Refocusing Research and Development of Paediatric HIV Treatments on the Needs of Children in Resource-Poor Settings

A PAEDIATRIC HIV ROUNDTABLE WITH INDUSTRY & JOINT CALL TO ACTION ON PAEDIATRIC HIV

24 October 2013, Dakar, Senegal
Hosted by the Drugs for Neglected Diseases *initiative* (DND*i*)

DND*i*
Drugs for Neglected Diseases *initiative*

PAEDIATRIC HIV ROUNDTABLE WITH INDUSTRY MEETING PARTICIPANTS AND AGENDA

Facilitators:
DNDi: Janice Lee, Paediatric HIV Project Coordinator; Marc Lallemant, Head of Paediatric HIV Programme

Industry participants (onsite and via teleconference):
AbbVie: Marisol Martinez, Medical Director, Global Medical Affairs, Virology
Gilead: Erin Quirk, Senior Director, HIV Clinical Research; Jim Rooney, Vice President of Clinical Affairs; Aaron Brinkworth, Director, Acc Ops & Emerging Markets; Ruth Diazaraque-Marin, Senior Director, Public Health & Medical Affairs
J&J: Carol Ruffell, Director, Global Access and Partnerships; Magda Opsomer, Director, Clinical Leader, PREZISTA and INTELENCE; Ruud Leemans, Senior Director, Global Chemical and Pharmaceutical Development; Peter Williams, Compund Development Leader for rilpivirine
Merck: Hedy Teppler, Senior Director, Clinical Research; Tidiane Ndao, Sub-Saharan Africa Medical Affairs Manager; Isabelle Girault, Executive Director, Access & Strategy, HIV & Hepatitis, Emerging Markets
Mylan: Emmanuel Patras, DGM Business Development
ViiV: Katy Hayward, Physician Project Lead, Global Lead Paediatrics

Unable to attend:
BMS, Cipla, Ranbaxy, Hetero, Aurobindo

Non-Industry participants:
Elaine Abrams, Professor of Epidemiology and Pediatrics, Columbia University, Mailman School of Public Health, USA
Arax Bozadjian, Pharmacist, Médecins Sans Frontières, Switzerland
Edmund Capparelli, Director, Center for Research in Pediatric and Developmental Pharmacology (RPDP) Pediatric Pharmacology and Drug Discovery University of California, USA
Benjamin Cheng, VP of Technology and Innovation, Pangaea Global AIDS Foundation, USA
Polly Clayden, Director, HIV i-Base, UK
Nonhlanhla Dlamini, Chief Director: Child, Youth and School Health, National Department of Health, South Africa
Meg Doherty, Coordinator, Treatment and Care Unit, HIV/AIDS Department, WHO
Lora Du Moulin, ELMA Philantropies, USA
Shaffiq Essajee, Senior Advisor on HIV, Clinton Health Access Initiative (CHAI), Kenya
Patricia Fassinou-Ekouevi, EGPAF Project Djidja Director, Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), Côte d'Ivoire
Nathan Ford, Project Manager, Treatment 2.0, HIV/AIDS Department, WHO
Diana Gibb, Professor in Epidemiology/Hon. Consultant Paediatrician, MRC Clinical Trials Unit, UK
Raul Gonzalez-Montero, Paediatric Technical Lead, HIV/AIDS Department, WHO
Rohan Hazra, Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH, USA
Shirin Heidari, Research Promotion, International AIDS Society, Switzerland
Ioannis Hodges-Mameletzis, Consultant, WHO
Sandeep Junega, Business Development Director, Medicines Patent Pool
Chewe Luo, Senior Advisor and Team Leader Country Program Scale Up, UNICEF
Imelda Mahaka, Country Coordinator, Pangea Global AIDS Foundation, Zimbabwe
Helen McIleron, Division of Clinical Pharmacology, University of Cape Town, South Africa
Angela Mushavi, National PMTCT and Pediatric HIV Care and Treatment Coordinator, Zimbabwe
Atieno Ojoo, Technical Specialist, UNICEF Supply Division
Fernando Pascual, Medical advisor, Medicines Patent Pool
Martina Penazzato, Paediatric Consultant, HIV/AIDS Department, WHO
Jorge Pinto, Professor of Pediatric School of Medicine, Federal University of Minas Gerais, Brazil
Pablo Rojo-Conejo, Associate Professor, Hospital de 12 de Octubre, Spain
Sostena Romano, Consultant, UNICEF
Agnes Saint-Raymond, Head of Programme Design Board, European Medicines Agency
Nandita Sugandhi, Clinical Advisor, Clinton Health Access Initiative, USA
Mariatou Tala Jallow, Procurement Support Services, The Global Fund to Fight AIDS, TB and Malaria
Denis Tindyebwa, Executive Director, African Network for the Care of Children Affected by HIV/AIDS
Isseu Toure, PMTCT Regional Advisor, WHO AFRO
Catherine Tuleu, Director of the Center for Paediatric Pharmacy Research, University College London, UK
Clara van Gulik, Paediatric HIV and TB advisor, Médecins Sans Frontières, France
Kouadio Yeboué, HIV/AIDS Treatment and Care West and Central Africa Advisor, WHO

MEETING AGENDA

09:00-09:30 Summary of recommendations from WHO Paediatric Antiretroviral Drug Optimization Meeting. **Martina Penazzato**

09:30-09:45 Summary of paediatric formulation of interest and potential application in resource poor settings. **Catherine Tuleu**

09:45-10:15 Q & A

10:15-10:30 Coffee break

10:30-11:30 Long-acting and other formulations to help adolescents overcome adherence issues and start their adult life with better treatment options. (>10 years old)

Chair: **Diana Gibb**

Presentations from industry and open discussion
- What are the advances with of long acting compounds and formulations for specific high-risk group such as the adolescent?

11:30-12:30 Child-adapted formulations for infants and young children (0 to 3 years of age). Better formulations and second line regimen for older children (3 to 10 years)

Chair: **Edmund Caparelli**

Co-chair: **Angela Mushavi**

Presentations from industry on the following:
- What are the advances and pipeline ARVs for 2013-2023?
- What is in the pipeline that might offer advantages over the current options?
- Can we accelerate paediatric drug development safely and close the gap between availability of new compounds for adults and the youngest children?
- Can we harmonise regimens and formulations with adults for this age group (e.g. with easy to split tablets). What are the challenges in formulation development?

Participating industry:
Merck: Hedy Teppler 11:00 by webex
J&J: Carol Ruffell and **Magda Opsomer** 11:30 by webex (presenter)
AbbVie: Marisol Martinez
ViiV: Katy Hayward
Mylan: Emmanuel Patras
Gilead: Erin Quirk 14:00 by webex (presenter) and **Jim Rooney** 11:00 by webex

12:30-13:30 Lunch

13:30-14:30 *Continue from above*

14:30-16:00 Panel discussion: How to ensure that the R&D priorities for children with HIV are being addressed systematically in a collaborative manner?

Moderator: **Polly Clayden**

Panelists: **Agnes Saint-Raymond**, **Catherine Tuleu**, **Nonhlanhla Dlamini**, **Clara van Gulik**, **Sandeep Junega**, **Atieno Ojoo**

16:00-16:15 Coffee break

16:15-17:00 Conclusion of meeting

INTRODUCTION

The past decade has seen significant improvement in the prevention of new infant infections of HIV, and an increase in treatment of children infected. In 2012, 260,000 infants were newly infected with HIV,[1] half the number of those newly infected in 2002. Whereas a decade ago, a mere handful of children in resource-limited settings were receiving combination antiretroviral (ARV) therapy, in 2012, 647,000 children were being treated.[2] However, these children represent only one-third of those who should be receiving lifesaving therapies. The 2013 WHO *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection* provide the technical guidance to close the gap between the treatment needs and reality of today, focusing on HIV diagnosis as early as possible in life, improved linkage of diagnosis to care, immediate initiation of ARV therapy for all children under five years of age regardless of their clinical or immunological status, treatment of older children at a higher immunological threshold, and improved monitoring of therapy.[3]

Fundamental to the success of this strategy, which aims to give HIV-infected children the best possible chance to reach adulthood in good health, is the availability of better treatments: effective, safe, well accepted and tolerated (over time); and easy to procure, store, dispense, and use in the resource-poor settings where the vast majority of HIV-infected children live. Of the 26 antiretrovirals (ARVs) approved by the USFDA and marketed, seven do not have paediatric indication and eight have no paediatric formulation.[4] The youngest children are the most neglected: only 11 ARVs are approved for use in children below two years of age.[5] Research and development (R&D) for safe and effective HIV drugs for children is a neglected field that has not progressed as fast as it has for adults.

The availability of easy-to-use paediatric fixed-dose combinations has nonetheless come a long way. Initially, adult tablets were used, which needed to be broken according to weight band for simplified dosing in resource-poor settings. Today there are more adapted, child-friendly formulations. These, however, are still far too few, and the newly available and more effective treatments currently (or about to be) available for adults still need to be adapted for children.

Relevant issues surrounding paediatric HIV were discussed by key stakeholders, including clinicians, scientists, funders, representatives of Ministries of Health, civil society, stringent regulatory agencies and United Nations agencies at a two-day 'Conference on Paediatric Antiretroviral Drug Optimization (PADO)', organized by WHO on 22 and 23 October 2013, in Dakar, Senegal. The main themes and conclusions are available in the technical update included in the WHO Guidelines Supplement (www.who.int/hiv). Following this meeting, DNDi hosted a 'Paediatric HIV Roundtable with Industry' on 24 October 2013, aimed at building upon the PADO meeting outcomes by bringing together experts and industry to identify ways to collaborate to expedite the urgent development of paediatric ARV formulations adapted to the needs of children in resource-poor settings.

"We have a large population of adolescents living with HIV here and they are mostly orphans as they were born before the public sector provided free ARVS in 2004. They struggle in child-headed households, and face difficulties in disclosure. Coming into puberty and adherence to medications is not the easiest to deal with. We need all stakeholders to assist in creating public awareness and education on paediatric HIV."

Nonhlanhla Dlamini, National Department of Health South Africa

[1] *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013. Geneva: UNAIDS; 2013.*
[2] *Ibid.*
[3] *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach. Geneva: WHO, June 2013.*
[4] *Drugs@FDA: FDA approved drug products [Online]. [cited 2013 December 20]; Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name*
[5] *Ibid.*

PAEDIATRIC HIV ROUNDTABLE WITH INDUSTRY MEETING SUMMARY

Following the PADO conference, the Drugs for Neglected Diseases *initiative* (DND*i*) invited representatives of all pharmaceutical companies involved in ARV development to engage with the WHO/PADO conference participants in a discussion on their current and future drug development plans for children.

This one-day 'Paediatric HIV Roundtable with Industry' built upon the PADO meeting, bringing together researchers, paediatricians, pharmacologists, regulatory representatives, NGOs, policy makers, funders, and industry. The outcome was a call to action (see back cover), jointly endorsed by industry and experts present at the meeting, focusing on key efforts to expedite the crucial development of paediatric ARV formulations adapted to the needs of children in resource-poor settings.

Following the presentation of the key recommendations and key challenges identified during the two-day PADO conference and a review of the challenges of the development of paediatric formulation, representatives of industry (originator and generic companies) were invited to present their current R&D activities and plans targeting the specific needs of children with HIV/AIDS within three specific age groups:

- Infants and young children who urgently need adapted paediatric formulations to start their lifelong therapy (‹ 3 years of age)
- Older children who need better formulations and some of whom may already need second-line treatment (3-10 years of age)
- Adolescents who struggle with adherence to therapy and may need long-acting formulations (›10 years of age).

As the format and scope of the presentations differed greatly and because each presentation was open to wide/overlapping discussions, individual summaries are not presented here. Rather, the following is intended to render the themes that emerged throughout the day. In addition, tables 1 and 2 summarize the paediatric ARV formulations under development and paediatric studies that will lead to approval for the age/weight-based indication of a particular ARV or combinations, and include estimated timelines for the approval of formulations. It should be noted that information from companies unable to participate was gathered after the meeting. Only paediatric formulations that are of interest, or are not yet available on the market, are presented here.

The development of paediatric ARV formulations has evolved from syrups for the youngest to solid formulations such as granules, chewable tablets, and powder formulation. This shift addresses the challenges seen in resource-poor settings, where difficulties exist in accessing clean water, in supply chain management of bulky solutions, and in dosing of multiple syrups by the caregivers. But most notably, paediatric fixed-dose combinations in dispersible tablets have changed significantly the way treatment is delivered to HIV-positive children in sub-Saharan Africa.

There was consensus, however, on the fact that there is still a great need for continued simplification of treatment by means of developing fixed-dose combinations, in formulations that are child and caregiver friendly, well taste masked, storable at room temperature, and with a long shelf-life and non-conspicuous packaging.

Progress was seen with the various industry presentations on new ARVs and formulations in development (see tables 1 and 2). As HIV-infected children grow into adulthood, adherence is a big problem, and there is great interest in the possibilities for long-acting formulations with certain ARVs, such as RPV and GSK 744 for adolescents.

"A lot of work has been done in developing paediatric ARV formulations and countries need to uptake what is available. There should be no fear in putting children on treatment due to the lack of drugs. We also need national quantification of the actual demand, not the current quantification based on funding mechanisms. With these data, we can work with manufacturers to plan product development and supply."

Atieno Ojoo, UNICEF

Paediatric studies required as part of new drug applications to USFDA since 1997 and incentives for pharmaceutical companies offered through marketing exclusivities are beginning to bear fruit. Combined with the 2007 EMEA (now EMA) incentives and requirements to include paediatric studies for marketing authorization applications, these policies have reduced the time-lag between adult and paediatric treatment indication. An equally important step is to address paediatric formulations earlier in the drug development process. These formulations must be adapted for use in resource-poor settings, where 90% of the HIV-positive children live.

A faster and smoother regulatory process is crucial to ensuring prompt access to these paediatric formulations for the children who need them. Harmonization of regulatory requirements across different countries is urgently needed. Similarly, harmonization is needed for dosing and weight bands. Previously, ARVs developed following stringent regulatory authority regulations were not necessarily adapted for use in resource-poor settings. This matter requires urgent attention as new ARVs are being studied in children and their availability in resource-poor settings will depend on dosing guidance for new FDCs and the time needed to adapt formulations accordingly.

A panel discussion on the topic 'How to ensure that R&D priorities for children with HIV are being addressed systematically in a collaborative manner' was held. Key messages presented by the panel are transcribed in the quotes throughout this document. During the discussions following the roundtable, there was a general willingness of companies to collaborate and make available paediatric ARV formulations adapted for use in developing countries.

Intellectual property (IP) rights were addressed in light of seeking to ensure that IP is not a barrier to access to affordable ARV combinations. This panel discussion, moderated by Polly Clayden (HIV i-Base), set the stage for the **Joint Call to Action on Paediatric HIV**. All participants joined in this statement calling for all stakeholders to work together, support paediatric HIV R&D, and streamline access to treatment and care of this neglected population (see back cover).

"When we develop paediatric ARV formulations, we must think of the end user's needs, the child and caregiver. We need to resolve practical issues such as making dispersible tablets and scoring bigger tablets that are easier to break, store in tropical climates, that have friendly packaging with clear instructions for use, product taste that is neutral, and accelerated access to these formulations."

Catherine Tuleu, University College London

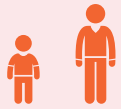
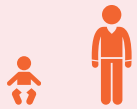
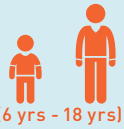
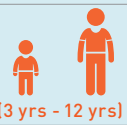
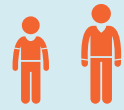
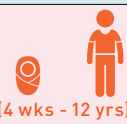
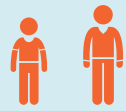
"There are multiple approvals of products at national level in low- and middle-income countries. Countries are encouraged to volunteer for procedures related to WHO supported harmonization of product approvals in order to accelerate access to them. We need to transform the thinking by addressing the paediatric formulation early in drug development. We need to think out of the box and work together."

Agnes Saint-Raymond, European Medicines Agency

"We need to explore the model of public financing for paediatric HIV as it is a very small market. We can learn from companies that have licensed drugs for paediatrics and use them as a model for future collaborations."

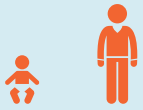
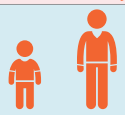
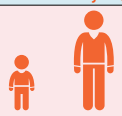
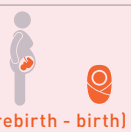
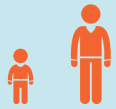
Sandeep Junega, Medicines Patent Pool

TABLE 1: SUMMARY OF ARVs DEVELOPED OR IN DEVELOPMENT FOR CHILDREN

DRUG	CLASS	COMPANY	STUDIES COMPLETED OR PLANNED	PAEDIATRIC FORMULATIONS	TIMELINE FOR FORMULATION APPROVAL
Abacavir (ABC)	NRTI	ViiV	 (3 months - 18 yrs) Ongoing regulatory submission of once a day ABC	20mg/ml solution	Available
			 (3 months - 18 yrs) Approved from 3 months		
Atazanavir (ATV)*	PI	BMS	 (3 months - 6 yrs) PRINCE 1, using powder formulation	150, 200, 300mg capsule **Oral powder (50mg sachet) in development****	Capsules are available
			 (3 months - 11 yrs) PRINCE 2, using powder formulation		
			 (6 yrs - 18 yrs) Approved		
Cobicistat (COBI)	Booster	Gilead	 (3 months - 17 yrs) GS-US-216-0128: enrollment to start in 2013	**Dispersible tablet for suspension and reduced dosage tablets in development****	In development
Darunavir (DRV)	PI	J&J	 (birth - 3 yrs) Regulatory waiver obtained	75mg, 150mg tablets and oral suspension	Available
			 (3 yrs - 6 yrs) ARIEL (DRV b.i.d), for treatment experienced including sub-study with DRV q.d.		
			 (6 yrs - 18 yrs) DELPHI (DRV b.i.d.), for treatment experienced		
			 (3 yrs - 12 yrs) PK modeling and simulations, for treatment naive		
			 (12 yrs - 18 yrs) DIONE, for treatment naive		
Dolutegravir (DTG)	INI	ViiV	 (4 wks - 12 yrs) IMPAACT 1093	10mg, 25mg tablets and **granule formulation in development****	2015
			 (12 yrs - 18 yrs) IMPAACT 1093		

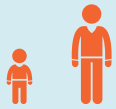
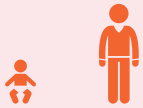
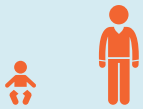
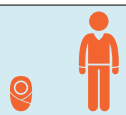
* Information not presented in this meeting but were compiled later
** Product in development
Regulatory approval obtained
Regulatory waiver obtained
Study ongoing
PI Protease inhibitor
NRTI Nucleoside reverse transcriptase inhibitor
NNRTI Non-nucleoside reverse transcriptase inhibitor
INI Integrase inhibitor
BMS Bristol Myers Squibb
J&J Johnson and Johnson
DNDi Drugs for Neglected Diseases initiative
BI Boehringer Ingelheim

TABLE 1: SUMMARY OF ARVs DEVELOPED OR IN DEVELOPMENT FOR CHILDREN (*cont'd*)

DRUG	CLASS	COMPANY	STUDIES COMPLETED OR PLANNED	PAEDIATRIC FORMULATIONS	TIMELINE FOR FORMULATION APPROVAL
Efavirenz (EFV)*	NNRTI	BMS (EU, USA) MSD (all other countries)	 (3 months - 18 yrs) >3.5kg and from 3 months to 18 yrs (USFDA approval); over 3 yrs (EMA approval)	30mg/ml suspension, 50mg tablet, 200mg tablet	Available
Elvitegravir (EVG)	INI	Gilead	 (4 wks - 17 yrs) GS-US-183-0160 studied with RTV: enrollment to start in 2013	**Powder for suspension and reduced dosage tablets in development****	In development
Emtricitabine (FTC)*	NRTI	Gilead	 (birth - 18 yrs)	10mg/ml solution	Available
Etravirine (ETR)	NNRTI	J&J	 (birth - 2 months) Regulatory waiver obtained  (2 months - 6 yrs) IMPAACT P1090  (6 yrs - 18 yrs) PIANO	25mg dispersible tablet (scored), 100mg dispersible tablet	Available
Fosamprenavir (FPV)	PI	ViiV	 (4 wks - 18 yrs)	50mg/ml oral suspension	Available
Maraviroc (MVC)	CCR5 receptor antagonist	ViiV	 (2 yrs - 18 yrs) Phase 4 in CCR5 tropic	**Oral suspension 20mg/ml in development****	2016
Raltegravir (RAL)	INI	Merck	 (prebirth - birth) P1097: Washout PK study  (prebirth - birth) P1110: Single/multiple HIV-exposed at high risk of acquiring HIV  (4 wks - 2 yrs) P1066  (2 yrs - 18 yrs) P1066	100mg (scored) and 25mg chewable tablets. Currently approved in US and EU Oral granules for suspension 100 mg sachet (USFDA approved Dec 2013)	25mg and 100mg chewable tablets available, granules for suspension in regulatory review
Rilpivirine (RPV)	NNRTI	J&J	 (2 wks - 12 yrs) IMPAACT P1111  (12 yrs - 18 yrs) PAINT	25mg tablet and **age appropriate formulations****	Under development

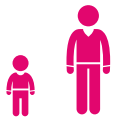
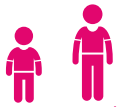
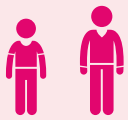
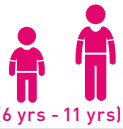
Continued on next page >

TABLE 1: SUMMARY OF ARVs DEVELOPED OR IN DEVELOPMENT FOR CHILDREN (*cont'd*)

DRUG	CLASS	COMPANY	STUDIES COMPLETED OR PLANNED	PAEDIATRIC FORMULATIONS	TIMELINE FOR FORMULATION APPROVAL
Tenofovir disoproxil fumarate (TDF)*	NRTI	Gilead	 (birth - 2 yrs) Planned, timeline unavailable  (2 yrs - 18 yrs)	Oral powder 40mg/1g, 150mg tablet, 200mg tablet, 250mg tablet	Available
Tenofovir alafenamide (TAF)	NRTI	Gilead	n/a	Information not available yet	
MK 1439	NNRTI	Merck	n/a	Information not available yet	
Lamivudine (3TC)	NRTI	ViiV	 (3 months - 18 yrs) Ongoing regulatory submission of once a day 3TC  (3 months - 18 yrs) Approved from 3 months	10mg/ml solution	Available
Lopinavir/ritonavir (LPV/r)	PI	AbbVie	 (2 wks - 18 yrs) From neonates with at least postmenstrual age of 42 weeks and a postnatal age of at least 14 days has been attained / (USFDA); EMA: 2 years and older	80/20mg per ml solution and 100/25mg tablet	Available
Lopinavir/ritonavir (LPV/r)*	PI	Cipla	 (birth - 13 yrs) CHAPAS 2	**40/10mg pellets in capsule (in regulatory review)****	QI 2014
Lopinavir/ritonavir (LPV/r)	PI	Mylan	n/a	**40/10mg sprinkles in development****	2014/2015
Nevirapine (NVP)*	NNRTI	BI	 (15 days - 18 yrs)	50mg/5ml oral suspension	Available
Ritonavir (RTV)	PI/booster	AbbVie	 (1 month - 18 yrs) › 1 month of age (USFDA); EMA label: 2 years and older	80mg/ml solution, **100mg powder in stick pack with syringe and dosing cup in development****	Solution available
Ritonavir (RTV)*	PI/booster	Cipla & DNDi	 (1 month - 6 yrs) Study at planning stage	**30mg granules in capsule in development****	Mid 2015
Ritonavir (RTV)	PI/booster	Mylan	n/a	**25mg tablet in development****	2014
Zidovudine (AZT)	NRTI	ViiV	 (birth - 18 yrs) › 4 kg	10mg/ml solution	Available

* Information not presented in this meeting but were compiled later
** Product in development
▫ Regulatory approval obtained
□ Regulatory waiver obtained
▫ Study ongoing
PI Protease inhibitor
NRTI Nucleoside reverse transcriptase inhibitor
NNRTI Non-nucleoside reverse transcriptase inhibitor
INI Integrase inhibitor
BMS Bristol Myers Squibb
J&J Johnson and Johnson
DNDi Drugs for Neglected Diseases initiative
BI Boehringer Ingelheim

TABLE 2: SUMMARY OF ARVs IN FDC FORMULATION DEVELOPED OR IN DEVELOPMENT FOR CHILDREN

DRUG	CLASS	COMPANY	STUDIES COMPLETED OR PLANNED	PAEDIATRIC FORMULATIONS	TIMELINE FOR APPROVAL
Abacavir/Lamivudine/ Dolutegravir (ABC/3TC/DTG)	FDC	ViiV	 (2 yrs - 18 yrs) Study at planning stage	**Fixed-dose combination tablet planned****	n/a
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir (EVG/COBI/ FTC/TDF)	FDC	Gilead	 (6 yrs - 11 yrs) Study planned  (12 yrs - 17 yrs) GS-US-236-0112: underway	**Reduced dosage tablets planned for 6-11yrs****	7 to 18 years completion 2020
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide (EVG/COBI/FTC/TAF)	FDC	Gilead	 (6 yrs - 11 yrs) Study planned  (12 yrs - 17 yrs) GS-US-292-106: underway	**Reduced dosage tablets planned for 6-11yrs****	n/a
Zidovudine/ lamivudine/ lopinavir/ritonavir (AZT/3TC/LPV/r)*	FDC	Cipla & DNDi	 (2 wks - 6 yrs) Implementation study at planning stage	**30/15/40/10mg granules in capsule****	Mid 2015
Abacavir/ lamivudine/ lopinavir/ritonavir (ABC/3TC/LPV/r)*	FDC	Cipla & DNDi	 (2 wks - 6 yrs) Implementation study at planning stage	**30/15/40/10mg granules in capsule****	Mid 2015
Lopinavir/ritonavir/ lamivudine (LPV/r/3TC)	FDC	AbbVie	 (12 yrs - 18 yrs) Study planned	**Dosage not available****	2015
Lopinavir/ritonavir/ zidovudine (LPV/r/AZT)	FDC	AbbVie	 (12 yrs - 18 yrs) Study planned	**Dosage not available****	2015
Abacavir/ lamivudine/ nevirapine (ABC/3TC/NVP)	FDC	Mylan	n/a	**60mg/30mg/50mg dispersible tablet****	2014
Abacavir/lamivudine (ABC/3TC)	FDC	Mylan & ViiV & CHAI	n/a	**60/30mg and 120/60mg dispersible tablet****	2014
Abacavir/lamivudine (ABC/3TC)*	FDC	Ranbaxy	n/a	**60/30mg dispersible tablet****	n/a

* Information not presented in this meeting but were compiled later
** Product in development
Study ongoing

FDC Fixed-dose combination
J&J Johnson and Johnson
DNDi Drugs for Neglected Diseases initiative

The following issues emerged from the industry roundtable discussion on child-adapted formulations for infants and young children (0 to 3 years of age), better formulations and second-line regimens for older children (3 to 10 years of age), and long-acting and other formulations to help adolescents overcome adherence issues and start their adult life with better treatment options (>10 years of age).

Issue 1. There is a need to study drugs in younger children as early as possible.

The time from drug approvals in adults to approval for use in children, particularly the youngest ones, can take many years. One approach that can be taken with compounds that have good placental transfer is the collection of 'washout pharmacokinetic data' of babies born to women who took a particular drug during pregnancy. The approach has been successful with raltegravir in developing neonatal dosing regimens for future study. Many participants raised the question of whether this was being done for other ARVs (e.g. ETV, RPV). There are, as yet, no plans for such studies. Clinical studies in children are usually performed in **older age groups first, before proceeding to the younger age group**. This strategy as well as difficulty in recruitment can delay approval of treatments for the younger children. Most paediatric investigation plans (PIPs) use this de-escalated approach.

Issue 2. There is a need to align ARV weight-band dosing used by companies for regulatory filing and WHO dosing recommendations.

WHO dosing recommendations for children have been simplified, using the same standardized weight bands for all ARVs. In addition, specific dosing recommendations are being issued in order to allow ARV regimens in FDCs across weight bands. Paediatric dosing of ARVs developed by companies **do not follow standardized weight bands**, but rather tailor the dose by weight and age of the child according to pharmacokinetic properties of the drug. Many ARVs for children are developed with specific reduced-dose tablets, powder, or granules to deliver exact doses for particular weight or age of a child (e.g. TDF, EVG, COBI, RAL, DTG, DRV, ETV: see table 1). An example of this is the ratio of the protease inhibitor DRV with the booster RTV, which is not uniform across different weight bands. **This poses difficulties in finding a unique FDC dose** that can be used across weight bands, and there are currently no plans to revisit these ratios.

Issue 3. New formulations are needed to better adapt to patient needs.

Companies are moving from developing liquid formulations to solid powder, tablet, or granule formulations, which are more adapted for resource-poor settings. Examples of drugs in development, which will have solid formulations for children, are EVG, COBI, RAL, ATV, RTV, DRV. RTV is reformulated into powder for suspension or sprinkles, which will be heat stable. Its taste is acceptable, but not significantly improved from the current liquid formulation. Generic companies are also developing various FDCs for children with a pipeline of products in development (see tables 1 and 2).

Issue 4. It is important to develop fixed-dose combinations for children with HIV.

During the discussions, there were recurring questions from the experts about potential fixed-dose combinations of the ARVs in development (e.g. DTG, RAL, TAF). ARVs planned for FDC are ARVs developed by the same company (e.g. for EVG/COBI/TDF/FTC; EVG/COBI/TAF/FTC; ABC/3TC/DTG), ARVs of companies with existing collaboration (e.g. TDF/FTC/RPV), or ARVs with expired patents (AZT and 3TC patents expired, e.g. LPV/r/3TC and LPV/r/AZT). There was a clear interest from companies to develop FDCs for children for which the ARVs for the FDCs have yet to be defined. This interest is **an important sign of greater willingness to collaborate across companies** to resolve intellectual property barriers in developing FDCs, pointing to the potential utilization of existing mechanisms, notably the Medicines Patent Pool, to make this happen.

Issue 5. Long-acting formulations and simplification of treatment for adolescents are urgently needed.

Long-acting formulations that would involve monthly injections are currently being studied for RPV and GSK 744 in adults. A proof-of-concept study is taking place in adults, whereby therapy is initiated with oral treatments to achieve viral suppression before commencing once-a-month injections. Other formulations of interest in adolescents are once-a-day TDF/FTC/RPV (Gilead and J&J), LPV/r/3TC (AbbVie), and LPV/r/AZT (AbbVie) currently in development. The latter formulations by AbbVie are two-tablet twice daily regimens, which will be studied for children weighing 40kg and more (around 12 years and older) and are expected to be available before 2015.

Issue 6. TAF needs to be studied in unboosted regimens (without pharmaco-enhancer cobicistat).

Currently the development plan for tenofovir alafenamide (TAF) is prioritizing regimens that require the pharmaco-enhancer cobicistat, and currently no data exists on TAF alone. The need for TAF to be studied separately from cobicistat has been raised by activists for adult treatment and for children's treatment. Gilead responded positively that there are internal discussions on the possibility of co-formulating TAF and FTC for paediatric development, which will allow flexible use with other drugs.

Issue 7. Cost of ARVs is a serious issue.

The cost of the new ARVs was brought up numerous times. Country representatives raised questions about the cost of the new paediatric formulations and pointed to the need to ensure they are affordable in developing countries.

PADO MEETING SUMMARY

With the objective of providing an overview of the paediatric HIV market dynamics and drug R&D pipeline, identifying priority drugs and formulations for different age groups, and to develop a roadmap to streamline access to paediatric ARVs, the two-day WHO/PADO ('Conference on Paediatric Antiretroviral Drug Optimization') meeting was structured around three main topics:

1) Landscape of paediatric HIV: new paediatric treatment recommendations; projections of the paediatric HIV population in the medium and longer term; potential impact on the paediatric ARV market; and mapping of the international patent status relevant to paediatric antiretroviral therapy.

2) Medium and longer term needs for paediatric formulations: paediatric ART scale-up challenges for national AIDS programmes; supply management perspective on innovation and development of new formulations; update of the Inter Agency Task Team (IATT) optimized formulary list of paediatric ARVs; alternative drug delivery models for paediatric medicines; monitoring of drug toxicity; and regulators' perspectives on new drug development and registration.

3) Paediatric ARV research pipeline and ART sequencing: nucleoside reverse transcriptase, integrase and protease inhibitors; treatment of the newborn; ARV regimen sequencing and harmonization with adult therapy.

The PADO expert group identified several priorities for drug and formulation development to optimize drug delivery and treatment sequencing. For the medium term, the formulations needed are: AZT or ABC/3TC/LPV/r fixed-dose combinations (FDCs) for children under three years of age; ABC/3TC/EFV FDC, which can be given once a day for children over three years of age; DRV/r co-formulation and ATV/r co-formulation for older children; and RTV granules as booster for TB/HIV co-infected children on PI therapy. In the long term, the paediatric development of DTG and TAF were prioritized, with particular emphasis on DTG-containing FDCs.

Accelerating drug approval from older children down to neonates was considered crucial, and harmonizing regulatory approvals across countries and adoption by country programmes were seen as essential steps towards increased access to improved regimens and formulations.

Critical research gaps were also highlighted, in particular the need for better knowledge of the pharmacokinetics, tolerability, and toxicity of the newest drugs in newborns and infants.

Lastly, a roadmap to streamline both access and uptake of paediatric-specific ARVs was developed, including the definition of sequencing strategies that maximize simplicity and safety/tolerability, and increase durability of treatment combinations that will be used in resource-limited settings, where ease of procurement, storage, dispensing, and use is of paramount importance. Central to these objectives are the need for addressing intellectual property obstacles to the development of optimal fixed-dose combinations, forecasting demand, coordination with all stakeholders to protect a paediatric ARV market always at risk of fragmentation, and the development of strategies to reduce treatment costs.

ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
BMS	Bristol Myers Squibb
COBI	cobicistat
DTG	dolutegravir
DRV	darunavir
EFV	efavirenz
EMA	European Medicines Agency
ETR	etravirine
EVG	elvitegravir
FDC	fixed-dose combination
FPV	fosamprenavir
FTC	emtricitabine
HIV	Human Immunodeficiency Virus
INI	integrase inhibitor
J&J	Johnson and Johnson
LPV/r	lopinavir/ritonavir
MVC	maraviroc
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
RAL	raltegravir
RIF	rifampicin
RPV	rilpivirine
RTV	ritonavir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
USFDA	United States Food and Drug Administration
WHO	World Health Organization

A JOINT CALL TO ACTION ON PAEDIATRIC HIV

The discussions of this meeting led to a joint call to action among participants of both the Paediatric Antiretroviral Drug Optimization (PADO) meeting and the ensuing Paediatric HIV Roundtable with Industry, based on the following premises:

- The treatment coverage of children remains low at 35%. Therefore, it is urgent to identify and treat children today, with appropriate regimens for their age. All participants in the roundtable call on national AIDS programmes to step up testing and treating children.
- Accelerating R&D of paediatric antiretrovirals, for neonates up to adolescents, is a matter of emergency. Despite the relatively small paediatric market, there needs to be a continued commitment from industry to continue drug development for these children.

It is thus that the participants jointly issued the following call.

CALL TO ACTION:

- **To donors**, to continue to support R&D, treatment, and care of this specific neglected population, from neonates to adolescents with HIV.
- **To all paediatric HIV stakeholders**, to prioritize and streamline paediatric development plans.
- **To industry**, to collaborate with each other, and explore ways to share patents, which will enable the development of FDCs with drugs from different companies.
- **To national regulatory bodies**, to fast-track and accelerate paediatric ARV approvals by engaging in harmonized regulatory mechanisms at regional level.
- **To researchers, academics, industry, governments, and civil society** to collaborate in accelerating the progress in bringing new drugs and formulations to children infected with HIV.
- **To decision makers** (Ministries of Health, financing institutions, and development partners) to optimize paediatric ARVs aligned with WHO recommendations and thereby limit market fragmentation.

"From a paediatrician's perspective, there is a tremendous need for simplification of treatment, increase in treatment coverage for children, community sensitization, and tackling stigma as it is still one of our biggest obstacles. The dispersible fixed-dose combinations we have today have really changed the way we deliver treatment to children. Child friendliness or granny friendliness; palatability of the formulation: sweetness is the way to go. Acceptable packaging for caregivers: big bottles are difficult to hide. These are some of the formulation issues we need to address."

Clara van Gulik, Médecins Sans Frontières

DNDi
Drugs for Neglected Diseases *initiative*

15 Chemin Louis-Dunant, 1202 Geneva, Switzerland
Tel: +41 (0) 22 906 9230 ; Fax: +41 (0) 22 906 9231
dndi@dndi.org ;