Today’s agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Duration</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:00</td>
<td>Welcome and introduction</td>
<td>5 minutes</td>
<td>Sébastien Morin (IAS)</td>
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<tr>
<td>16:05</td>
<td>PADO 3 priorities</td>
<td>25 minutes</td>
<td>Martina Penazzato (WHO)</td>
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<td>Philippa Easterbrook (WHO)</td>
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<tr>
<td>16:30</td>
<td>PAWG plans</td>
<td>10 minutes</td>
<td>Martina Penazzato (WHO)</td>
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<td>16:40</td>
<td>Q&amp;A (from the chat)</td>
<td>15 minutes</td>
<td>Facilitated by Sébastien Morin (IAS)</td>
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<tr>
<td>16:55</td>
<td>Closing remarks</td>
<td>5 minutes</td>
<td>Sébastien Morin (IAS)</td>
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Drug Optimisation remains a critical enabler of scaling up ART and reaching super fast track targets.
New efforts to accelerate development of priority paediatric ARVs are being put in place.
Promoting innovative thinking and prioritizing formulations to be developed are critical steps

- **Review medium- and long-term priorities** for the development of new pediatric ARV drugs and formulations for pediatric 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 pediatric hepatitis and tuberculosis.

**PADO 3**

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

- Potency/safety
- Harmonisation
- Simplification
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
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
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.
**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 1\textsuperscript{st} and 2\textsuperscript{nd} 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 3\textsuperscript{rd} line or as simplification strategy in 2\textsuperscript{nd} line
Long-term prioritisation

- DTG + 3TC: for naive or simplification
- Long acting oral and injectable
- Neutralizing antibodies (VRC01) in treatment or postnatal prophylaxis
<table>
<thead>
<tr>
<th>PADO 1-2013</th>
<th>PADO 2-2014</th>
<th>PADO 3-2016</th>
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<tbody>
<tr>
<td>LPVr 4-in-1</td>
<td>LPVr 4-in-1 (30/15/40/10 mg)*</td>
<td>In advanced development</td>
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<tr>
<td>ABC/3TC/EFV</td>
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<td>ATVr</td>
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<td>Removed§</td>
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<tr>
<td>NVP 20 mg</td>
<td>NVP/AZT</td>
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<tr>
<td>DRVr</td>
<td>DRVr</td>
<td>DRVr (120/20 mg)*</td>
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<tr>
<td>RAL</td>
<td>RAL</td>
<td>RAL (50 mg scored)*</td>
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<tr>
<td>DTG single</td>
<td>DTG paeds single</td>
<td>DTG paeds single (5 mg)*</td>
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<tr>
<td>DTG/3TC/ABC</td>
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*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)
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### 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 unsuppressed 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
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IMPAACT P1115, EPIICAL (novel agents, vaccines)
A. Dosing and formulations

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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
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• Nano-formulations & role in paediatric HIV
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)
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
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
THANK YOU!!!!