Today's agenda

16:00 CET	**Welcome and introduction**
5 minutes	Sébastien Morin (IAS)
16:05 CET	**PADO 3 priorities**
25 minutes	Martina Penazzato (WHO)
	Philippa Easterbrook (WHO)
16:30 CET	**PAWG plans**
10 minutes	Martina Penazzato (WHO)
16:40 CET	**Q&A** (from the chat)
15 minutes	Facilitated by Sébastien Morin (IAS)
16:55 CET	**Closing remarks**
5 minutes	Sébastien Morin (IAS)

Paediatric ARV Drug Optimization 3 Meeting

Dr Martina Penazzato
HIV Department
WHO-Geneva

28 February 2017

World Health Organization

Drug Optimisation remains a critical enabler of scaling up ART and reaching **super fast track targets**

MAKING THE RIGHT DRUGS AVAILABLE FOR CHILDREN WITH HIV

5-9 December 2016, Geneva, Switzerland

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There are over 1.8 million children living with HIV, but only half of them are receiving the treatment they need. The World Health Organization (WHO) and partners are organizing a series of events in Geneva during the *Paediatrics Week on drug optimization*, from 5-9 December. The events aim to respond to the four key pillars of paediatric treatment optimization:

1. Optimizing HIV treatment options and identifying priority products for children
2. Developing priority paediatric products
3. Optimizing selection and procurement of existing paediatric products
4. Enabling effective introduction, procurement and supply of paediatric products.

FAST TRACKING THE DEVELOPMENT AND INTRODUCTION OF PAEDIATRIC FORMULATIONS

Meeting of the Global Paediatric Antiretroviral Commitment-to-Action (CTA), 5 December

The Paediatric HIV Commitment-to-Action is identifying innovative approaches to fast-track development of priority paediatric formulations. A new financing mechanism in support of a collaboration framework is being considered with the goal of overcoming existing challenges to the timely development of drugs and formulations for infants and children. This framework focuses on: accelerating the development of new drugs for children, accelerating the development and market uptake of new child-friendly formulations of existing drugs, and financing the development of new formulations of existing drugs. ***Open to members and invitees. Focal point: George Siberry, OGAC***

IMPROVING GUIDANCE FOR PAEDIATRIC HIV TREATMENTS

Meeting of the Paediatric ARV Drug Optimization group - (PADO 3), 6-7 December

Building upon the progress made after the first and second *Paediatric antiretroviral (ARV) drug optimization meeting*, held in Dakar in 2013 and in Geneva in 2014, WHO is convening a third meeting (PADO3) to further advance optimization in paediatric ART. Participants will establish priorities for drug and formulation development and identify research gaps on the use of ARVs for infants, children and adolescents.
Open to members and invitees. Focal point: Martina Penazzato, WHO

DEVELOPING PRIORITY PRODUCTS

Meeting of Paediatric HIV Treatment Initiative (PHTI), 8 December

The *Paediatric HIV Treatment Initiative (PHTI)* aims to accelerate the development and registration of paediatric formulations. Currently, partners are in charge of running several projects in a collaborative manner to optimize the paediatric formulary in line with WHO recommendations. Coordinated by UNITAID, and building upon the expertise and the work of the convening partners — Clinton Health Access Initiative (CHAI), Drugs for Neglected Diseases initiative (DNDi), the Medicines Patent Pool (MPP), UNITAID, and WHO —PHTI aims to create synergies and promote collaboration among various key partners and stakeholders through optimizing development and regulatory pathways for paediatric products. This meeting will review progress and outline key next steps to be undertaken. ***Open to PHTI partners and invitees. Focal point: Robert Matiru, UNITAID***

OPTIMIZING EXISTING PRODUCTS

Interagency Task Team (IATT) formulary revision meeting, 8 December

The *Optimal List of paediatric ARV formulations* jointly published by IATT, WHO and UNICEF provides guidance to funders, implementing partners, procurement agencies and countries to enable a consolidated demand for optimal products and to ensure a sustainable supply of medicines for children living with HIV. The most recent revision was completed in early 2016 to complement the 2016 WHO Consolidated ARV Guidelines. This meeting will focus on implementation guidance for country programs including discussion of strategies to address the phasing-in of newer optimal products and phasing-out of suboptimal options.
Open to members and invitees. Focal point: Nandita Sugandhi(CHAI)

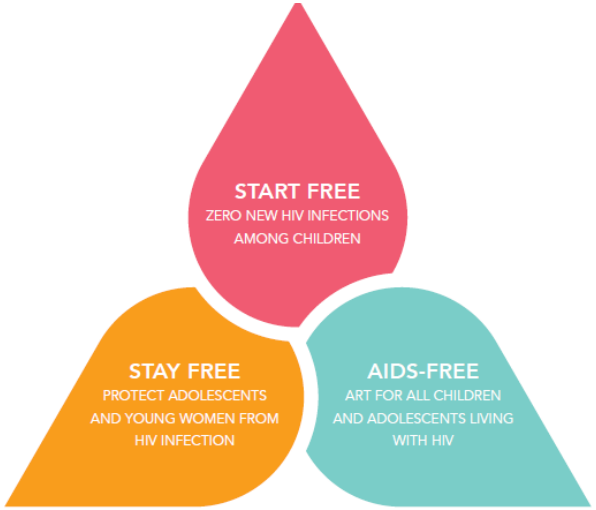
ENABLING EFFECTIVE PROCUREMENT AND SUPPLY

Meeting of the ARV Procurement Working Group, 9 December

The *ARV Procurement Working Group (APWG)* was established to adopt a coordinated approach to the procurement of paediatric ARVs that are challenging to procure as they have low volume demand, including because they are of limited/specialised use or new products or formulations. The group has recently expanded its scope to include adult and adolescent products with the same dynamics. The Global Fund is convening this meeting with partners to share updates as well as to define priorities in innovation and expected outcomes.
Open to members and invitees. Focal point: Martin Auton, the Global Fund, Wesley Kreft, PFSCM

1.6 million children (0-14) on ART by 2018

1.2 million adolescents (15-19) on ART by 2018



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New efforts to accelerate development of priority paediatric ARVs are being put in place

Prioritisation (PADO/PAWG)

Development and introduction of priority products

UPSTREAM

Develop-ment

Research

Regulatory (SRAs)

GAPf

Regulatory (NRAs)

Intro-duction

Procurement

DOWNSTREAM

Promoting **innovative** thinking and **prioritizing** formulations to be developed are critical steps

- **Review medium- and long-term priorities** for the development of new paediatric ARV drugs and formulations for paediatric HIV treatment and prevention.
- **Identify research gaps** to be addressed and inform optimal use of ARVs in infants, children and adolescents to enable future development and uptake of priority products.
- **Identify synergies and promote alignment** with drug and formulations development for other anti-infective agents to be used in paediatric **hepatitis and tuberculosis**.

PADO 3

The key principles of drug optimisation continue to be the drivers of our thinking!

- Potency/safety
- Harmonisation
- Simplification

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PADO3 discussed several issues taking stock of the progress made and the persisting challenges

- ARV pipeline for children, adolescents and adults
- Current timelines for development and introduction of new formulations
- Target product profile characteristics
- Optimal regimens to be used to prevent and treat HIV in newborns
- Sequencing in the context of INSTI introduction
- Simplification strategies and dual therapy options
- Consideration for co-infections with TB and hepatitis
- Evidence base required for introduction of new drugs that are proven to be effective in adults

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The PADO vision for optimal use and sequencing of key drugs is crystallizing towards…

- INSTI introduction to be fast-track
  - DTG: role in all line of treatment once available
  - RAL: to fill the gap in newborns and infants
- ATVr de-emphasized as a bPI for 2nd line
- Simplification strategies to be considered
  - DTG/DRVr: current 3rd and potential future 2nd line
  - DTG/3TC: mostly as a switch strategy
- Long acting oral and injectable key for adolescents
- Neutralizing antibodies to be investigated

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Ongoing development from PADO2

LPVr 4-in-1: first line for under 3 years to address the lack of optimal formulations

EFV triple: first line 3-10 years to provide an FDC to maximise adherence and simplify procurement

Concrete progress was made to develop key PADO 2 priorities: the 4-in-1 and EFV triple development plans need to be completed.

PHTI partners will explore opportunities to support and assist what is expected to be a time limited demand/market

across the full age spectrum

Mid term prioritisation

- **RAL better formulation:** use in infants and young children to enable rapid introduction of INI for use in 1st line regimen
- **DRVr:** use in 2nd and 3rd line formulations and overcome issues with separate administration of RTV
- **NVP-AZT** for postnatal prophylaxis
- **DTG** paeds formulations and **DTG+3TC+ABC** for 1st and 2nd line
- **F/TAF** paeds formulation (<6 year) and **DTG+XTC+TAF** (under the assumption that this will be a viable product for adults)
- NEW **DTG + DRVr** for use in 3rd line or as simplification strategy in 2nd line

Long-term prioritisation

- DTG + 3TC: for naive or simplification
- Long acting oral and injectable
- Neutralizing antibodies (VRC01) in treatment or postnatal prophylaxis

PADO 1-2013	PADO 2-2014	PADO 3-2016
LPVr 4-in-1	LPVr 4-in-1 (30/15/40/10 mg)*	In advanced development
ABC/3TC/EFV	ABC/3TC/EFV (150/75/150 mg)*	In advanced development
ATVr	ATVr (100/33mg)*	Removed§
NVP 20 mg	NVP/AZT	NVP/AZT
DRVr	DRVr	DRVr (120/20 mg)*
RAL	RAL	RAL (50 mg scored)*
DTG single	DTG paeds single	DTG paeds single (5 mg)*
DTG/3TC/ABC	DTG/3TC/ABC	DTG/3TC/ABC (5/30/60 mg)*
F/TAF	F/TAF	F/TAF
DTG/XTC/TAF	DTG/XTC/TAF	DTG/XTC/TAF
		DTG/DRVr
		DTG/3TC
		Long acting oral/ injectable
		Neutralizing antibodies

*Dosing and ratio are endorsed/recommended by PAWG
§ Deprioritized due to lack of progress on development in the context of a potential time limited demand

10 (6 mid+4 long)	10 (6 mid+3 long)	11 (8 mid+3 long)

PADO 1-2013	PADO 2-2014	PADO 3-2016
LPVr 4-in-1	LPVr 4-in-1 (30/15/40/10 mg)*	In advanced development
ABC/3TC/EFV	ABC/3TC/EFV (150/75/150 mg)*	In advanced development
ATVr	ATVr (100/33mg)*	Removed§
NVP 20 mg	NVP/AZT	NVP/AZT
DRVr	DRVr	DRVr (120/20 mg)*
RAL	RAL	RAL (50 mg scored)*
DTG single	DTG paeds single	DTG paeds single (5 mg)*
DTG/3TC/ABC	DTG/3TC/ABC	DTG/3TC/ABC (5/30/60 mg)*
F/TAF	F/TAF	F/TAF
DTG/XTC/TAF	DTG/XTC/TAF	DTG/XTC/TAF
	(Long acting)°	DTG/DRVr
	(Rilpivirine)°	DTG/3TC
	(Doravirine)°	Long acting oral/ injectable
		Neutralizing antibodies
		(Bictegravir)°
		(Attachment inhibitors) °

*Dosing and ratio are endorsed/recommended by PAWG
°Considered of interest but not formally included in the priority list
§ Deprioritized due to lack of progress on development in the context of a potential time limited demand

	PADO3 RESEARCH PRIORITIES
Newborns	**A. Neonatal Prophylaxis** • PMTCT risk on maternal DTG – Transmission risk and risk of transmission of DR virus • PMTCT in low risk infants: No ART vs standard of care • Duration of infant prophylaxis in unsupressed BF mother • AZT prophylaxis dose older than 6 week **B. Newborn Treatment:** • Long acting agents in neonates – PK and safety, muscle bulk issues • Monoclonal antibodies – long acting formulations, • Novel delivery systems • ABC down to <3M • Safety in HIV exposed uninfected **C. Remission research:** • IMPAACT P1115, EPIICAL (novel agents, vaccines)
Sequencing	**A. Dosing and formulations** • TB-HIV trials: nest PK studies in ongoing trials to gather data in children that acquire TB while on studies • Taste masking and bioequivalence of crushed tablets • LATs-injectables/patches: 1mo vs 2 mo • Collection of more toxicity data (i.e. in children < 3 years and bone/renal effect of TAF) **B. Alternative agents** • INSTIs vs bPIs (i.e. DTG vs bPIs) in NNRTI resistance • Future third line : DTG/RIL and DTG/DRV **C. Innovative strategies** • Dual therapy: DTG/3TC, DRV/r/3TC, DRV/r/DTG in a **non-inferiority trial** including naïve and experienced • Weekend off with DTG/EFV (?)
Novel antivirals	• Broadly neutralizing antibodies: VRC01 in phase II in adults; vedolizumab (anti-a4b7 integrin) in phase I • Adnectins = molecules that target CD4 and gp41: Combinectin (SC): anti-CD4, anti-gp41,fusion inhibitor, HAS • Nano- formulations & role in paediatric HIV

Research gaps (newborns)

A. Neonatal prophylaxis

- PMTCT risk on maternal DTG – Transmission risk and risk of transmission of DR virus
- PMTCT in low risk infants: No ART vs standard of care
- Duration of infant prophylaxis in unsupressed BF mother
- AZT prophylaxis dose older than 6 week

B. Newborn treatment:

- Long acting agents in neonates – PK and safety, muscle bulk issues
- Monoclonal antibodies – long acting formulations,
- Novel delivery systems
- ABC down to <3M
- Safety in HIV exposed uninfected

C. Remission research:

IMPAACT P1115, EPIICAL (novel agents, vaccines)

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Research gaps (sequencing)

A. Dosing and formulations

- TB-HIV trials: nest PK studies in all ongoing trials to gather data in children that acquire TB while on studies
- Taste masking and bioequivalence of crushed tablets
- LATs-injectables/patches: 1mo vs 2 mo
- Collection of more toxicity data (i.e. in children < 3 years and bone/renal effect of TAF)

B. Alternative agents

- INSTIs vs bPIs (i.e. DTG vs bPIs) in NNRTI resistance
- Future third line : DTG/RIL and DTG/DRV

C. Innovative strategies

- Dual therapy: DTG/3TC, DRV/r/3TC, DRV/r/DTG in a **non-inferiority trial** including naïve and experienced children
- Weekend off with DTG/EFV (?)

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Research gaps (novel antivirals)

- Broadly neutralizing antibodies
  - VRC01 in phase II in adults
  - Vedolizumab (anti- a4b7 integrin) in phase I
- Adnectins = molecules that target CD4 and gp41
  - Combinectin (SC): anti-CD4, anti-gp41,fusion inhibitor, HAS
- Nano- formulations & role in paediatric HIV

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Considerations for Research

- Adaptive designs: inclusion of more arms in existing studies for switching & simplification
- Tolerability/acceptability studies need to be nested in at early stages of investigation
- Implementation science to explore real world issues
  - Administration of new products
  - Introduction of new products (i.e. moving to new regimens when groups are tolerating existing regimens)

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Overall a number of **IMPORTANT overarching** recommendations were made to speed up development and introduction of new ARVs

- **Extrapolation of efficacy from adults** combined with safety and PK to be considered the evidence base for introduction in ARV guidelines.
- **Simultaneous enrolment for all children >4 weeks in** registrational trials unless specific rationale exists (biology or different BE)
- **Triple FDCs to preferred but not necessary** to avoid preventing rapid introduction of new drugs for children
- **Crushable, chewable or dispersible solid forms** still to be considered the most desirable TPP (exceptions to be defined on a case by case basis).
- **Adaptive designs** to be encouraged in paediatric ARV research
- **Implementation research** to be expanded in order to fully address programmatic challenges of providing ARVs in children

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Publications

Completed:

- Drug optimization – JIAS 2015
- EFV triple modeling – Clinical Pharmacology 2016
- Research innovations – CID 2017

Under development:

- PADO3 outcomes
- Optimal use of ARVs in neonates

To be potentially developed:

- Adolescents
- WHO Generic tools

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THANK YOU!!!!

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