2nd Long-Acting Treatment and Prevention Conference

29 October 2024 | Johannesburg


# Progress towards bringing Long-acting ART to children and adolescents

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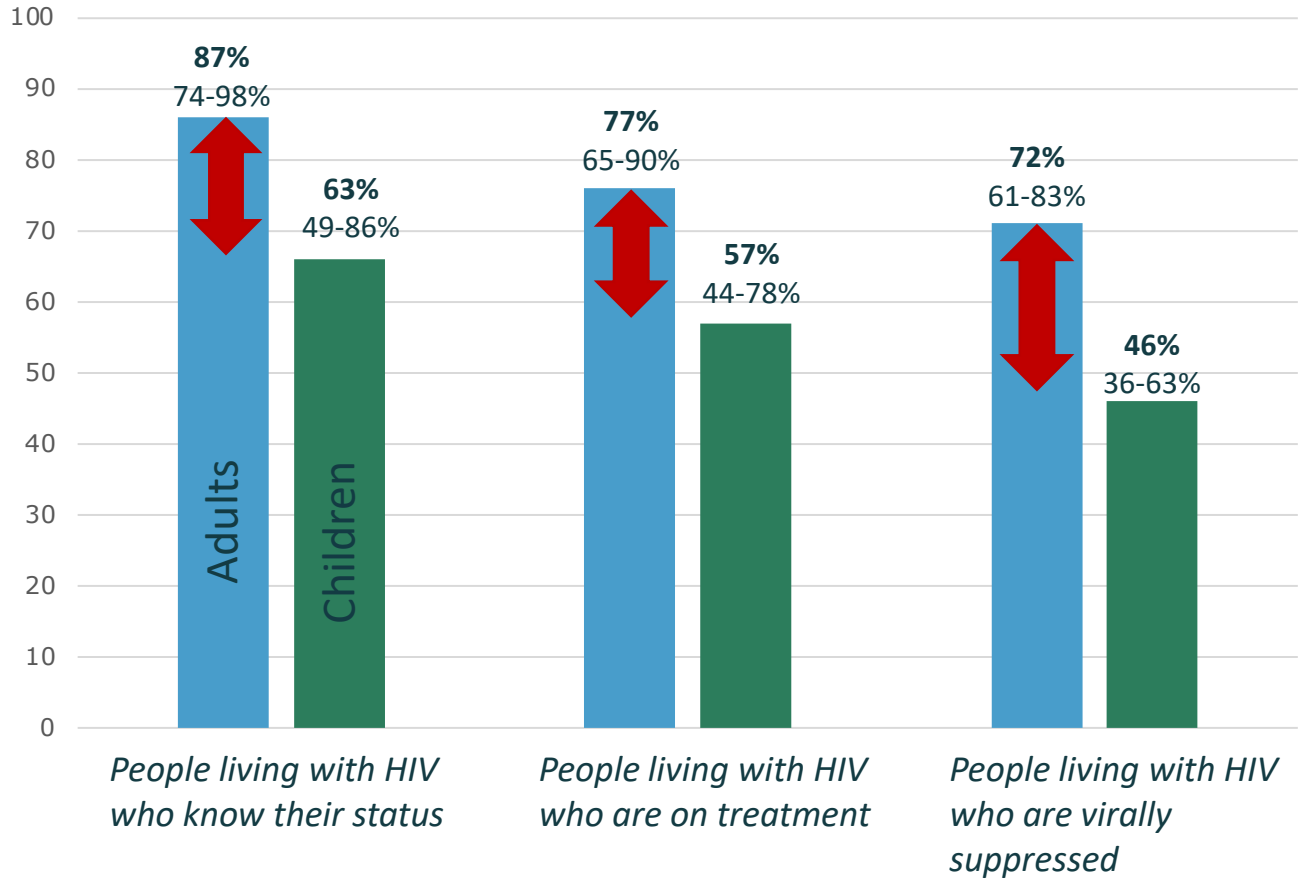
# Disclosures

- Advisory Boards – ViiV, Mylan, GSK
- Speaking Honorarium – Cipla
- Grants/Research Support – GSK, ViiV/Jansen, Novovax

# Treatment Cascade in Children

- Outcomes across the treatment cascade in children are poor compared to adults

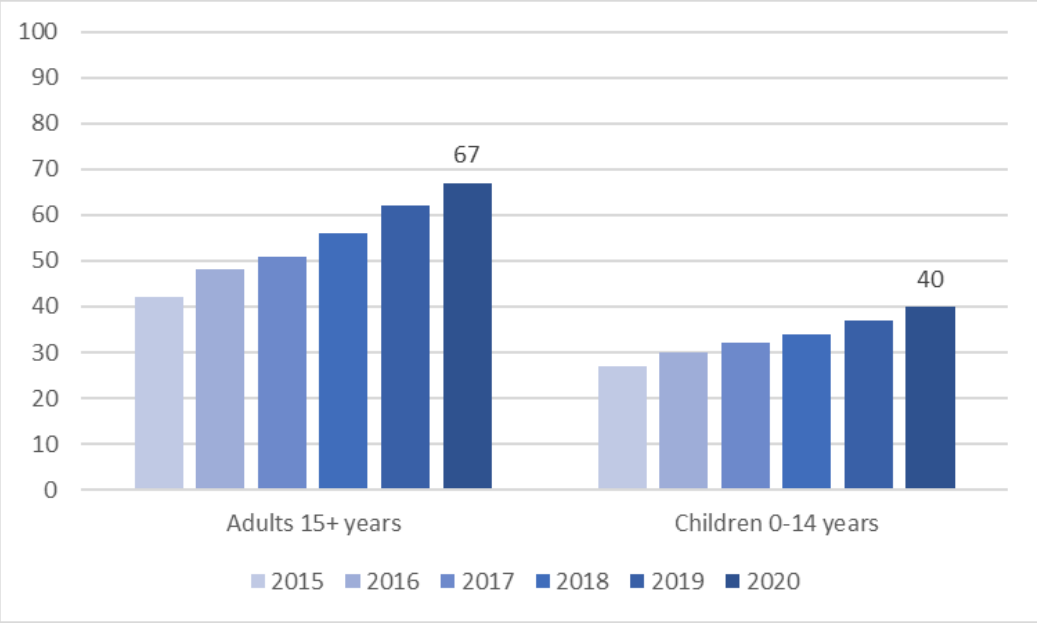
- Widening gap across the cascade
  - **63%** known HIV status
  - **57%** started on ART
  - **46%** virally suppressed

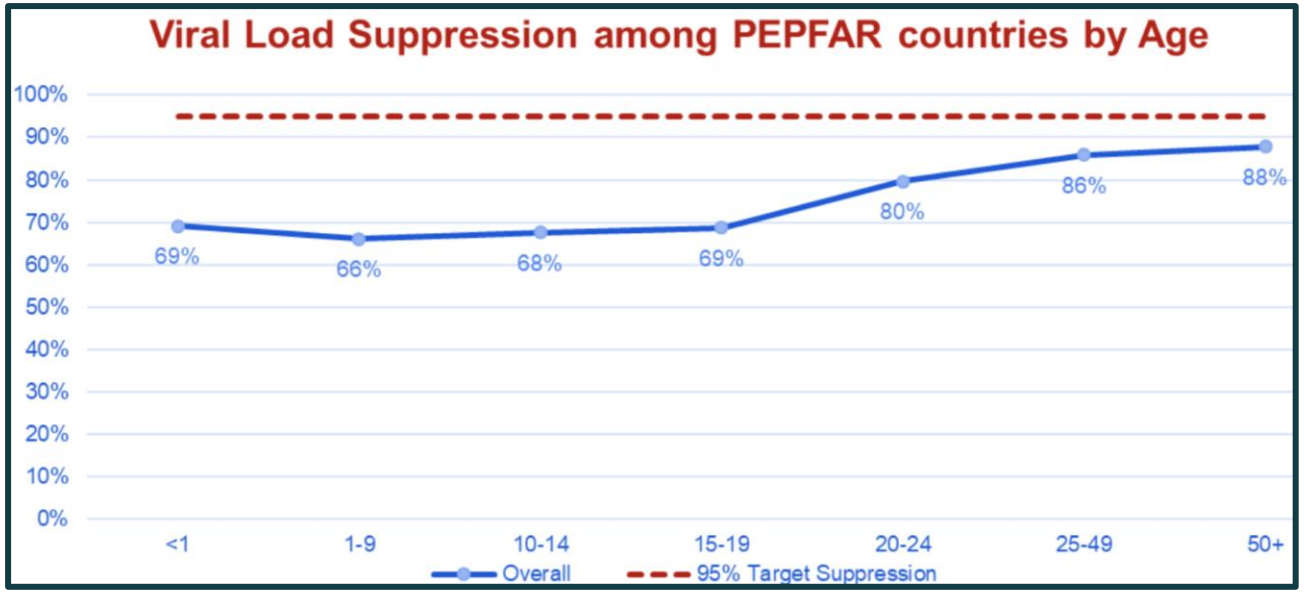



*UNAIDS epidemiological estimates, 2023 (https://aidsinfo.unaids.org/)*

# Paediatric Treatment Cascade

Percentage of people living with HIV with suppressed viral load, by age, Global, 2015-2020




Source: UNAIDS 2021 epidemiological estimates.

# Adult - Paediatric Divide

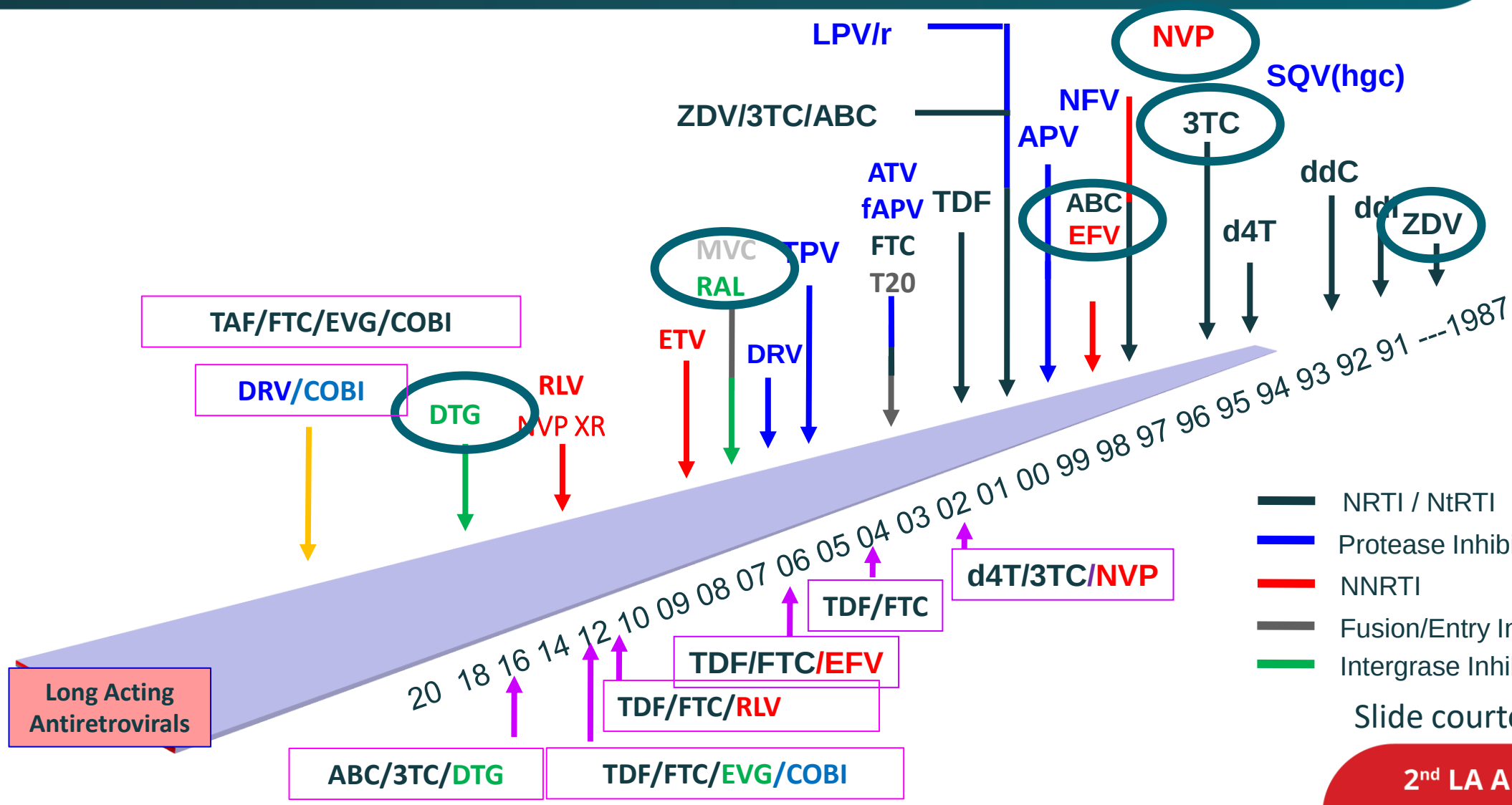
VS

SIMPLICITY
Highly potent Fixed Dose Combination ART

MOVE to SIMPLICITY

| Weight | No. of DTG Daily Tablets | No. of ABC/3TC 120/60 mg Daily Tablets |
|---|---|---|
| 3 to < 6 kg | 0.5 | 1 |
| 6 to < 10 kg | 1.5 | 1.5 |
| 10 to < 14 kg | 2 | 2 |
| 14 to < 20 kg | 2.5 | 2.5 |

# ART Development Timeline




Slide courtesy of Tim Cressey

# Drug Development considerations

## Age Classification of Pediatric Patients

### Preterm newborn infants

(the day of birth through the expected date of delivery + 27 days)

- Small numbers of patients with high heterogeneity
- Immature CNS
- Naive renal and hepatic clearance
- Unique neonatal diseases states
- Weight and age (gestational and postnatal) stratification
- Small total blood volume
- Difficulties in assessing outcomes

### Term and post-term newborn infants

(the day of birth + 27 days)

- Different body water and fat content
- ↑ body surface-area-weigh ratio
- BBB is not fully mature
- Naive renal and hepatic clearance
- Less predictable oral absorption

### Infants & Toddlers

(28 days to 23 months)

- Rapid CNS maturation
- Immune system development
- Total body growth
- Hepatic and renal maturation
- Considerable inter-individual variability in maturation

### Children

(2 to 11 years)

- Drug clearance (hepatic and renal) are mature
- Psychomotor development
- Physical growth
- Onset of puberty
- Neurocognitive development
- Stratify based on pharmacokinetic and/or efficacy

### Adolescent

(11 to 18 years)

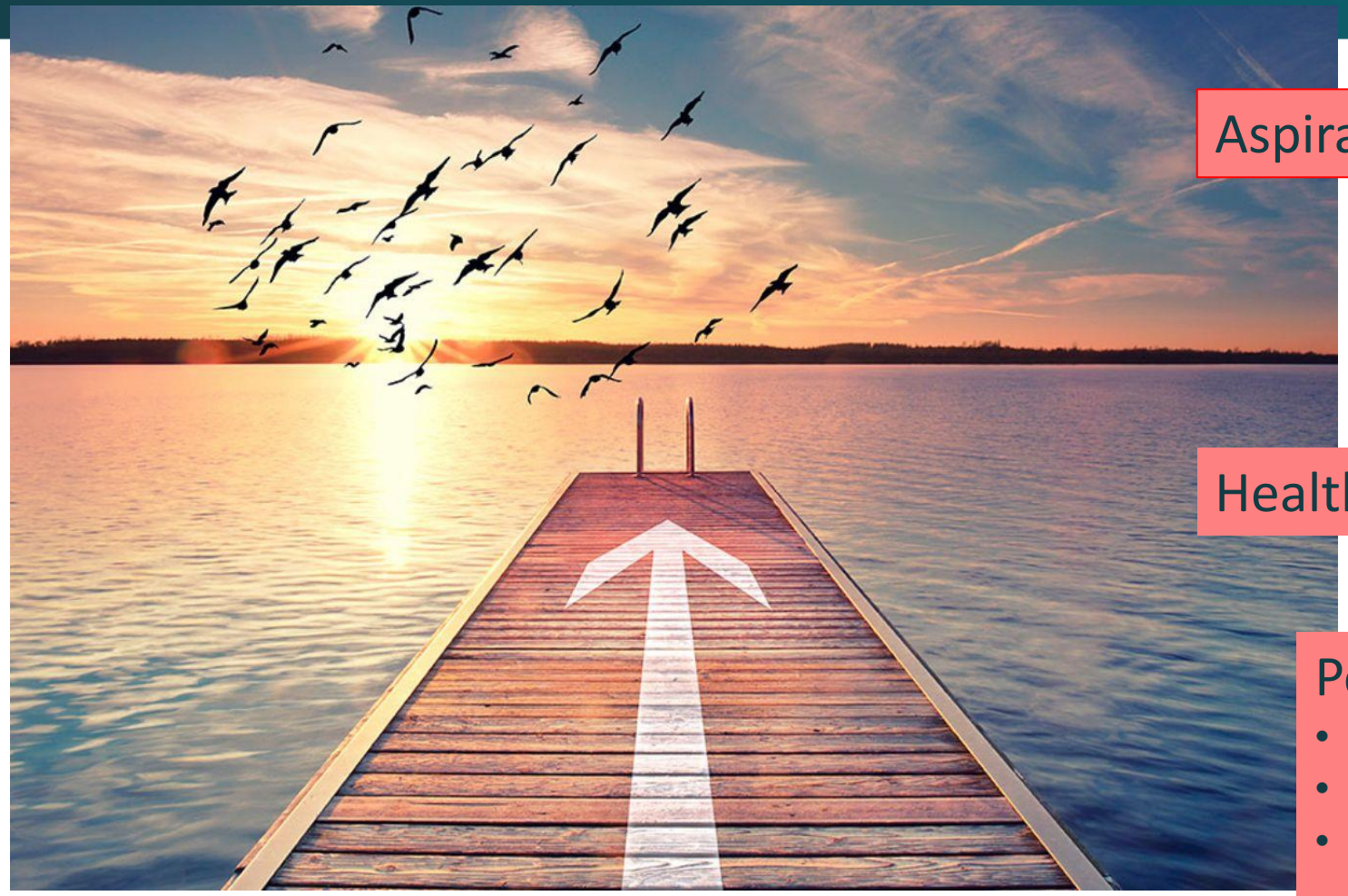
- Sexual maturation
- Hormonal changes
- Rapid growth
- Neurocognitive development
- Noncompliance is a singular problem
- The upper age limit varies among regions

# Antiretroviral Therapy regulatory delays

ABC/3TC: 120/60mg Dispersible tablet


https://www.theglobalfund.org/media/6486/psm_2017-01-arvprocurementworkinggroup_newsletter_en.pdf?u=636547412730000000

# Beyond the horizon



Aspirational

Ideal product profile for children and adolescents

Health system considerations

Positioning/Sequencing

- Maternal ART
- Prevention (PNP)
- Treatment:
  - ART naïve
  - PI/INST experienced

# Beyond the horizon

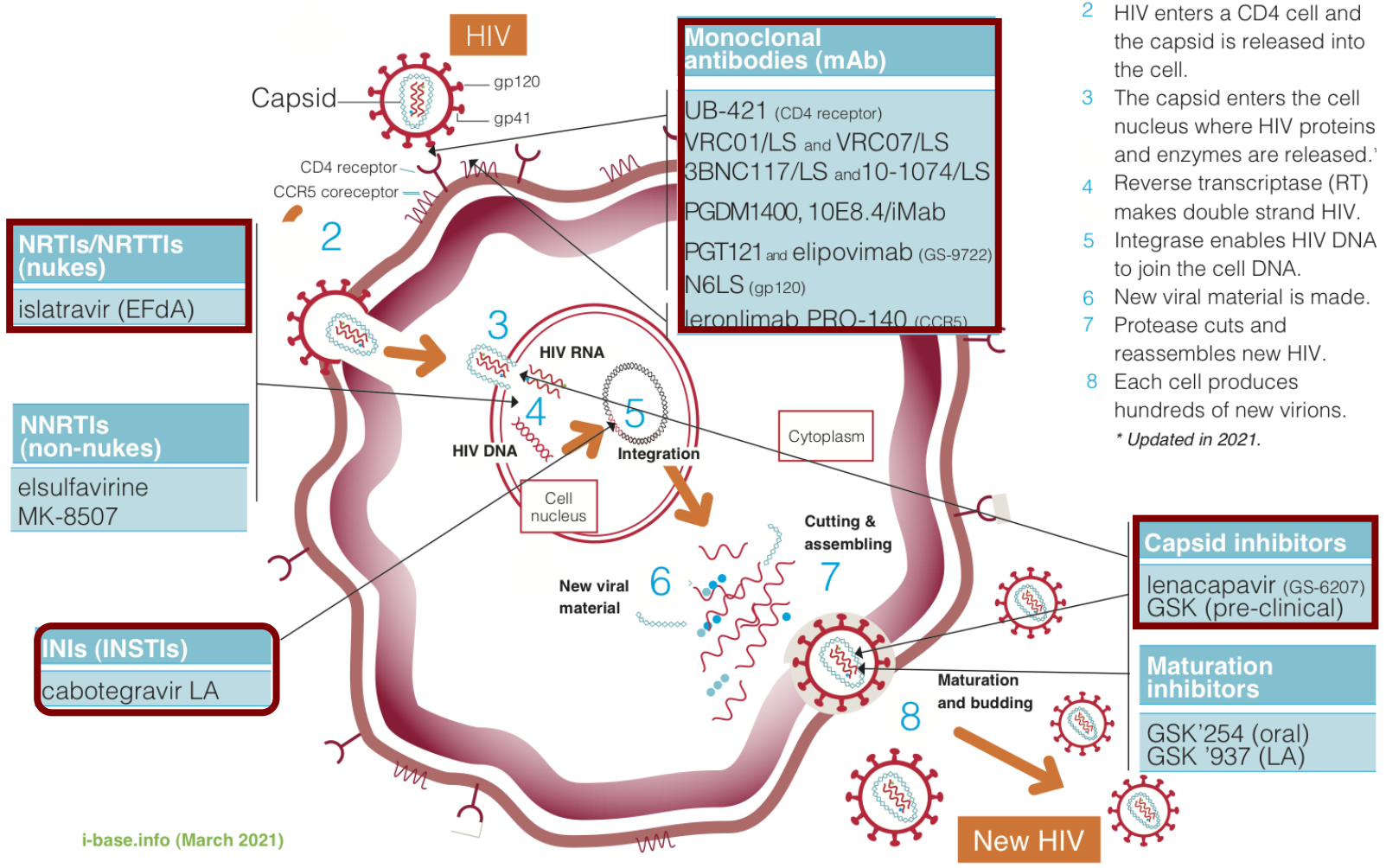
## Better formulations

- High genetic barrier
- Novel mechanism of action
- Lack of shared HIV DR
- Limited side-effects
- Favorable PK across Paediatric ages

## Better drug delivery mechanisms

- Long-acting formulations
- Pain free delivery (for injectables)
- Ease of administration
- Health system consideration:
  - Need for cold storage
  - Additional HS requirements
  - Convenient frequency

# HIV pipeline 2021: targets in the HIV lifecycle




**Stages in the HIV lifecycle**

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and the capsid is released into the cell.
3. The capsid enters the cell nucleus where HIV proteins and enzymes are released.
4. Reverse transcriptase (RT) makes double strand HIV.
5. Integrase enables HIV DNA to join the cell DNA.
6. New viral material is made.
7. Protease cuts and reassembles new HIV.
8. Each cell produces hundreds of new virions.

** Updated in 2021.*

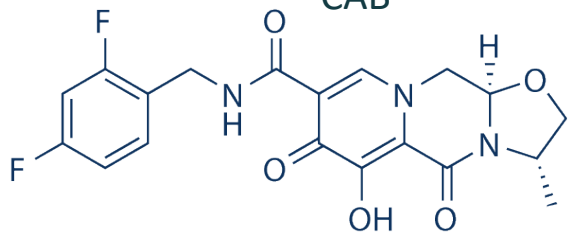
i-base.info (March 2021)

https://i-base.info/htb/41142

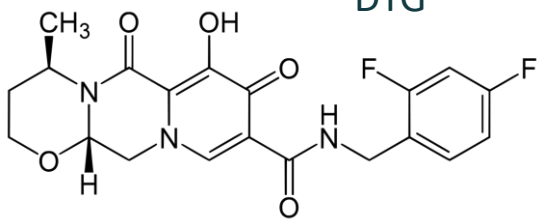
# Cabotegravir/Rilpivirine LAI

- Cabotegravir (CAB) – Integrase strand transfer inhibitor
  - Similar structure to DTG
- Rilpivirine (RPV) – NNRTI
  - NNRTI cross-resistance conferred by: K101P, Y181I and Y181I. K103N + L100I

CAB




DTG




**Adult indication supported by:**

- Every Month injections with CAB + RPV was non-inferior to current triple drug antiretroviral treatments in virologically suppressed HIV-1 infected adults (ATLAS and FLAIR).
- Every two months injections with CAB + RPV was non-inferior to the monthly injection regimen in virologically suppressed adults (ATLAS 2M)

SAPHRA approval for Cabotegravir >18 years

# Paediatric Studies

- **MOCHA** (More Options for Children and Adolescents)
  - 12 – 18 years (>35kgs)
  - Currently completing enrolment at US and International IMPAACT sites
  - New addition – Optional oral lead-in
  - FDA approval (Mar 2022) – Adolescents >12 years and >35kgs
- **CRAYON** (**C**abotegravir and **R**ilpivirine Long-**A**cting Injections in **YO**ung Childre**N**)
  - Children between 10 – 50kg and over 2 years of age
  - Started in 2023
- **Breather Plus – LATA**
  - Implementation study of CAB/RPV in adolescents
  - Enrollment complete – participants in followup
- **AFINAty**
  - Adolescents and young adults (12-24 yrs)
  - 3 groups – virally suppressed, virally unsuppressed/non-adherent and ART naïve given up to 24 weeks to suppress before starting CAB/RPV

# MOCHA

- CAB-LA and RPV-LA, when given individually and with a background ART regimen, are well-tolerated and achieve targeted pharmacokinetic concentrations in these adolescents using the same dose as using in adults.
- No new or unanticipated safety concerns were identified. Of the injection site reactions which occurred, all were Grade 1 or 2, and none led to treatment discontinuation.
- Adolescents and their parents/caregivers found the long-acting injection formulation and the single injectable study drug to be acceptable.

# MOCHA - Acceptability

- Overall, perceptions of injections were favourable
- Health-related QoL was similar before vs. after initiation of LA
- Of 21 adolescents who received 3 study injections, 90.5% (19/21) reported wanting to receive LA ARV even after the study ended (15/21 (71.4%) definitely, and 4/21 (19.1%) probably).
- Selected Quotes:
- “Parents are trying to give them more independence, but we don’t know for sure if they’re actually taking their meds or when they’re skipping them. Versus being able to say, hey, you gotta go to the clinic and get your shot today. And then, knowing they go and get their shot. And just feeling good that they have that independence, but also, were not missing that medicine.” (parent of 12-year-old)
- “Even when I was telling him that I don’t want him to get it, he was like, ‘oh, mommy, please, please, please, let me get it, let me get it, I just want to get out of this medication…’” (parent of 14- year-old)
- “(after the loading dose) I couldn’t walk for a while because it would hurt, and I would start to limp… ..And it felt like my butt was gonna fall off.” “ The second dose was fine… ..(it hurt) for around five minutes, ten minutes… ..but the second time was just two milliliters. So, it was less than the first time.” (17-year-old female)

# Crayon Study

IMPAACT 2036
Cabotegravir and Rilpivirine Long-Acting Injections in Young Children

## Cohort 1

Enroll up to 70 children (50 evaluable) → Discontinue pre-study ART → CAB + RPV PO (4 weeks) → CAB LA + RPV LA IMI (Q4W/Q8W) through Week 72

## Cohort 2

20-40 children

(at least 4 in Cohort 2a and 4 in Cohort 2b)

### Cohort 2a (with oral dosing)

Discontinue pre-study ART → CAB + RPV PO (4 weeks) → CAB LA + RPV LA IMI (Q4W/Q8W) through Week 48

### Cohort 2b (direct to inject)

Discontinue pre-study ART → CAB LA + RPV LA IMI (Q4W/Q8W) through Week 44

- Phase I/II, multi-center, open-label, non-comparative dose finding study with the primary objectives of evaluating the safety, and PK of oral and long-acting injectable cabotegravir (CAB) and rilpivirine (RPV LA) in virologically suppressed children living with HIV-1 aged two to less than 12 years

# Unique Challenges in Infants

- Injection site:
  - Deltoid
  - Ventrogluteal
  - Dorsogluteal
  - Vastus lateralis (lateral thigh)
- Injection volumes:
  - IM injections
  - Slow SC infusions

| Location | Age | Amount |
|---|---|---|
| **Deltoid muscle** | 6 to 15 yrs | 0.5mL |
| **Ventrogluteal** | 3 to 6 yrs | 1.5mL |
| | 6 to 15 yrs | 1.5 to 2.0 mL |
| **Dorsogluteal** | 6 to 15 yrs | 1.5 to 2.0 mL |
| **Vastus lateralis** | Birth to 1.5 yrs | 0.5mL |
| | 1.5 to 3 yrs | 1.0 mL |
| | 3 to 6 yrs | 1.5 mL |
| | 6 to 15 yrs | 1.5 to 2.0 mL |

https://www.vnhcsb.org/media/data/papers/pdf/458_20.16.3.pdf

Lower BMI

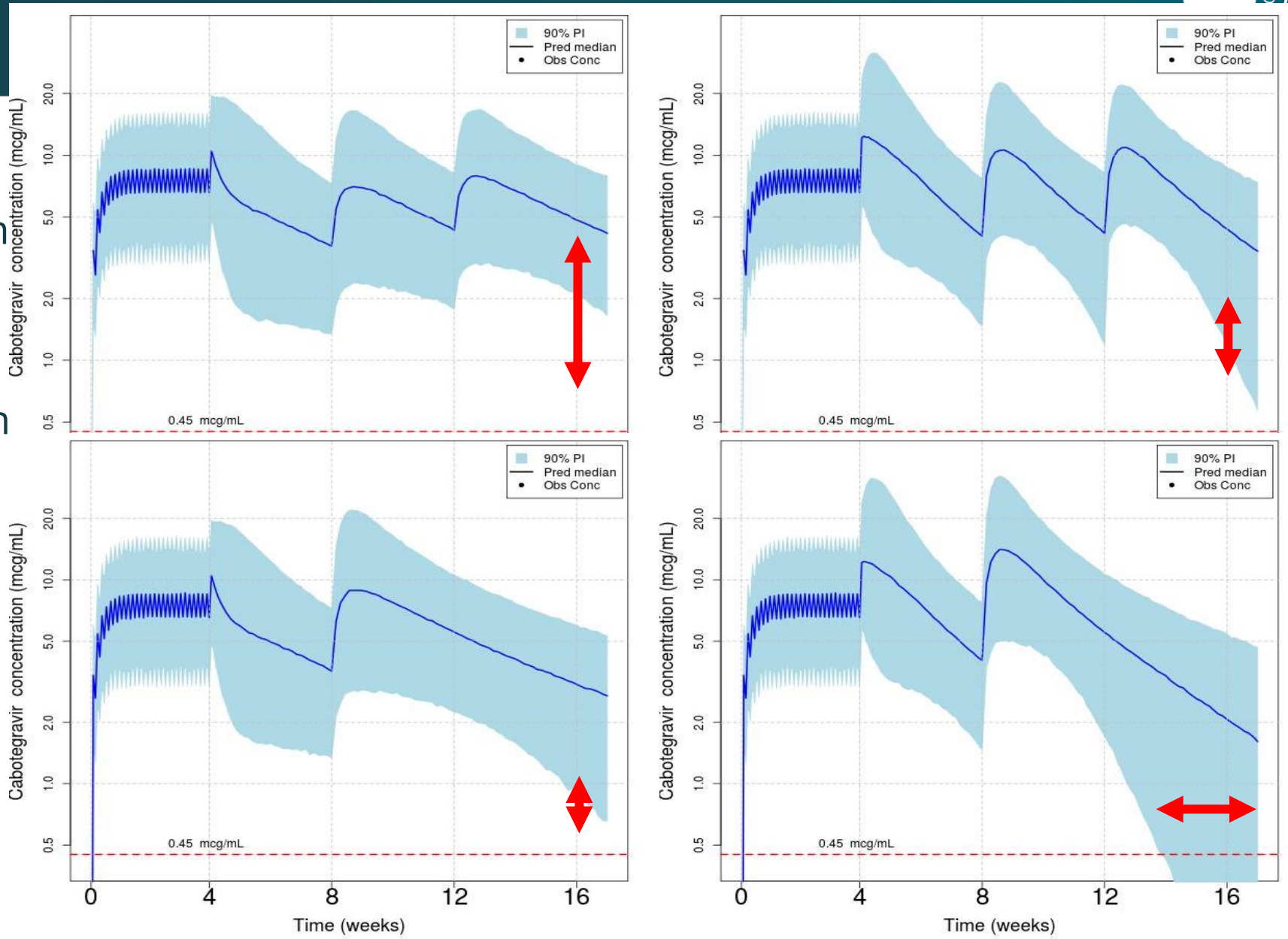
Increased Absorption

Increased Elimination

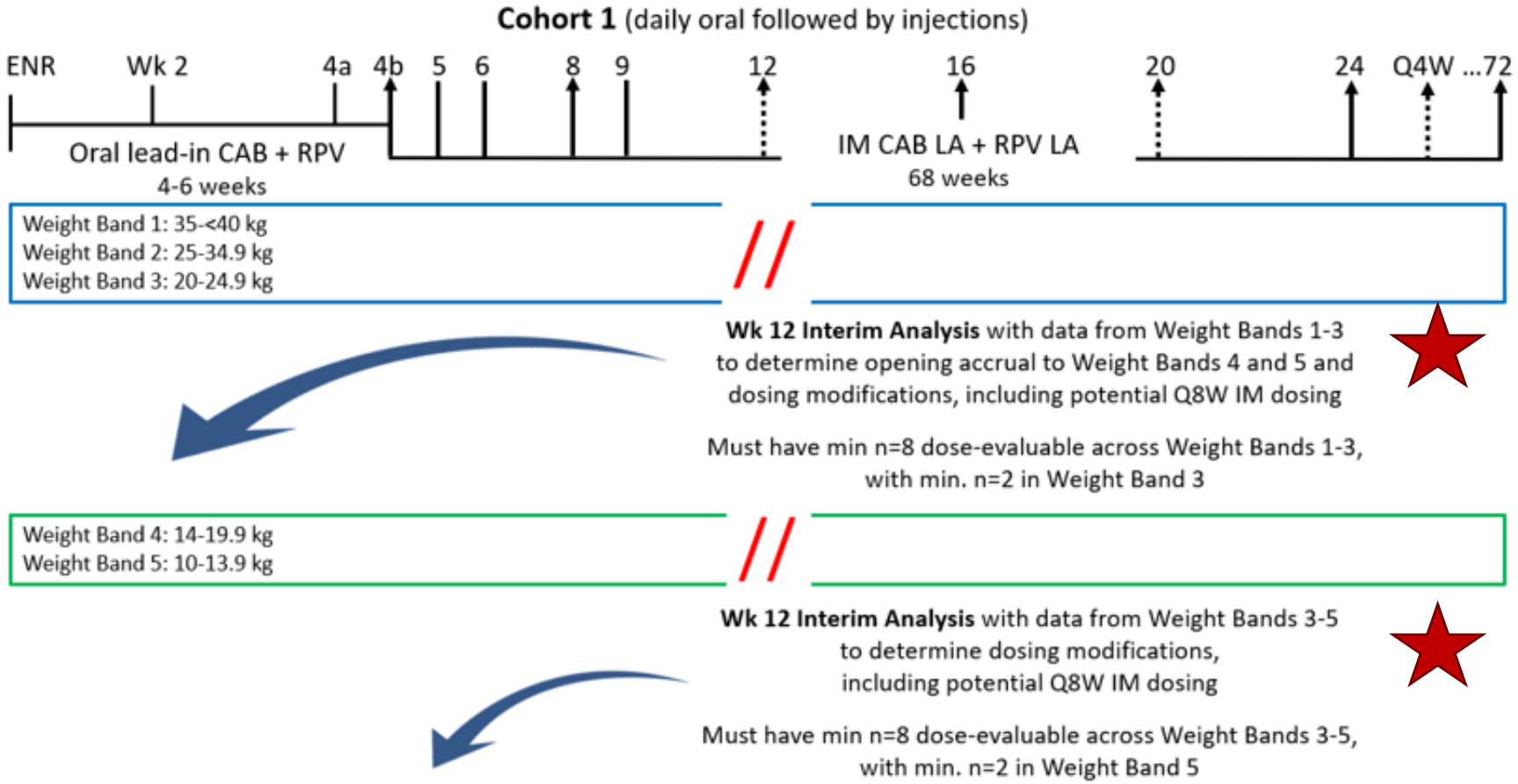
Impact of potential dosing frequency

No change in absorption rate from IM site

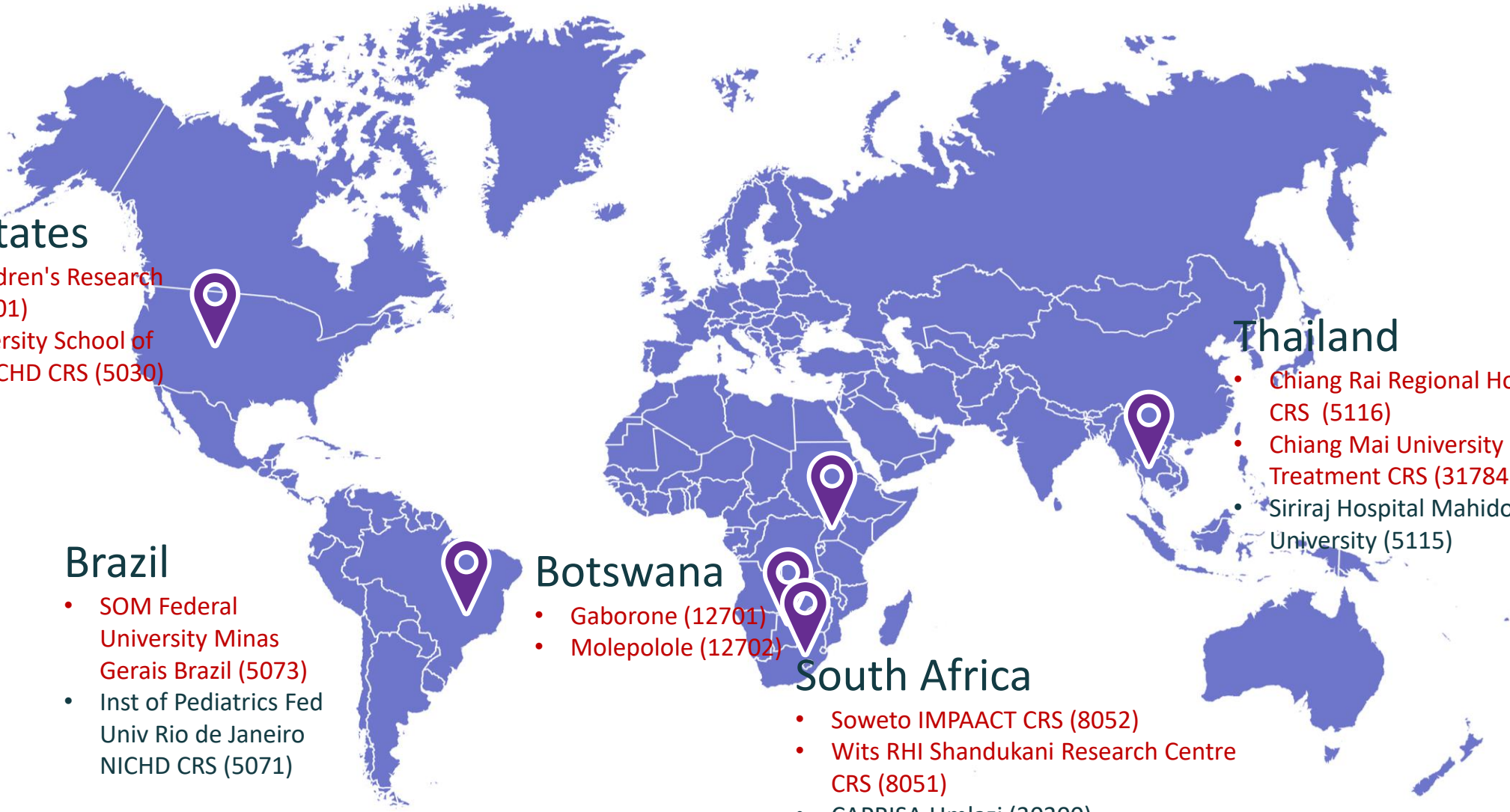
2xs higher absorption rate from




Goyal N, GSK




| | Weight Bands (minimum accrual per weight band) | Total Minimum Accrual Across Weight Bands |
|---|---|---|
| **1.** | 35-<40 kg (min n=6) | Minimum of n =18 across Weight Band 1 and 2 |
| **2.** | 25-34.9 kg (min n=6) | |
| **3.** | 20-24.9 kg (min n=6) | Minimum of n=32 across Weight Band 3,4, and 5 |
| **4.** | 14-19.9 kg (min n=6) | |
| **5.** | 10-13.9 kg (min n=10) | |



## United States

- St. Jude Children's Research Hospital (6501)
- Emory University School of Medicine NICHD CRS (5030)

## Brazil

- SOM Federal University Minas Gerais Brazil (5073)
- Inst of Pediatrics Fed Univ Rio de Janeiro NICHD CRS (5071)

## Botswana

- Gaborone (12701)
- Molepolole (12702)

## South Africa

- Soweto IMPAACT CRS (8052)
- Wits RHI Shandukani Research Centre CRS (8051)
- CAPRISA Umlazi (30300)

## Thailand

- Chiang Rai Regional Hospital CRS (5116)
- Chiang Mai University HIV Treatment CRS (31784)
- Siriraj Hospital Mahidol University (5115)

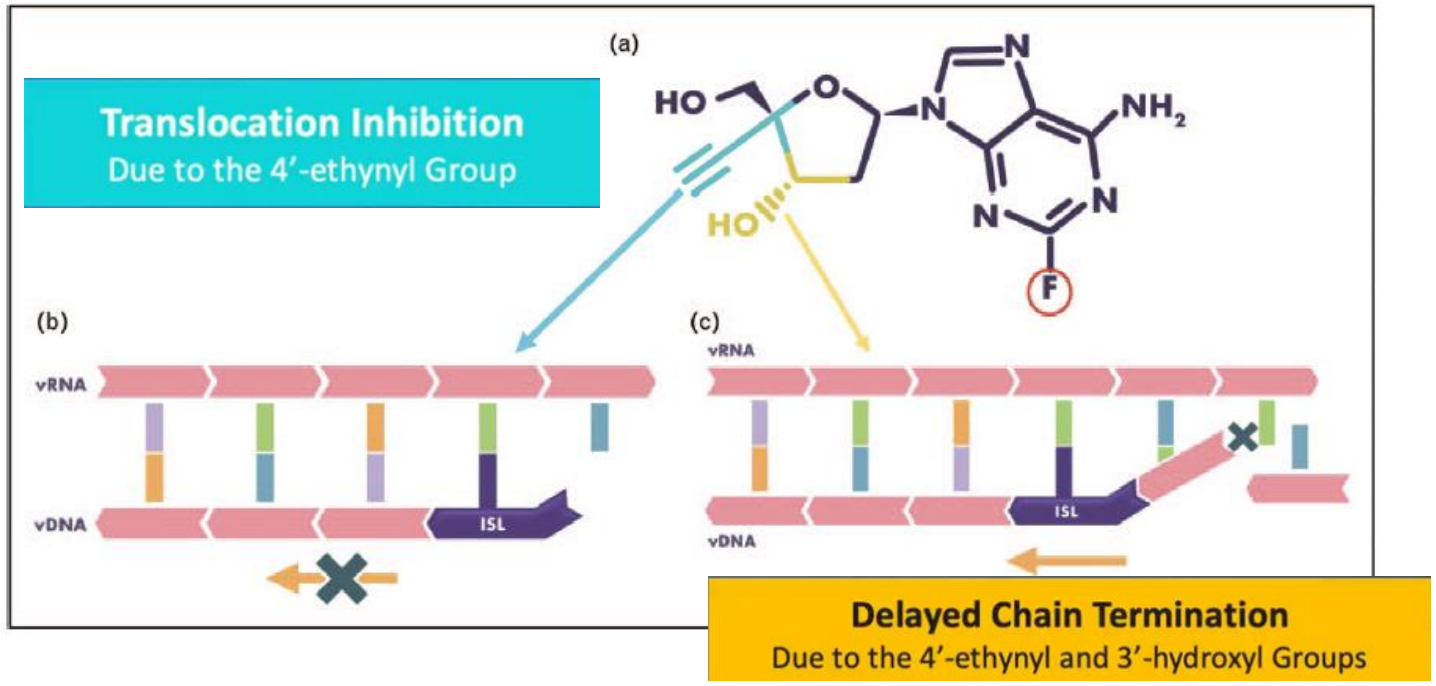
# Islatravir (ISL, MK-8591)

- High potency, NRTTI, with long half-life, under evaluation in clinical trials for:
  - **HIV treatment**: Oral daily (0.75 mg ISL + Doravirine), oral weekly (20 mg ISL + MK-8507)
  - **PrEP**: Oral monthly (60 mg), Implant yearly (58 mg)

**ISL has unique pharmacology**

- Multiple mechanisms of action, active against resistant NRTI/NNRTI variants
- ISL is converted intracellularly to its active triphosphate (TP) form: **ISL-TP**

ISL-TP half-life : **~118–171 hours**




PK target: ISL-TP trough >0.05 pmol/$10^6$ PBMCs

IQ – Inhibitory Quotient ; defined as $\frac{ISL\text{–}TP\ Concentration}{in\text{–}vitro\ IC50}$

IQ ~5 wild-type
IQ >1 for M184I/V

**Adenosine deaminase (ADA)**
only known contributor to ISL metabolism

- Low risk for DDIs

*Markowitz et al. 2019. Curr Opin HIV AIDS 2020, 15:27–32*

# Paediatric Studies

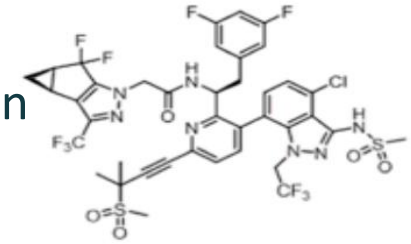
- MK-8591 – 028
  - Children Less than 18 years of age
  - DOR/ISL 100/0.75mg tablet (adult formulation)
  - Currently study stopped due to drop in CD4 counts

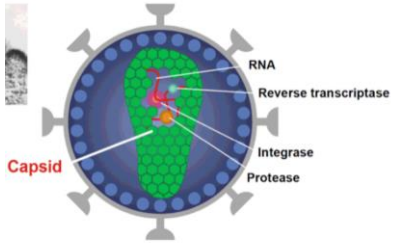
  - Anticipated: Paediatric formulation – mini-tablet
  - Weekly dose being evaluated in adults
  - In very young children – challenge will be to develop a formulation to deliver very low doses of ISL

# Lenacapavir (LEN, GS-6207)

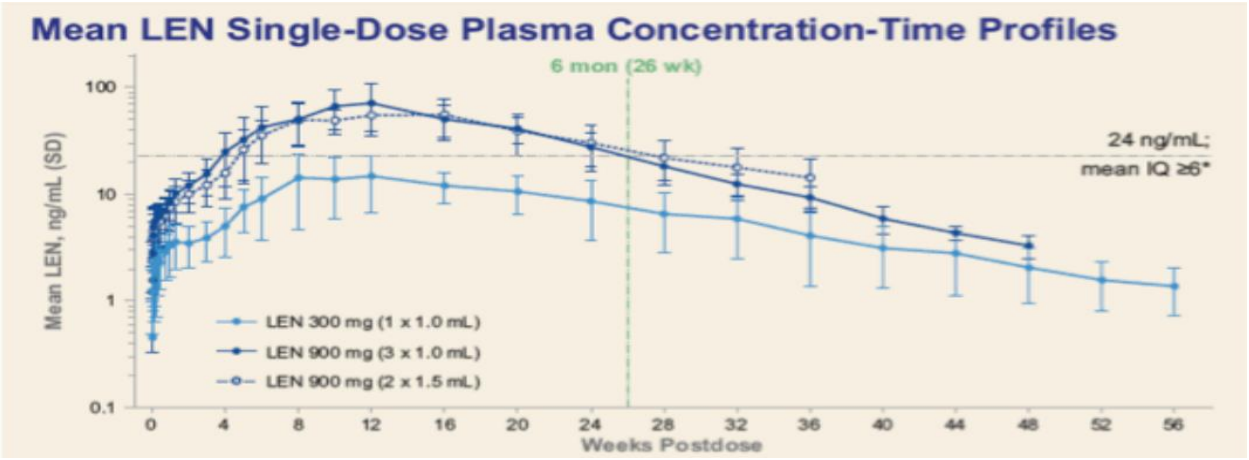
Highly potent, 1st-in-class capsid inhibitor, under evaluation in clinical trials :

- Active at multiple stages of viral life cycle (early uncoating, core assembly and maturation phases)
- **HIV treatment**: Oral and subcutaneous (SC) formulations (6-monthly dosing); MDR population
- **HIV Prevention:** LEN monotherapy or LEN + GSCA1 (SC Q6 monthly)






**SC 900 mg**: therapeutic concentrations for 6 months post-dose



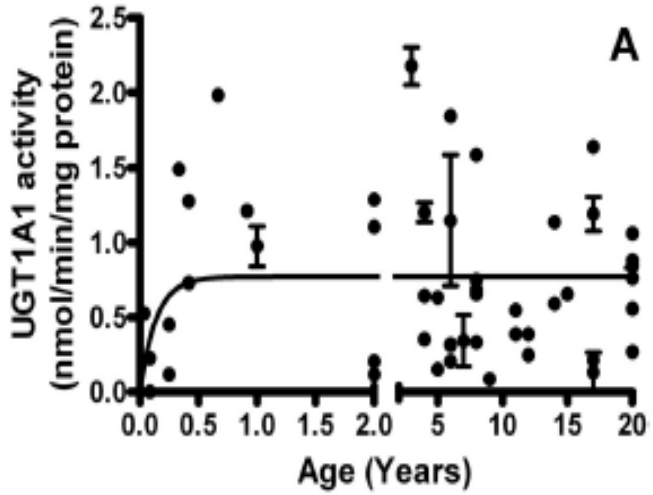

- SC 300 mg/mL, slow release (2x 1.5 mL)
- Phase 2/3 studies --> oral PK loading + SC
- PK target: 24 ng/mL (IQ ≥6)

*Miyagi et al Drug Met. & DIS., 39:912–919, 2011*

*Begley et al AIDS 2020*

# Metabolism Studies

**Metabolized via glucuronidation by UGT1A1**, and to a lesser extent, CYP3A.

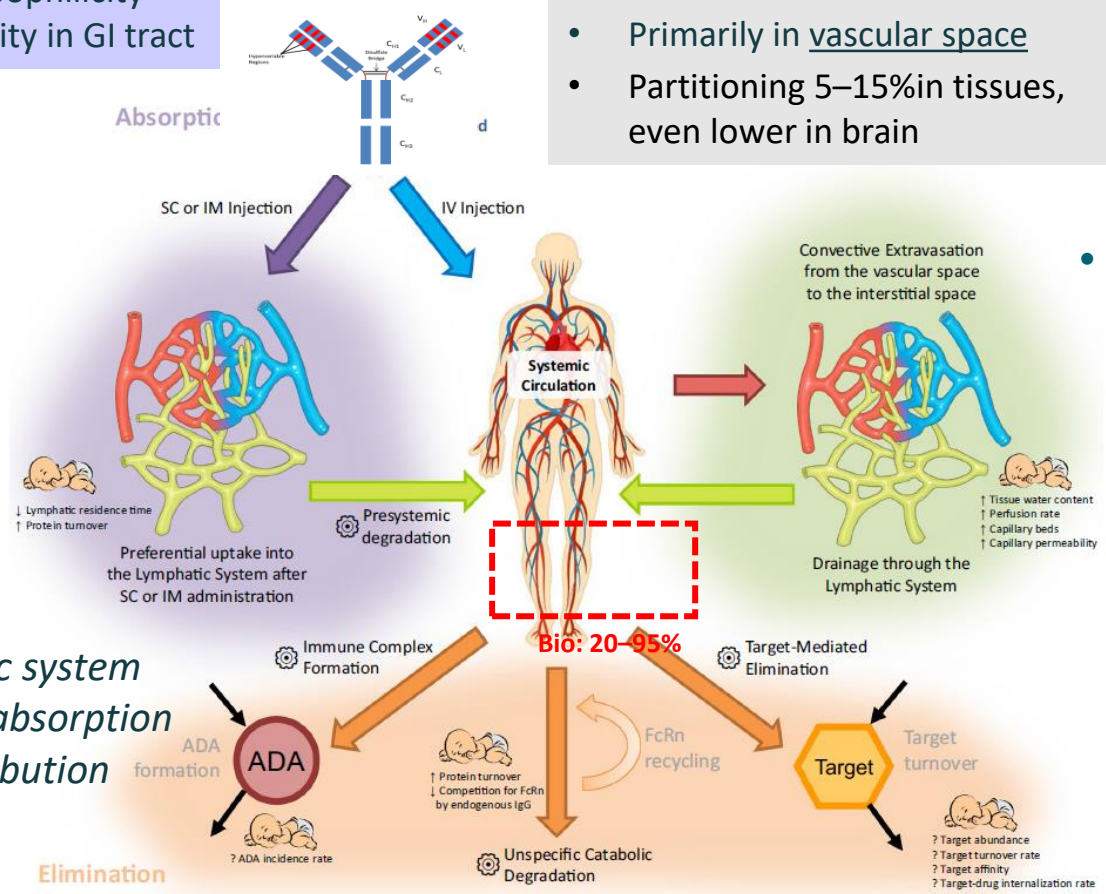



- LEN is a substrate for P-glycoprotein (efflux)
- *Interaction with RIF - TB drugs*

- Phase 3 in highly treatment experienced adults presented at CROI/IAS 2021 (No adolescents recruited)
- Phase 2 in ART naïve adults presented at IAS 2021
- Phase 3 PrEP studies in adults and adolescents presented at IAS 2024

# bNAbs in neonates/infants

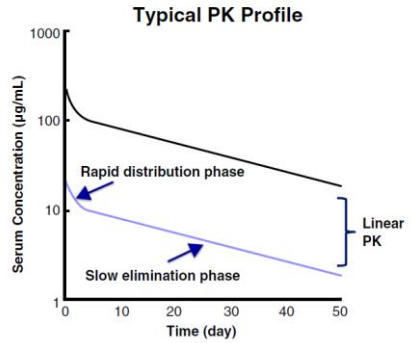
**Absorption**
- Large size, poor permeability,
- Poor lipophilicity
- Instability in GI tract




*Lymphatic system facilities absorption and distribution*

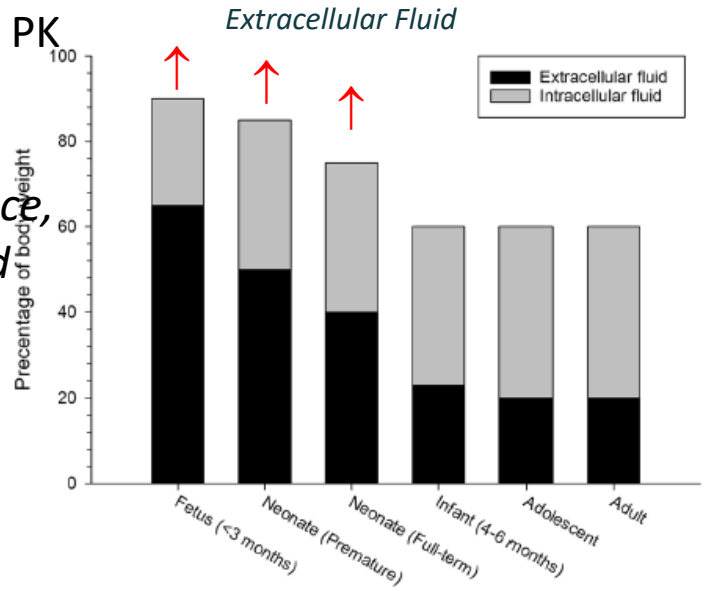
**Distribution**
- Primarily in vascular space
- Partitioning 5–15%in tissues, even lower in brain

**Elimination**
- **Intracellular catabolism via lysosomes**
- 'Target-mediated drug disposition' (**TMDD**) + Anti-therapeutic antibodies (**ATAs**)




Majority IgG molecules - target soluble or membrane bound antigens - unique PK characteristics

- **General PK profile**: *slow absorption, slow clearance, long half-life, and limited tissue distribution*




**Absorption rates in infants?**

*HIV Prevention/Rx s.c. VRC01, VRC01LS..++*

*Temrikar et al, Pediatric Drugs 2020*

*Kamath et al, Translational pharmacology, 2020*

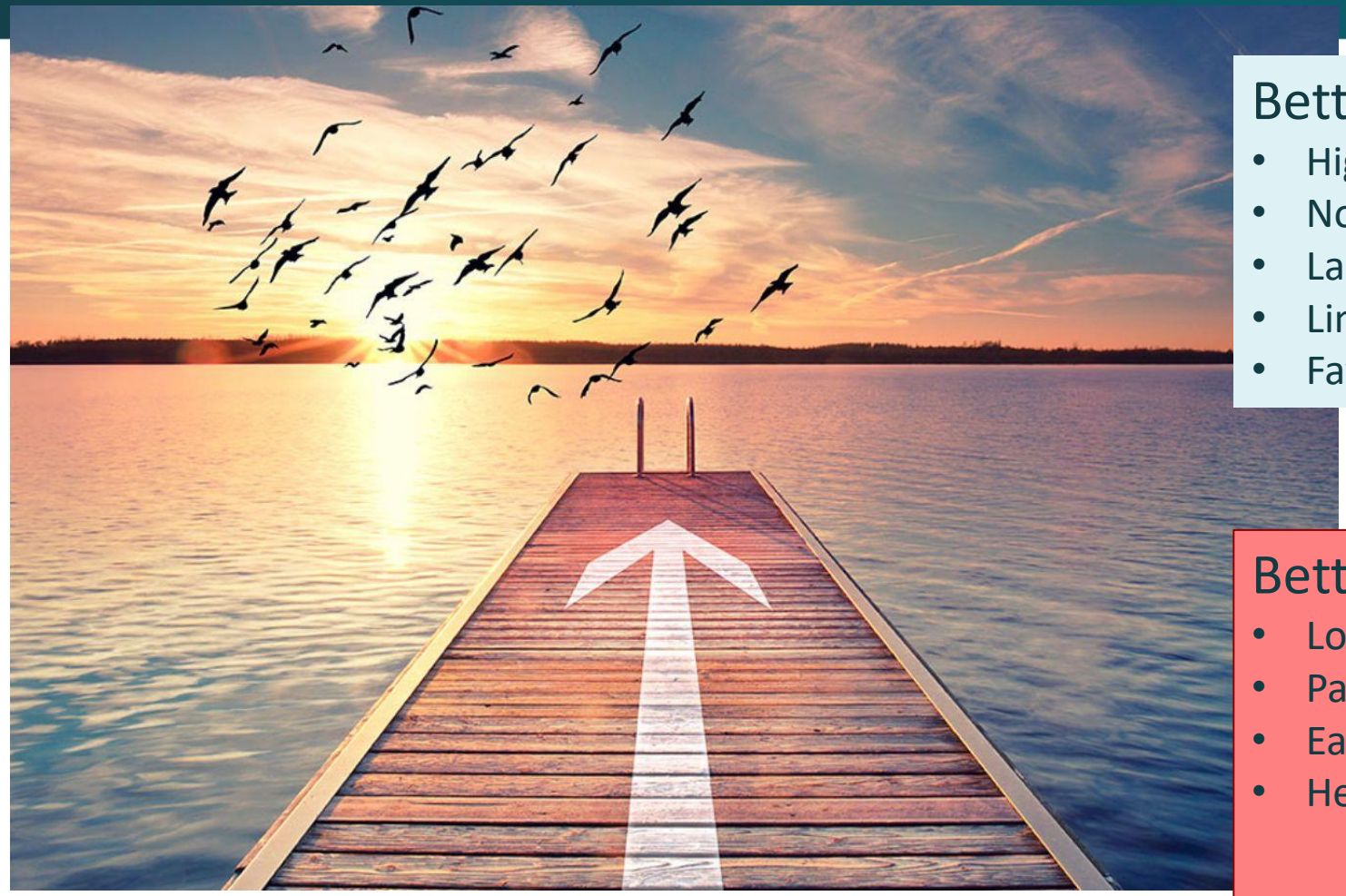
## Ongoing bNabs trials

| | | | | | | |
|---|---|---|---|---|---|---|
| **PGDM1400, VRC07-523LS, PGT121** | **IAVI** | **PGDM1400 mAb alone or combination of PGDM1400 mAb + PGT121** | **Intravenous infusion** | **1** | **Apr-20** | **NCT03205917** |
| **VRC07-523LS** | NIAID | IV infustion of VRC07-523LS | Intravenous infusion | 1 | Dec-20 | NCT03735849<br>NCT03387150 |
| **3BNC117-LS** | Rockefeller University | 3BNC117-LS administered as either a subcutaneous injection or IV infusion | Injection (subcutaneous) or Intravenous infusion | 1 | Dec-20 | NCT03254277 |
| **PGT121, PGDM1400, 10-1074, VRC07-523LS** | NIAID | IV administration of antibody combinations at a 4 month interval. Combinations include PGT121 + VRC07-523LS, PGDM1400 + VRC07-523LS, and 10-1074 + VRC07-523LS | Intravenous infusion | 1 | Jan-21 | NCT03928821 |
| **10-1074-LS, 3BNC117-LS** | Rockefeller | 10-1074-LS with 3BNC117-LS given every 3 months as either a subcutaneous injection or IV infusion | Injection (subcutaneous) or Intravenous infusion | 1 | Jun-21 | NCT03554408 |
| **3BNC117-LS-J and 10-1074-LS-J** | IAVI | 3BNC117-LS-J and 10-1074-LS-J alone and in combination as either a subcutaneous injection or IV infusion | Injection (subcutaneous) or Intravenous infusion | 1/2A | Dec-21 | NCT04173819 |
| **VRC-HIVMAB091-00-AB (N6LS)** | NIAID | VRC-HIVMAB091-00-AB (N6LS) with or without recombinant human hyaluronidase PH20 given on a 4 month interval | Injection (subcutaneous) or Intravenous infusion | 1 | Dec-21 | NCT03538626 |
| **VRC01, VRC01LS, VRC07-523LS** | NIAID | Monthly injections of VRC01, VRC01LS, or VRC07-523LS in HIV-1-exposed Infants | Injection (Subcutaneous) | 1 | Jan-22 | NCT02256631 |
| **PGT121.414.LS<br>VRC07-523LS** | NIAID | PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions | Injection (subcutaneous) or Intravenous infusion | 1 | Feb-22 | NCT04212091 |
| **SAR441236 (VRC01–10E8v4-PDGM-1400-LS)** | NIAID | Tri-specific bNAb, SAR441236, given as an IV infusion | Intravenous infusion | 1 | Feb-22 | NCT03705169 |
| **iMab/10e8v2.0** | Aaron Diamond AIDS Research Center | Bispecific antibody 10E8.4/iMab given as either a subcutaneous injection or IV infusion | Injection (subcutaneous) or Intravenous infusion | 1 | Apr-22 | NCT03875209 |
| **PGT121, VRC07-523LS, PGDM1400** | IAVI | Ab combinations, including PGT121 + VRC07-523LS, and PGT121 + VRC07-523LS + PGDM1400 | Intravenous infusion | 1/2A | Oct-22 | NCT03721510 |
| **CAP256V2LS, VRC07-523LS and PGT121** | CAPRISA | CAP256V2LS alone and in combination with VRC07-523LS and PGT121 | Injection (subcutaneous) or Intravenous infusion | 1 | | PACTR202003767867253<br>CAPRISA 012B |
| **PGT121 and VRC07-523LS** | CAPRISA | VRC07-523LS and/or PGT121 administered subcutaneously | Subcutaneous injection | 1 | | PACTR201808919297244 |

# Adverse effects

| Drug | Side-effect |
|---|---|
| Lencapavir (CAPELLA) | Injection site reactions (SC injection) - no study discontinuations<br>Other reported: Headache, nausea, cough, diarrhea, back pain, fever, rash, and urinary tract infections<br>Laboratory Aes: Abn renal fxn/ Blood sugar (?related) |
| Islatravir (ISL/DOR)<br>ISL (px) | Drop in CD4/CD8<br>Headache, diarrhea, and nausea<br><br>2 discontinuations – 1 x rash/ 1 x increased Liver enzymes |
| BNAbs (VRC01) | Injection site reactions (mild)<br>1 x discontinuation for uricarial rash |
| MK-8507 (studies in combination with ISL) | ? |

# Beyond the horizon



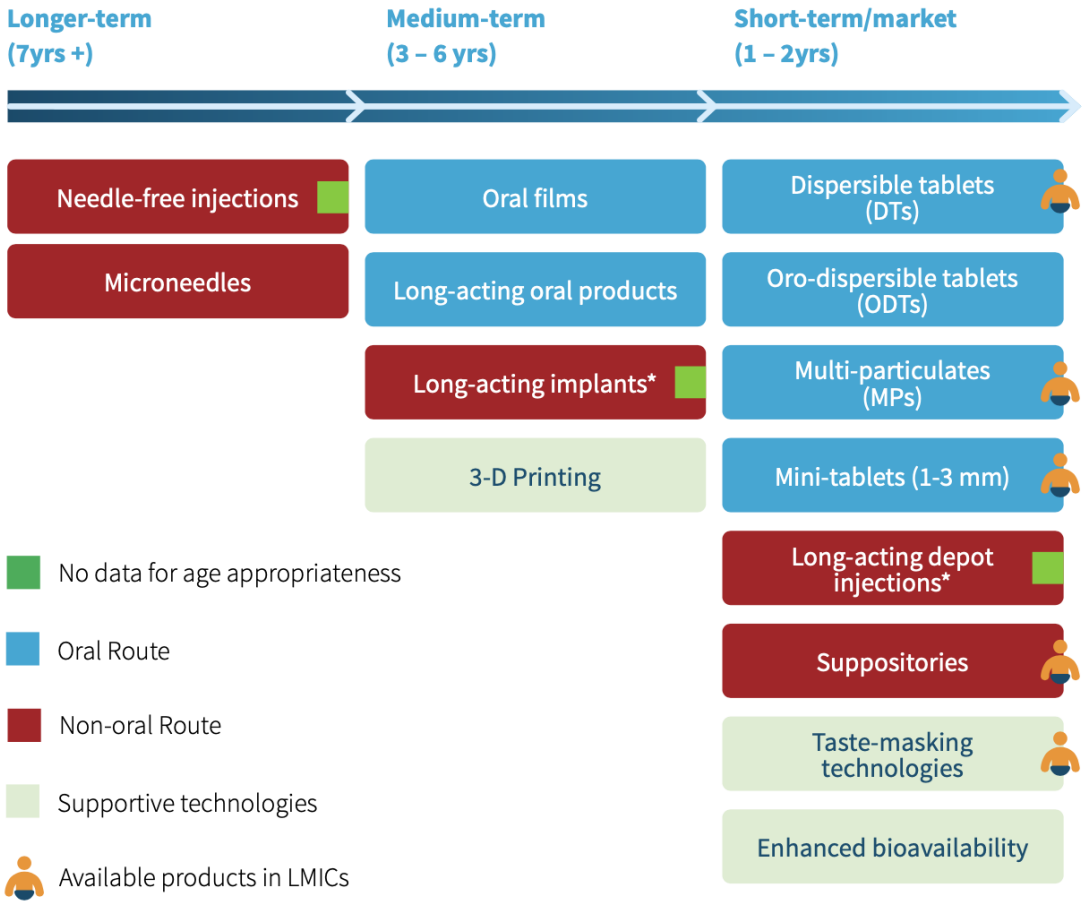
## Better formulations

- High genetic barrier
- Novel mechanism of action
- Lack of shared HIV DR
- Limited side-effects
- Favorable PK

## Better drug delivery mechanisms

- Long-acting formulations
- Pain free delivery (for injectables)
- Ease of administration
- Health system consideration:
  - Need for cold storage
  - Additional HS requirements
  - Convenient frequency

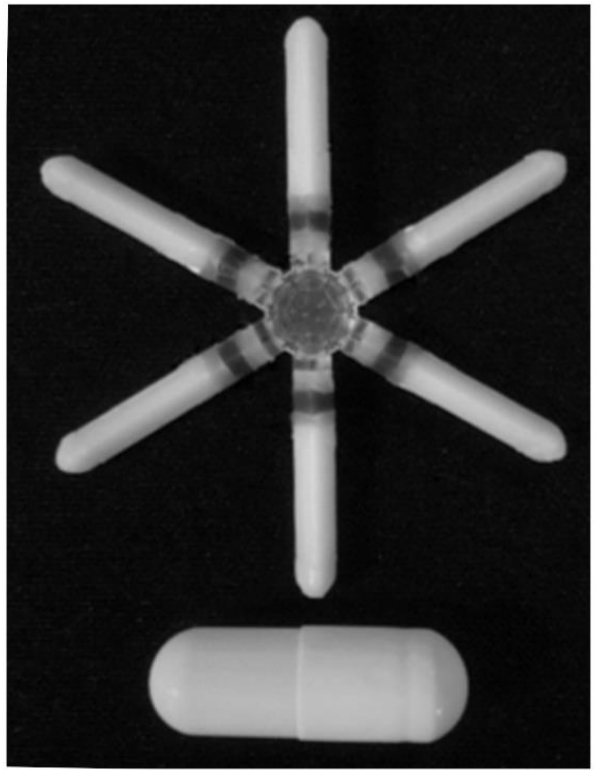
# Technology Landscape



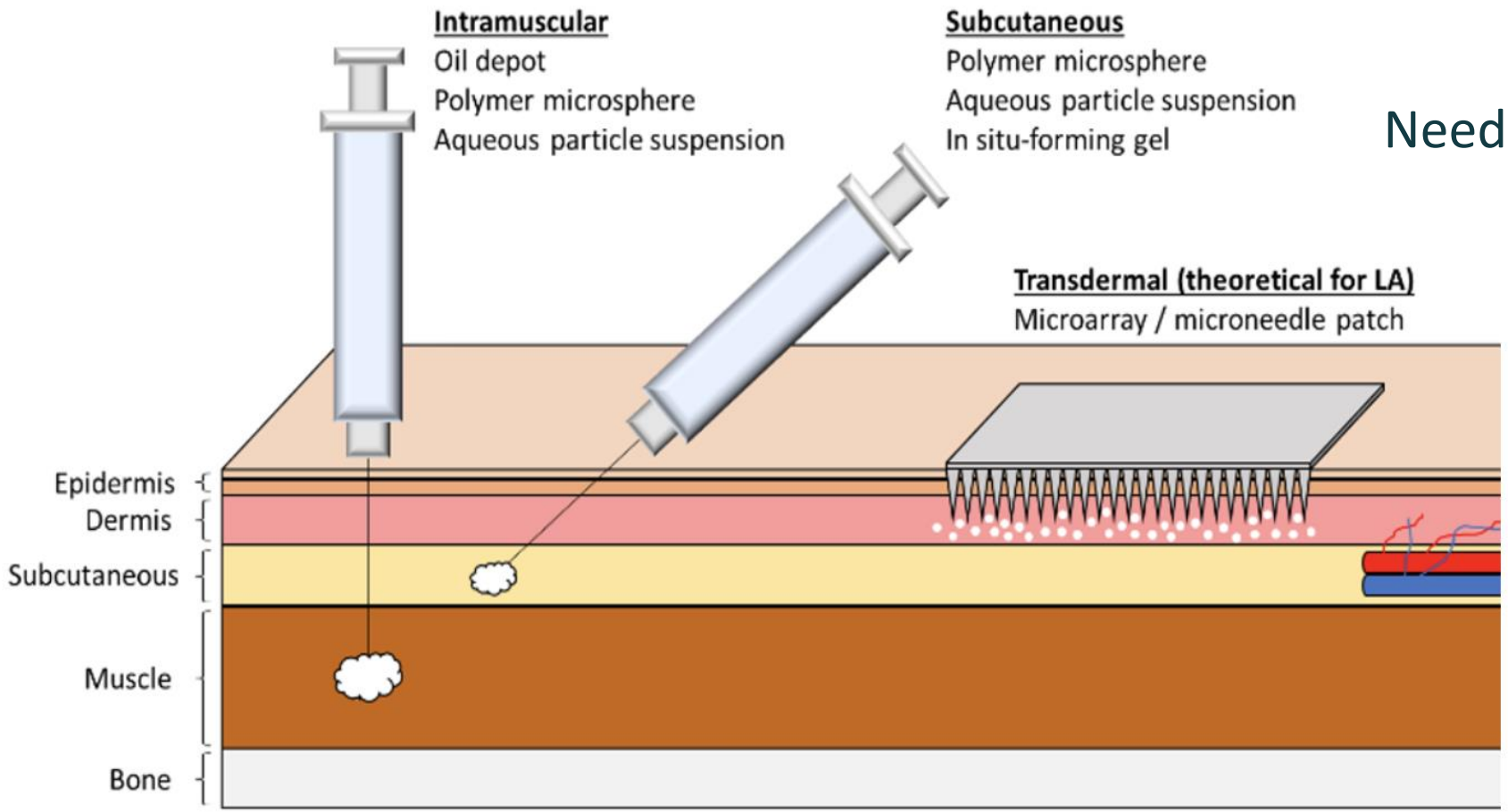

**pipeline contains only application* for older ages

# Long-acting Oral Drug delivery

- Gastro retentive oral dosage forms are designed to stay in stomach for longer than normal to maximise drug absorption in the proximal GIT.
- A long-acting gastro-retentive capsule (Lyndra capsule)163 has been recently developed that to deliver drug for a week or more. Within the capsule is a folded star-shaped drug containing element. There is a central “core”, drug-containing “arms” radiating from the core delivering controlled drug release and disintegrating matrices that join the arms to the core.
- The capsule dissolves in the stomach and the dosage form unfolds. The drug containing element remains in the stomach and starts to deliver drug to the patient. The disintegrating matrices break down after approximately 7 days and are eliminated via passage through the lower GI tract.

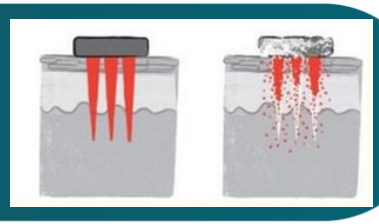


# Long-acting Injectables



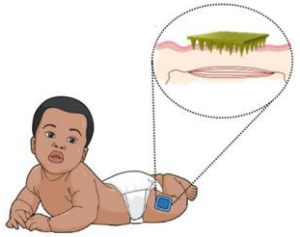

Needle-free delivery

# Micro-array Patch (MAP)

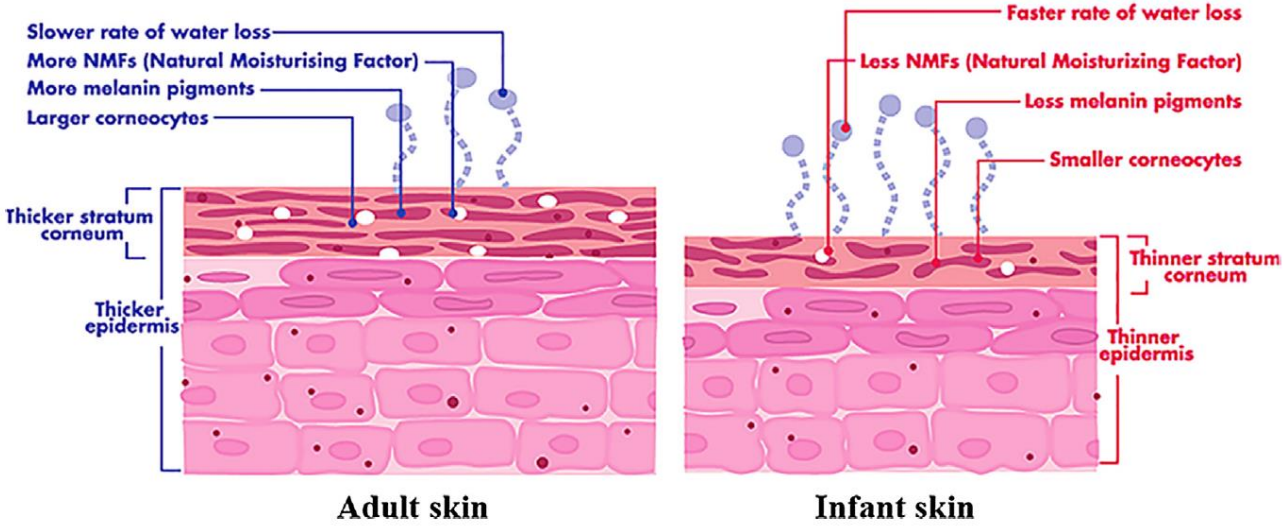


- Minimally-invasive intradermal delivery of nanoformulated ARVs into the skin (e.g. CAB, RPV, 3TC, ETV)
- MAPs: small doses of large and potent drugs (*types*: coated, dissolving, hollow and hydrogel-forming

## Pediatric Considerations



- **Full-term neonate**, well-developed epidermis similar to child/adults
- Thinner skin in infants and children may affect the PK of drug
- Rapidly developing skin barrier function + age-dependent issues
- **Premature neonates**: suitability of a patch adhesive for fragile premature skin + risk associated with accidental overabsorption etc.




Key structural/composition differences between infant and adult

| Parameters | Infant | Adult |
|---|---|---|
| Thickness of epidermis | ~ 40–50 µm | ~ 50–150 µm |
| Sweat glands | Not fully developed | Fully developed |
| Elastin fibres | Absent | Present |
| Collagen fibres | Less dense | Dense |
| Corneocyte and keratinocyte size | Smaller | Larger |
| Lipid content | Less | More |
| Melanin content | Lower | Higher |
| Skin surface-to-body weight ratio | 700 $cm^2$/kg | 250 $cm^2$/kg |
| Water content | Higher | Lower |
| Natural moisturizing factor | Significantly lower | Higher |

*McCrudden et al 2018 Journal of Controlled Release 292 119–129*

*Duarah et al. et al European Journal of Pharmaceutics and Biopharmaceutics 136 (2019) 48–69*

# Conclusion

- Rich pipe-line of new paediatric formulations and drug delivery development but progress has been slow

- To ensure ongoing drug development in a shrinking paediatric treatment market:
  - Merging of treatment and prevention regimens
  - Evaluation of drugs in adolescents during Phase 3 adult trials will ensure easier access to new formulations

- Advances in drug development in HIV has the potential to accelerate research in other disease areas