Focus Group 1 – Progress in the Development of LA ART dosing strategies for pediatric populations.
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Image (crushing weight of a lifetime of daily pills: youth-developed patient facing materials of the LATA study).
Outline – intended as a resource to gain a view of the current state of the field. Much progress in LA HIV therapeutics in children!

- Major hurdles and how to clear them.
- Data gaps.
- Priority research areas.
- Priority products.
- Future directions.

Progress in LA HIV therapeutics in children.

Overview.

LA landscape.

- CAB and RPV for HIV treatment.
  - MOCHA and LATA studies have enrolled over 500 VS CWH aged 12 to 19y.
  - CRAYON enrolled the first of 100 VS CWH aged 2 to 12y in Jan 2024.
- Exploratory studies are paving way for LA CAB in neonates.
- TLC-ART 101 in DcNP.
- MAP formulations.

Lessons learned – recommendations for pediatric trials.

- Use WHO weight-band dosing.
- Leverage PK modeling methods to better predict dosing, particularly in neonates.
- **Simultaneous enrolment across weight bands is key, especially for younger children.** T
  - Avoids the enormous delay introduced by staggering weight bands and waiting for interim analysis results. (i.e., only enrolling the one-year younger age group when interim analysis data are available).
- **Unanimous agreement to enroll adolescents in adult clinical trials to accelerate access to key technologies**.
- Extrapolate efficacy data from adult trials for regulatory approvals.
- Use innovative pediatric trial designs to maximize the use of available data.
- Wide collaboration across stakeholders early in the development of technologies (i.e., youth boards, parents, caregivers, public health officials).

LA CAB and RPV in CWH – injection volume, site, and route.

Volume speaks volumes.

- Dose-volume table of commonly used therapeutics highlights that minimizing volume is a key consideration.
  - 0.5ml is the maximum volume for a thigh injection in neonates.
- How do we nest LA ART alongside other needed injections in the pediatric immunization schedule?
- Is it feasible to co-formulate CAB/RPV as a single injection for HIV treatment?
  - Divergent viscosity and storage temperature.
- ULA approaches to minimize volume were discussed as critical approaches.
  - Two approaches pioneered by ViiV healthcare: purchased rHuPH20 to increase SC injection volume of CAB 200; and developed a novel ULA CAB formulation for Q4M dosing.

Site of injection – thigh (vastus lateralis) vs buttock (ventrogluteal).

- Perhaps where you inject LA products matters (thigh [and may have differential acceptability compared to adults.
- Subgroup analysis of ATLAS 2M – PK and acceptability of thigh vs gluteal administration of Q8W CAB+RPV IM.
  - Thigh PK was slightly higher than gluteal – perhaps could be leveraged to reduce the dosing interval.
  - Vast majority preferred gluteal injection (one-third preferred thigh injection).
- Acceptability could be different for young children, adolescents, and adults.
  - Studies need to solicit opinions from adolescents and caregivers/parents of young children and infants.

Route of injection – SC (abdomen) vs IM (gluteal).

- Self-administration (i.e., SC injections) is appealing for the pediatric age group, but also has stigma potential.
  - More frequent SC injections may be feasible and acceptable given the potential for home/auto-injection (e.g., diabetes); circumvents barriers of the health system (frequent visits to implement the technology).
  - Having medical equipment, needles, or patches in the home could potentially label a caregiver, parent, or child as having HIV.
- PK and safety of LAI CAB SC vs IM.
  - Erythema and nodules were more common after SC injection vs IM.
  - General trend of higher plasma exposures after: SC administration in females and IM administration in males.
  - Can be considered as a PK bridging study.

PK modeling of LAI CAB IM in neonates.

Infant washout data from the CREATE study (IMPAACT 2040).

- PK of CAB among infants born to mothers receiving LA CAB/RPV IM during pregnancy.
  - CAB is expected to cross the placenta; Data collected during the post-delivery washout period.
  - No infant depot, and infants may or may not be ingesting CAB via breastmilk (lipophilic, but MW > 300g/mol).
- These data lay the foundation for modeling.
  - PBPK model predicted neonatal dose is 20mg IM CAB in 0.1 mL administered on day 1 of life.

Target product profiles for DcNP and MAP formulations.

DcNP formulations for pediatric HIV treatment.

- Preferred user characteristics.
  - SC route; 1mL (single injection) to 2mL (two injections) injection volume; and Little to no local reaction.
- LA PK (Q4-6 weeks); DcNP characteristics (2 to 3 HIV targets with 3 HIV drugs); antiviral activity ≥ free-form daily therapy.

MAP formulations for pediatric HIV prevention or treatment.

- HCP or caregiver administration; Dose aligned with WHO pediatric ARV weight bands; 7cm^2 is the largest acceptable size for newborn weight-band dosing (multiples used for remaining weight bands); QW or QM dosing interval; Wear time 20 min.
  User acceptability data from PATH indicate QW neonatal CAB patch was acceptable to caregivers.
- PKPB modeling work.
  - QW CAB MAP is feasible and acceptable.
  - QM ISL MAP is feasible (all weight bands require an acceptable number of MAPs).

Preclinical PK/antiviral study is ongoing in a NHP SIV model.

- RPV is not potent enough: an unacceptable number of MAPs is required for QW and QM dosing.
- LEN has an unfavorable PBPK profile and delivery efficiency/unacceptable number of MAPs required. ***Formulation optimization is ongoing for new rat studies and PK/antiviral efficacy in a NHP SIV model.***

Hurdles to launch a novel therapeutic for pediatrics.

Regulatory challenges were repeatedly noted.

- Registrational studies have been hampered by early stipulation of injection site in the pediatric investigation plan (PIP) or initial pediatric study plan (iPSP) – narrow regulatory pathway until licensing (frequently encountered).
  - It was noted that PIPs (EMA) and iPSPs (FDA) can be changed, if needed.
  - Does each route and site of administration need safety/efficacy data unless PK bridging studies?
- Innovation in pediatrics study design is needed.
  - All agreed that the amount of time required to complete traditional studies is prohibitive and delays access to novel therapeutics.
- LA CAB+RPV – how much safety data needs to accrue in young children before dosing a neonate?
  - bNAbs are used in neonates.
  - Will safety data in a 3-year-old inform how or whether to dose a neonate? If not, why not simultaneously enroll?
- Simultaneous enrollment of all weight bands is a challenge.

Higher-level hurdles need to be cleared before lower-level hurdles.

Access to the API – need to obtain LA therapeutics for studies.

- Post-trial access barriers now hinder pre-trial approvals.
- There is no pathway to licensure in most sub-Saharan Africa countries – room for regulatory advocacy?

Product cost.

- Cost needs to be compared head-to-head with oral TLD ($4-5 per month).
- LA CAB – can vials be multi-use?
  - Perhaps in the setting of CAB postnatal ARV prophylaxis (PNP).
  - Need to validate the formulation for single-use vials or ready-to-use devices.

Clinical scenarios (VS vs. viremic populations).

- Every study is among VS CWH.
- There are no studies among viremic adolescents who cannot adhere to oral ARVs – it could be argued that the biggest impact of these technologies would be realized if rolled out in that population.

Summary of data gaps and priority research areas.

- Guidance for developers of LA products in children?
  - Avoid absolutism and cutoffs in favor of the whole package (i.e., tolerability, who injects, etc.).
  - For PNP, QW CAB MAP is acceptable; For HIV treatment, the required MAP number poses challenges for less potent APIs.
- PK of LA CAB+RPV in neonates to age 2y.
  - CAB/RPV PK washout and breastfeeding infant PK in CREATE.
- **PK, safety, and efficacy of emerging QW oral treatments and Q6M injectables (LEN/ISL) in children and adolescents.**
- **How to implement LA therapeutics.**

- **Growth and development of children on LAIs.**
- bNAbs in children.
- Long-term acceptability of LA therapeutics (more frequent clinic visits; how to incorporate into routine pediatric visit schedule).
- **Optimal duration/dosing frequency.**
    - Could differ between adolescents and younger children.
    - Adults prefer Q8W over Q4W dosing, yet there is more VF with Q8W.
    - Adolescent endurance for maintaining Q8W dosing is limited. Is there endurance erosion with more frequent clinic visits? Do we need to think creatively about visit-window forgiveness in adolescents vs adults and female vs male patients?
    - What is the caregiver perspective on combining injections with immunization visits.
- **End-user preferences when they differ between child and caregiver or among key stakeholder groups.**

Conclusions.

- Neonates, children, adolescents with HIV/HBV/HCV/TB stand to benefit from LA therapeutics.
- Much progress has been made among studies of LA HIV therapeutics in and for children (MOCHA, LATA, CRAYON, Neonates, DcNP, MAPs, and DAISY).
- Creativity and innovation in trial design is essential and extends to the regulatory domain.
- Data gaps abound.
- Priority research areas have been identified.
- The future is bright – with collective will and collaboration, the future can be here.