy at 12 weeks showed 78 percent of the nine children achieved virological suppression, and by 24 weeks, 85 percent were suppressed. The twice-daily dose of 6 mg/kg will be investigated in this age group.
Raltegravir also has the potential for use as prophylaxis to prevent vertical transmission to infants, and for treatment of HIV-infected infants. IMPAACT P1097 is an ongoing phase IV washout (passive) pharmacokinetic and safety study of infants, born to women who received at least two weeks of raltegravir (400 mg twice daily) in pregnancy and through labor.\textsuperscript{45,46}

This is the first clinical trial of an investigational antiretroviral to look at neonatal pharmacokinetics. Raltegravir crosses the placenta well. It is metabolized primarily by a liver enzyme (UGT-1A1), which is immature in neonates. UGT pathways increase in activity hugely in the first weeks of life, reaching adult levels within three to six months.

Early results from this study show good placental transfer with cord blood to maternal plasma concentration ratio of approximately 1.5. Transplacental half-life is long—24 to 36 hours—in neonates. Neonatal raltegravir elimination is highly variable.

IMPAACT P1110 is an open label pharmacokinetic and safety single and multiple dose study of raltegravir granules in high-risk HIV-exposed neonates. Multiple dosing will be from birth to six weeks and HIV-infected infants will continue after six weeks.

**CCR5 RECEPTOR ANTAGONIST**

**Maraviroc**

The A4001031 study is ongoing in children aged two to less than 18 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with the CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.\textsuperscript{47}

Preliminary data in 29 children showed body surface area–based doses of maraviroc provided adequate exposures when administered with a protease inhibitor as part of their background regimen. Children who were not receiving a boosting agent in their background regimen required at least doubling of the initial dose.\textsuperscript{48}

A body surface area–scaled twice-daily tablet dose of maraviroc in treatment-experienced children six years and above concomitantly receiving boosted protease inhibitors (darunavir and lopinavir) achieved concentrations similar to those in adults receiving 150 mg maraviroc twice daily with a boosted protease inhibitor.\textsuperscript{49}
<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>Sponsor</th>
<th>Formulation(s) and Dose</th>
<th>Status and Comments</th>
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<tbody>
<tr>
<td>Atazanavir (ATV)</td>
<td>Protease inhibitor (PI)</td>
<td>Bristol-Myers Squibb</td>
<td>Powder 50mg sachet, Capsules 100, 150, 200, 300mg</td>
<td>Phase II/IIb RTV boosted 3 months to &lt;6 years ongoing</td>
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<td>Dolutegravir (DTG)</td>
<td>Integrase inhibitor (INI)</td>
<td>Shionogi/ ViiV</td>
<td>Tablets 10, 25, 50mg Granule formulation being evaluated for younger children</td>
<td>Adolescents 12 to &lt;18 years included in regulatory submissions, Phase I and II 6 weeks to &lt;18 years</td>
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<td>Dolutegravir/ABC/3TC (572-Trii)</td>
<td>INI/2NRTIs FDC</td>
<td>Shionogi/ ViiV</td>
<td>Pediatric formulation development planned Dosing to be determined</td>
<td>Dependent on ongoing studies confirming DTG dose in children</td>
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<td>Elvitegravir (EVT)</td>
<td>INI/booster</td>
<td>Gilead</td>
<td>EVG reduced-strength tablets and suspension in development COBI dispersible tablets for suspension</td>
<td>EVG PK completed, RTV boosted 12 to &lt;18 years RTV- and COBI-boosted EVG to be studied in all age groups</td>
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<td>Cobicistat (COBI)</td>
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<td>EVG/COBI/FTC/TDF (Stribild)</td>
<td>INI/booster /2NRTIs FDC</td>
<td>Gilead</td>
<td>Reduced strength tablets in development</td>
<td>Studies underway in treatment naive 12 to &lt;18 years 6 to &lt;12 years planned (waiver &lt;6 years)</td>
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<td>Etravirine (ETR)</td>
<td>NNRTI</td>
<td>Janssen</td>
<td>Dispersible tablets 25mg (scored), 100mg</td>
<td>Phase I and II treatment experienced 2 months to &lt;6 years enrolling</td>
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<td>Lopinavir-ritonavir (LPV/rtv)</td>
<td>Boosted PI</td>
<td>Cipla/DNDi</td>
<td>Granules 40/10mg (equivalent to 0.5mL liquid)</td>
<td>Phase I</td>
</tr>
<tr>
<td>LPV/rtv/ABC or AZT/3TC (4-in-1)</td>
<td>Boosted PI/2NRTIs</td>
<td>Cipla/DNDi</td>
<td>Granules FDC</td>
<td>Phase I Granule regimen for use in infants and young children in resource-limited settings</td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>CCR5 receptor antagonist</td>
<td>Pfizer/ViiV</td>
<td>Suspension 20mg/mL</td>
<td>Phase IV Treatment-experienced CCR5 tropic 2 to &lt;18 years</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>INI</td>
<td>Merck</td>
<td>Granules for suspension 6mg/kg (100mg sachet)</td>
<td>Phase II 2 weeks to &lt;2 years, Neonate passive PK study, Neonate prophylaxis study</td>
</tr>
</tbody>
</table>
What Needs to Be Done?

To repeat from last year’s Pipeline Report: there is a danger of pediatric HIV becoming an old story against a backdrop of targets to eliminate vertical transmission by 2015, which though they are laudable, must not happen at the cost of continual scale-up for children. And back to the reality check: currently only 28 percent of children with HIV in need of treatment are receiving it. Most of what is recommended below is spillover from previous years, but unfortunately has not been done yet.

Implementing recommendations

The new WHO guidelines for treating children strike a pretty good balance between aspirational and pragmatic. It is important that nevirapine-containing regimens still remain an alternative as the recommended lopinavir/ritonavir first-line regimens (including for rural neonates) will frequently not be feasible with the formulation currently available. If recommendations become too complex, children often do not receive anything. As a simpler formulation of lopinavir/ritonavir becomes available, countries must ensure that it is swiftly approved and distributed, with appropriate training for health workers.

Other missing formulations, needed to implement the guidelines, must be made available. If the market is too tiny to interest generic companies, donors need to step in to support this.

The news of the infant with a “functional cure” provoked much discussion. Researchers and implementers are already planning pilot programs and studies to advance research findings. The news should stimulate all programs to do infant PCR as early as possible and intensify post exposure prophylaxis (or early treatment) for neonates of at risk pregnancies (not to mention identifying and treating pregnant women). Successes must be followed by rapid advice from WHO.

Support new models of research and development

There is a lot of hope resting on the successful development and delivery of the DNDi product. That an initiative focusing on diseases of the poor has selected pediatric HIV as a focus speaks volumes. More innovative models of research and
development, and appropriate agreements between originator companies and generic ones to produce child-adapted formulations in a timely fashion must be made.

**Ensuring that patents are not an obstacle**

The Medicines Patent Pool (MPP) is putting a lot of emphasis on pediatric antiretrovirals. Even the most hesitant originator companies, as far as adult drugs are concerned, must recognise that pediatrics will never be much of a market let alone a money-spinner.

Gilead’s licence agreement with the MPP always has royalties waived for any new pediatric formulations. ViiV will grant MPP a voluntary licence for pediatric formulations of abacavir. There is also a commitment to do the same for dolutegravir. Other companies must follow suit and is very important to ensure availability beyond sub-Saharan Africa. What Abbvie decides to do about the lopinavir/ritonavir granules will be closely watched.

**Rationalizing available formulations**

Development, approval, and distribution of new formulations need to happen in ways that are timely and do not further fragment the market. The time from first approval to when products are available where they are most needed must shorten. This will require earlier access by generic companies to new products (which must include the possibility to develop FDCs with components from different innovators) and registration by the WHO and in country.

To reduce the current situation with too many formulations and too few real options, products need to be rationalized and unsuitable ones phased out.

**Consolidated procurement**

CHAI needs to continue with its successful model of price negotiations. Concerted efforts by international donors, including the Global Fund and PEPFAR, need to be made to facilitate the transition from previous reliance on UNITAID funding of pediatric products. In the many individual countries where orders do not meet manufacturer volume requirements, buyers must get together.
Endnotes

All links last accessed May 29 2013.


