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MAPs for Peds: Development of a microarray patch for delivery of pediatric antiretroviral therapeutics

Principles of Pediatric Clinical Pharmacology Lecture Series

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PATH

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Outline

- Introduction to PATH
- Problem statement: Pediatric HIV treatment gap
- Introduction to microarray patches (MAPs)
- Rat pharmacokinetics of ARV MAPs
- Physiologically based pharmacokinetic modeling, dose predictions
- Macaque pharmacokinetic studies
- Indicator development
- User acceptability studies
- Challenges and next steps

PATH is a global team of innovators working to eliminate health inequities so people, communities, and economies can thrive.

Photos: PATH/Aaron Joel Santos, PATH/Gabe Bienczycki | PATH/Gabe Bienczycki

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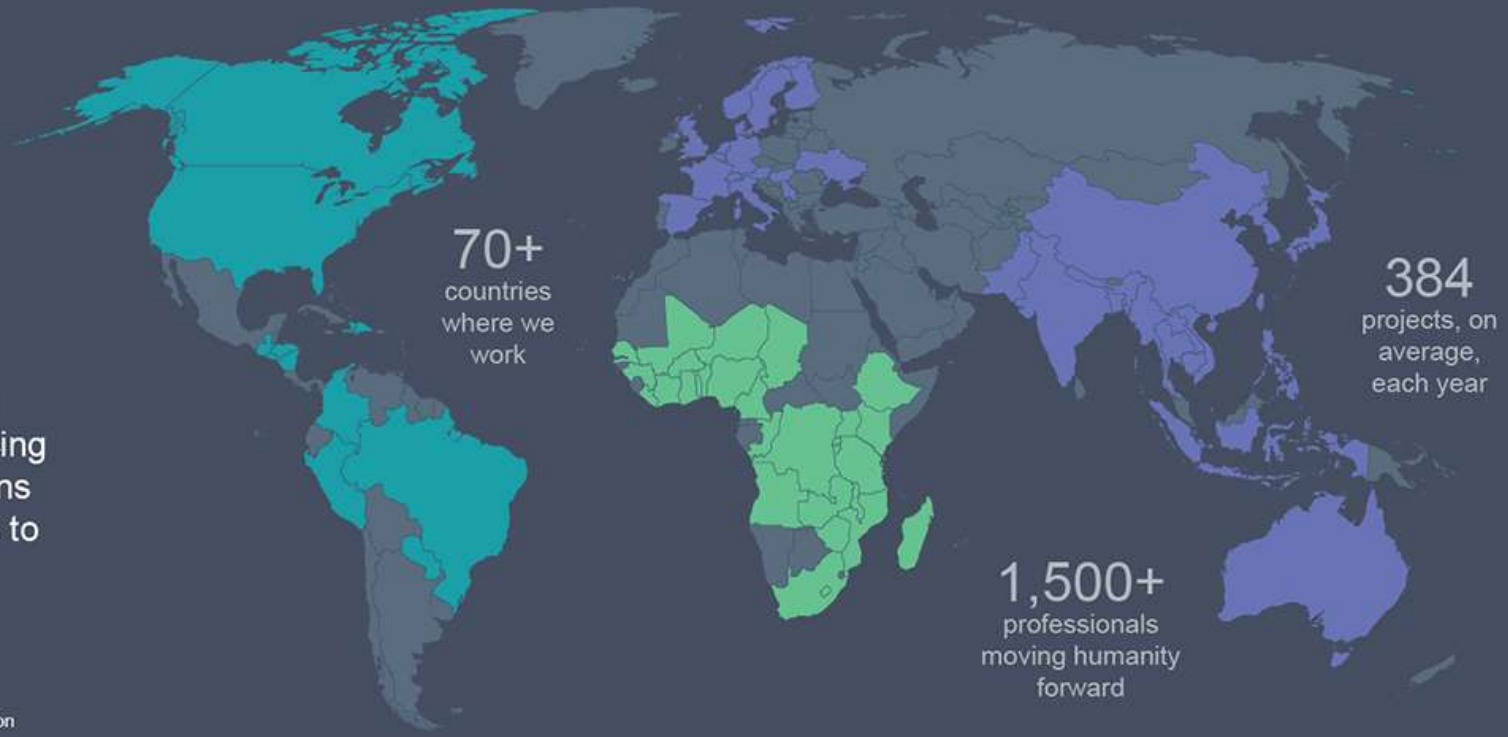
Unprecedented impact

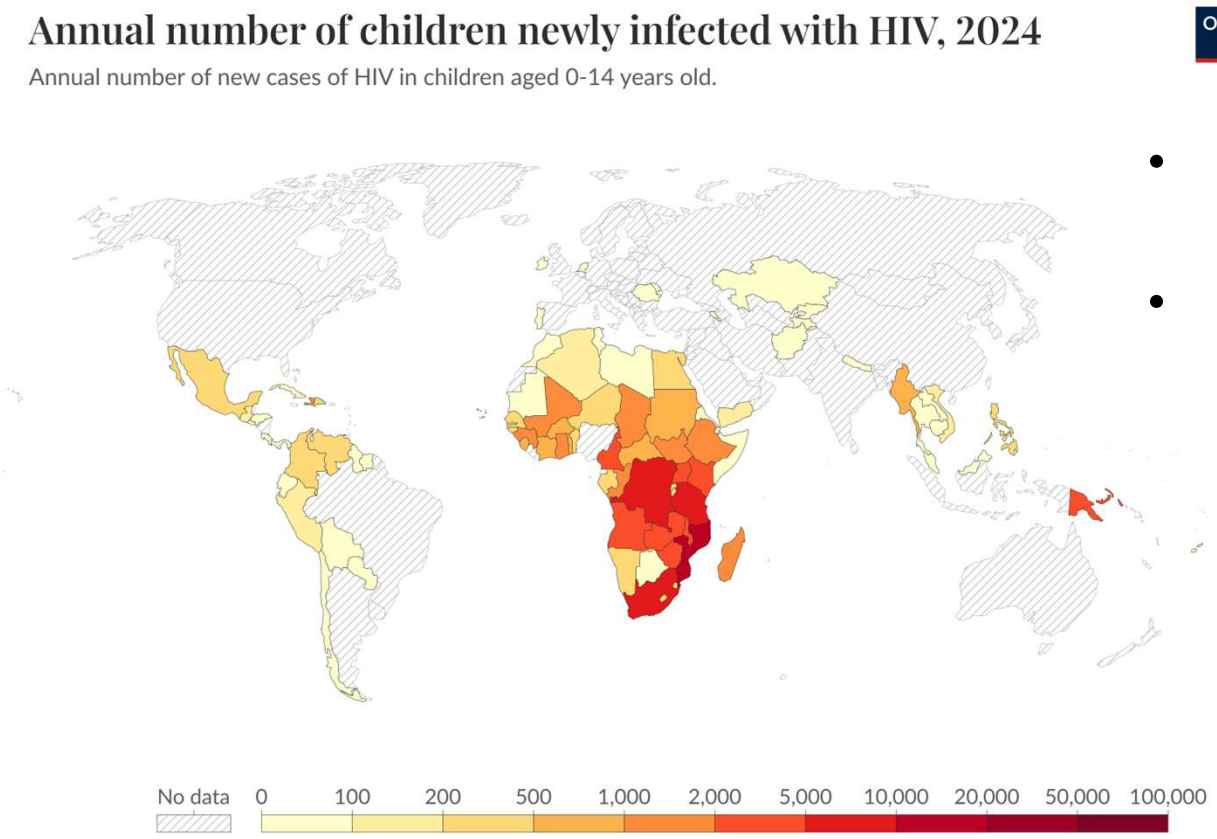
With the help of local and global partners, PATH generates evidence, advances innovation, and strengthens local capacity to improve health in countries and communities experiencing disproportionate burdens of disease and barriers to well-being.



COUNTRIES WHERE PATH WORKS

- Africa Region
- Asia, Middle East, Europe (AMEE) Region
- Americas Region

Problem statement: Pediatric HIV treatment gap



- 1.4 million children living with HIV
- More than 40% not receiving effective therapy

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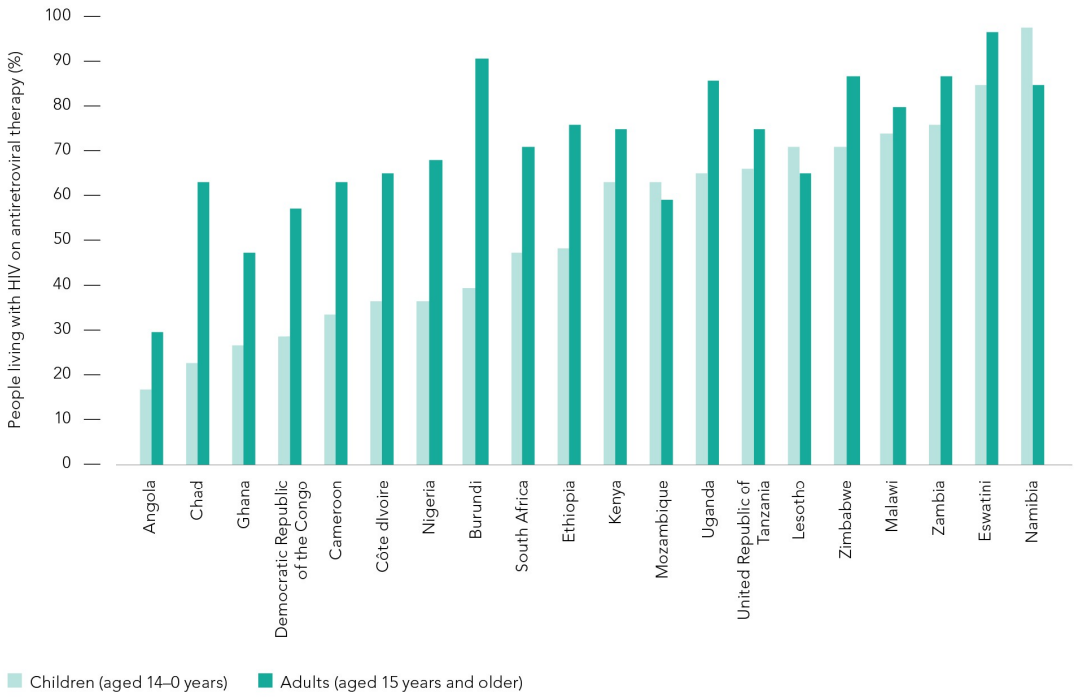
Problem statement: Pediatric HIV treatment gap

Antiretroviral therapy coverage among children and adults, sub-Saharan African focus countries of the Start Free, Stay Free, AIDS Free initiative, 2019



Source: UNAIDS epidemiological estimates, 2020 (see https://aidsinfo.unaids.org/).
Note: Botswana data are not available.

- Inappropriate formulations
- Poor palatability
- Nonoptimal dosage forms

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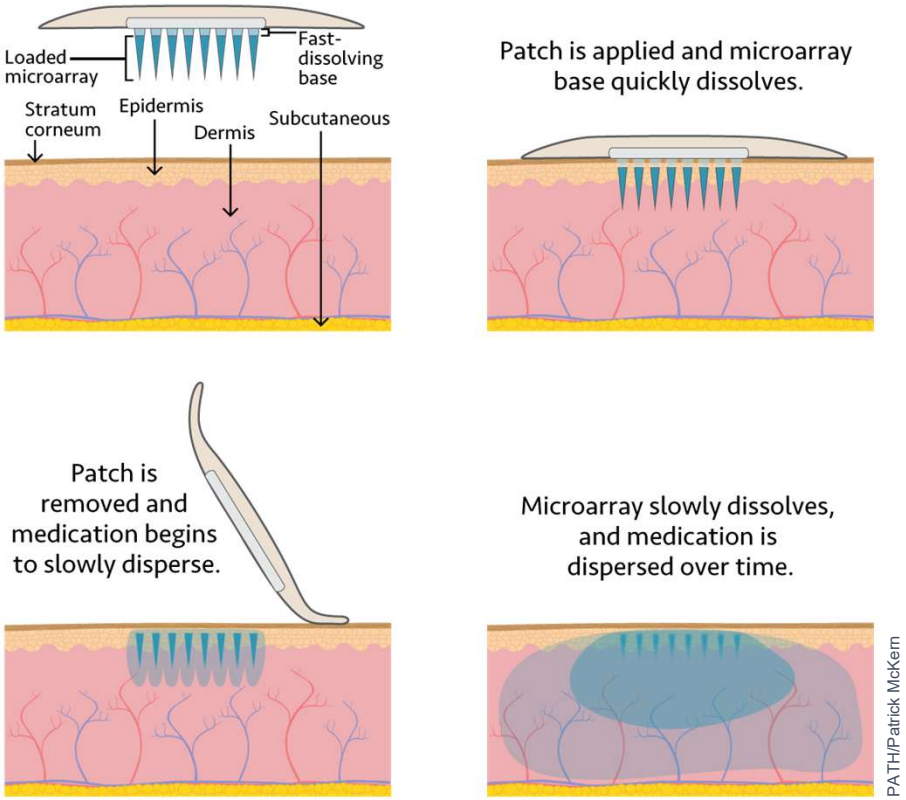
Pediatric ARV treatment and prevention recommendations

- Example treatment regimen (6 to 25 kg)
  - Abacavir/dolutegravir/lamivudine fixed-dose combination
  - 3 to 6 oral dispersible tablets = **20 ml suspension qd**

- Example prevention regimens (birth to 4 weeks)
  - Low risk: zidovudine 4 mg/kg = **1 to 2 ml of 10 mg/ml syrup bid**
  - High risk: zidovudine/lamivudine/nevirapine
    - Zidovudine 4 mg/kg = **1 to 2 ml of 10 mg/ml syrup bid**
    - Lamivudine: 2 mg/kg = **3 to 6 ml of 10 mg/ml syrup bid**
    - Nevirapine: 2 to 4 mg/kg = **1 to 5 ml of 10 mg/ml syrup bid**

Source: https://clinicalinfo.hiv.gov/

Introduction to dissolving microarray patches (MAPs)



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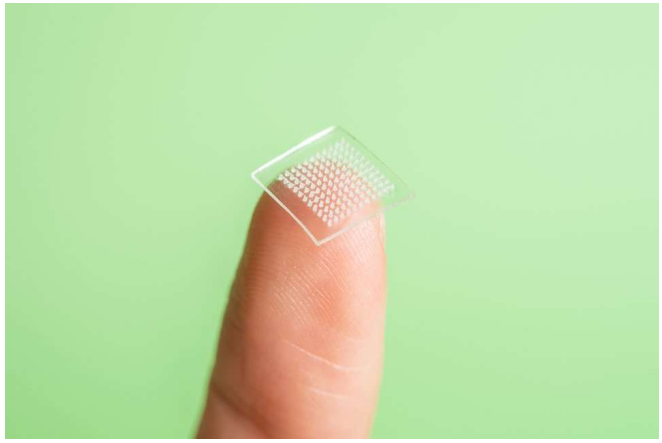

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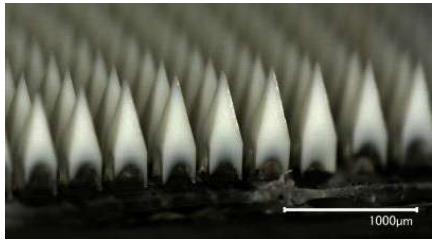
Drug MAP landscape: Examples by development phase

Zosano



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Preclinical:
Contraceptives
- Cardiff University
- Chinese Academy of Sciences
- Georgia Tech/Micron Biomedical
- IIT Bombay
- MIT
- Queen's University Belfast
- Tufts University

Phase 2:
Severe hypoglycemia
- Zosano (discontinued)

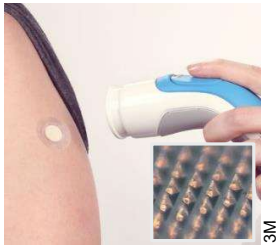
Registration:
Migraine
- Zosano (not approved)

Preclinical → **Phase 1** → **Phase 2** → **Phase 3** → **Reg approval**

Preclinical:
Antiretrovirals
- Queen's University Belfast

Preclinical:
GLP-1 agonists
- Vaxess Technologies

Phase 3:
Osteoporosis
- Radius (endpoint not met)



Radius/3M

Abbreviations: Georgia Tech, Georgia Institute of Technology; IIT, Indian Institute of Technology; MIT, Massachusetts Institute of Technology; QUB, Queen's University Belfast.

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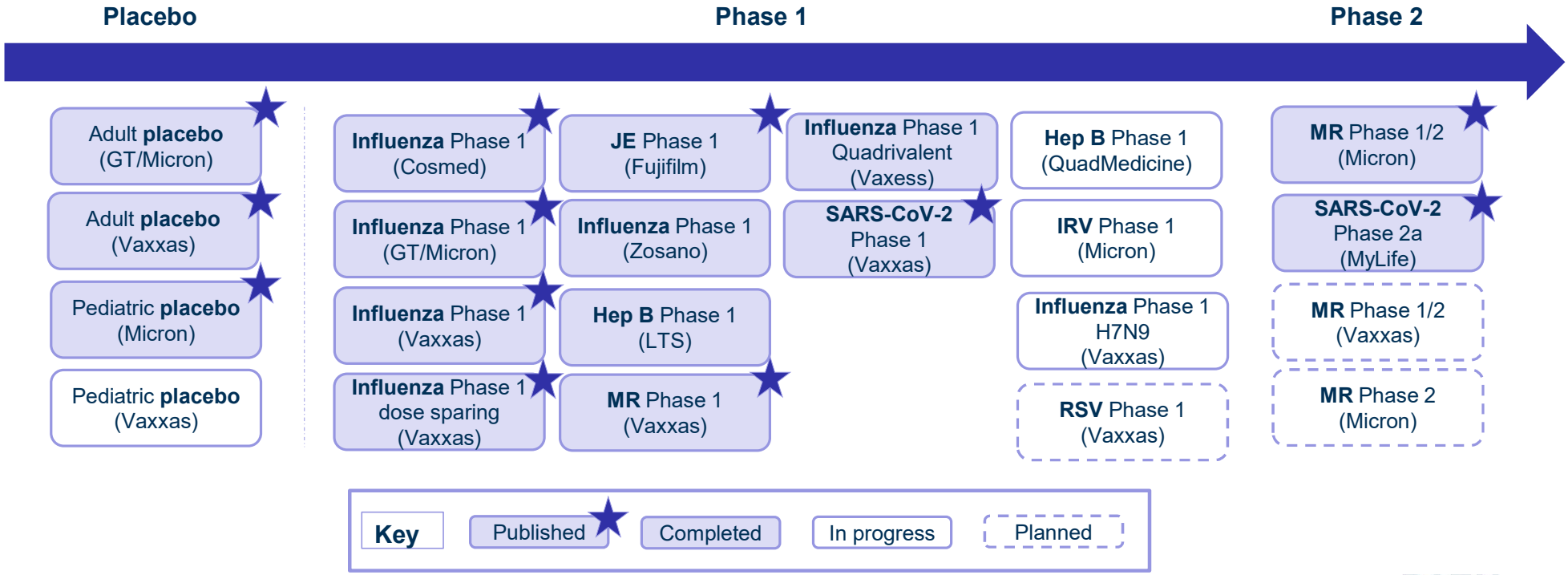
The clinical evidence base for vaccine MAPs is expanding

Phase 1 results are published or anticipated for measles-rubella, influenza, SARS-CoV-2, hepatitis B, and Japanese encephalitis, as well as for Phase 2 results for measles-rubella.



Abbreviations: GT, Georgia Institute of Technology; Hep B, hepatitis B virus; IRV, inactivated rotavirus; JE, Japanese encephalitis; LTS, LTS Lohmann Therapie-Systeme AG; MR, measles-rubella; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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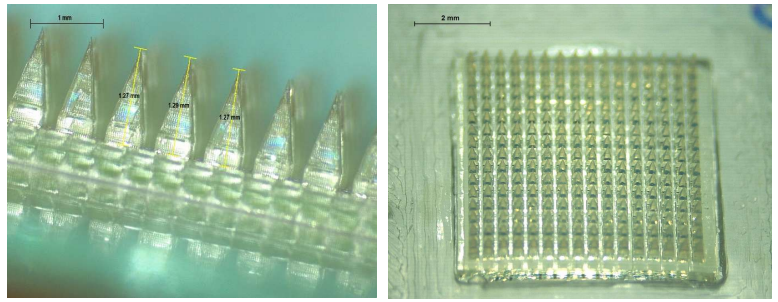
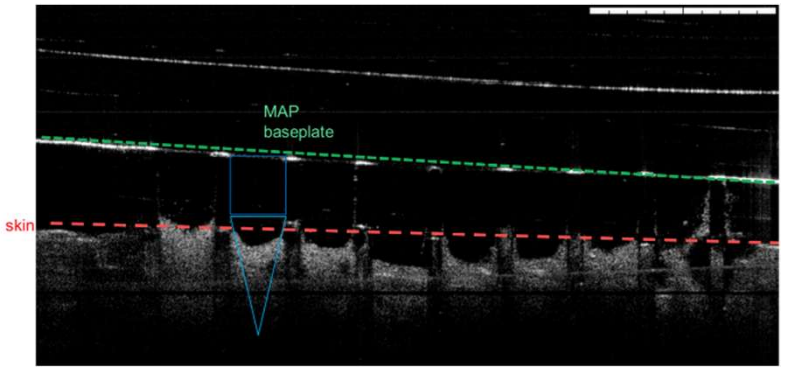
Pediatric antiretroviral microarray patch: target product profile

Attribute	Target
Indication	Treatment and/or prophylaxis of pediatric HIV
Target population	Neonates to 12 years old (35 kg), infected or at risk of infection with HIV
Use case	Administered by health care providers or caregivers
Dosage	Aligned with World Health Organization pediatric antiretroviral weight bands
Size (full MAP)	7 cm^2 is largest acceptable size for newborn weight band dosing (multiples used for larger weight bands)
Dosing regimen	Weekly or monthly
Wear time	20 minutes



Light microscope image of dissolving MAPs.



Images: Queen's University Belfast

OCT image of dissolving MAP inserted into ex vivo porcine skin.

Long-acting HIV therapeutics landscape

ARV drug (class)	Dose/route/duration	Target plasma concentration	$t_{½}$ (route)	Status
Cabotegravir (integrase inhibitor)	600 mg IM, q8 weeks	1,640 nM	5.6 to 11.5 weeks (IM)	Approved as combination treatment with rilipivirine for >12-year-olds and adults
Rilpivirine (NNRTI)	900 mg IM, q8 weeks (adult); 12.5 to 25 mg PO, qd (peds)	137 nM	13 to 28 weeks (IM)	Approved for >2 years old and >14 kg
Lenacapavir (capsid inhibitor)	600 mg PO, qd x2 lead-in; 927 mg SC, q6 months	16 nM (4x $paEC_{95}$)	8 to 12 weeks (SC)	Approved for treatment and prevention in adults
Islatravir (NRTTI)	2 mg PO, q1 week 0.25 to 0.75 mg PO, qd	50 fmol/10e6 cells (ISL-TP)	177 to 209 hours (PO, ISL-TP)	Phase 3 adult treatment trials ongoing
MK-8527 (NRTTI)	11 mg PO, q1 month	200 fmol/10e6 cells (MK-8527-TP)	216 to 291 hours (PO MK-8527-TP)	Phase 3 adult prophylaxis trial ongoing

Abbreviations: ARV, antiretroviral; IM, intramuscular; ISL-TP, islatravir triphosphate; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTTI, nucleoside reverse transcriptase translocation inhibitor; PO, per oral; SC, subcutaneous; $paEC_{95}$, protein-binding adjusted 95% effective concentration.

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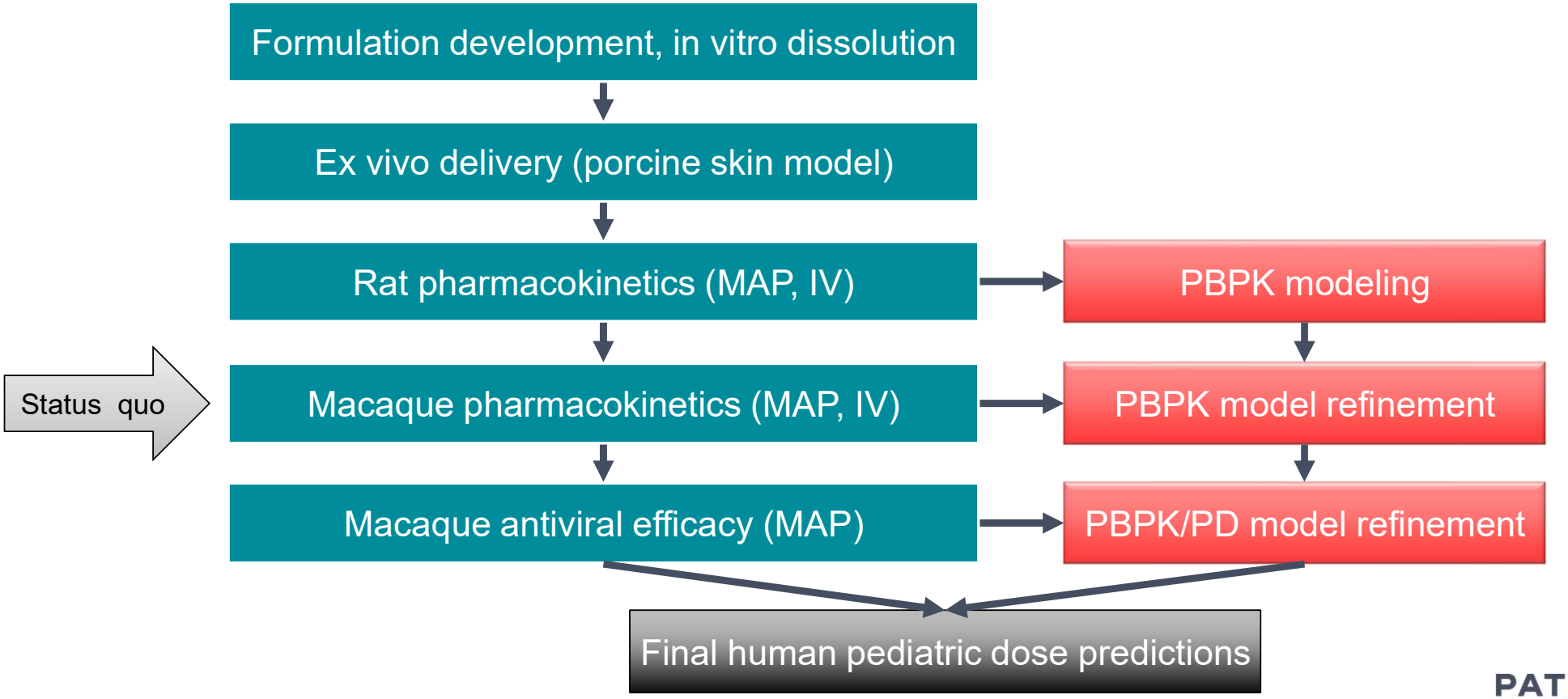
MAPs for Peds project aims

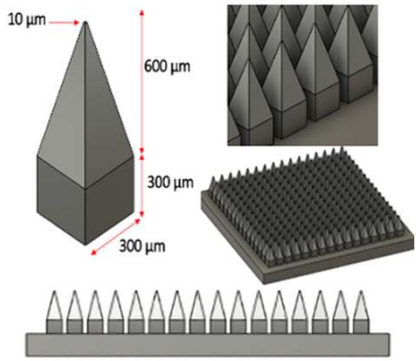
- Rat pharmacokinetics and physiologically-based pharmacokinetic (PBPK) modeling
- Macaque pharmacokinetics/antiviral efficacy; refinement of PBPK models
- User acceptability study, including indicator development

Development of a proof-of-concept pediatric ARV MAP

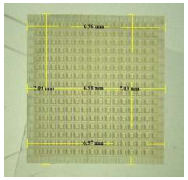


Abbreviations: IV, intravenous; PBPK, physiologically-based pharmacokinetic, PD, pharmacodynamic.

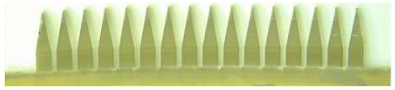
Design and production of dissolving MAPs



CAD files drawing



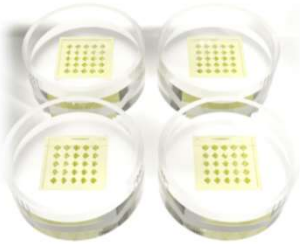
Front view



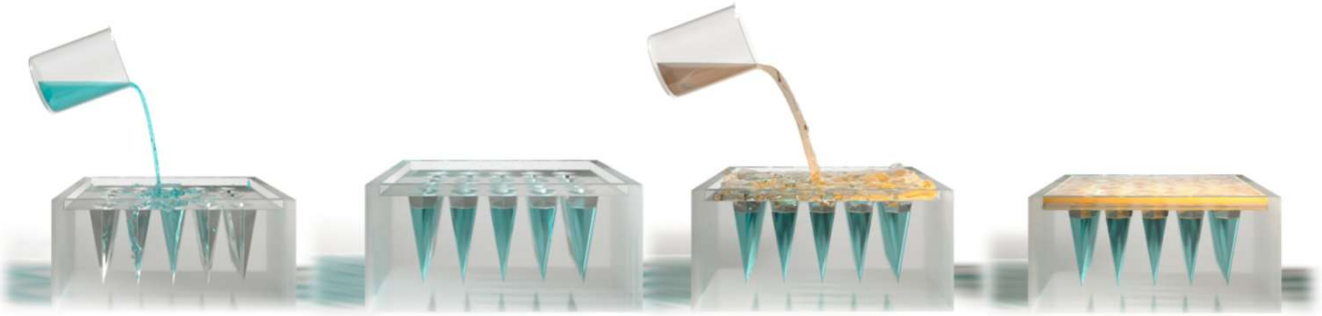
Side view

2-photon polymerization-based 3D-printed master template

Silicone elastomers mixed and dried atop the master template



Silicone elastomer molds ready for MAP preparation



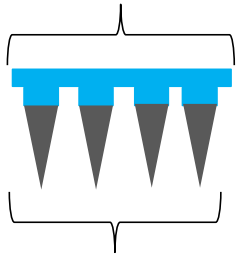
Casting of drug-loaded hydrogel in silicone molds

Use of pressure to dry formulation into mold cavities

Casting of drug-free hydrogel

Drying prior to removal from mold

Drug-free needle base and baseplate



Micronized drug-loaded tips

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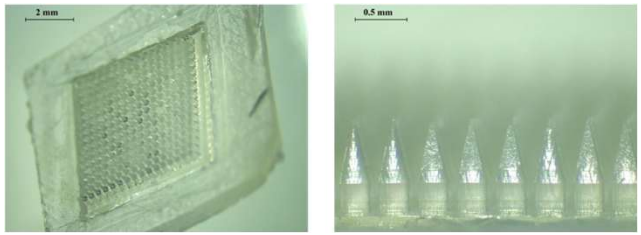
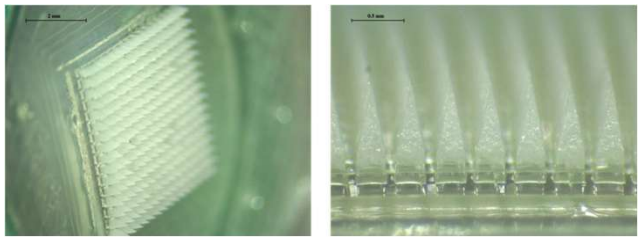
Images and figures: Queen's University Belfast

Lenacapavir and islatravir MAPs

- Consistent manufacturing (bench-scale)
- Mechanical integrity to penetrate skin
- Dissolve to deliver payload



Light microscope image of bilayer lenacapavir array.



Images: Queens University Belfast

Light microscope image of bilayer islatravir array.

Design	Surface area cm^2	# microneedles	Geometry	Tip length µm	Tip width µm	Interspacing µm
D1	0.5	256 (16 x 16)	Cuboidal base, pyramidal tips	600	300	100
D2	0.75	600 (24 x 25)	Pyramidal tips	750	300	50

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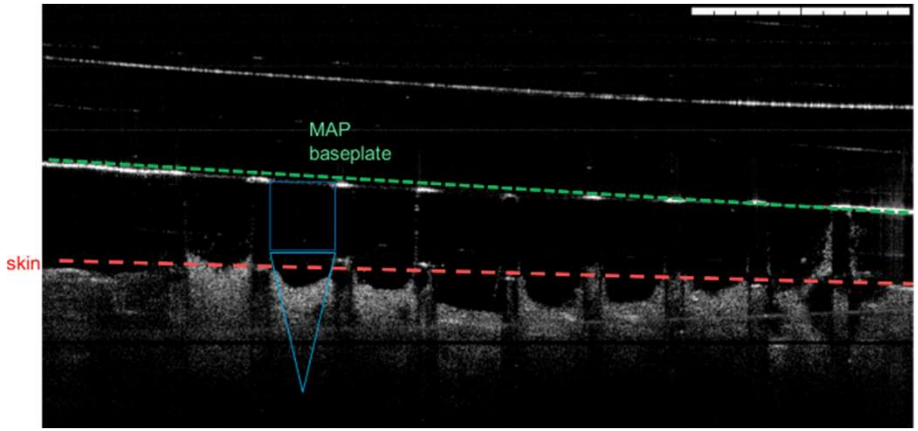
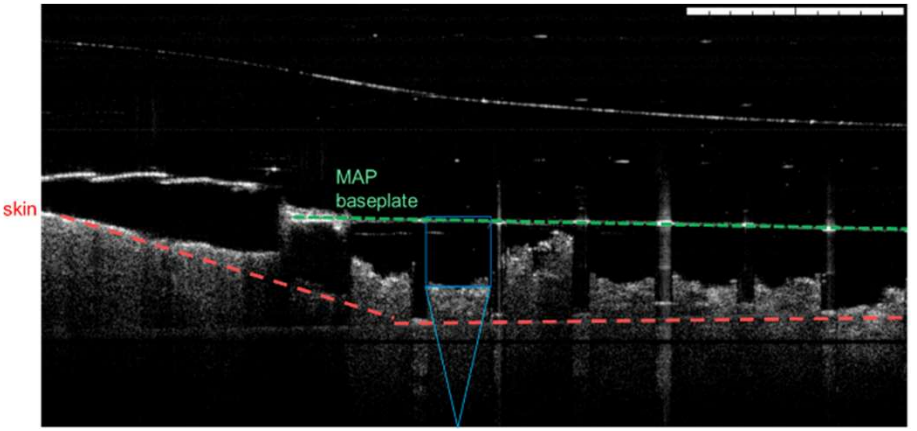
Lenacapavir and islatravir MAP drug loading and ex vivo deposition

Drug	Formulation	Drug loading (mg/0.5 cm^2 MAP)	Deposition ex vivo pig skin (mg)	% deposition
ISL	n/a	2.66 ± 0.14	0.98 ± 0.08	36.9 ± 3.0
LEN	Free acid, coarse	1.88 ± 0.17	0.56 ± 0.13	29.6 ± 6.6
LEN	Free acid, nanosuspension	1.44 ± 0.04	0.26 ± 0.9	17.9 ± 6.5
LEN	Sodium salt	2.59 ± 0.25	0.37 ± 0.12	14.3 ± 4.5



Optical computed tomography image of LEN array inserted into ex vivo pig skin.



Optical computed tomography image of ISL array inserted into ex vivo pig skin.

Images: Queens University Belfast

Abbreviations: ISL, islatravir; LEN, lenacapavir.

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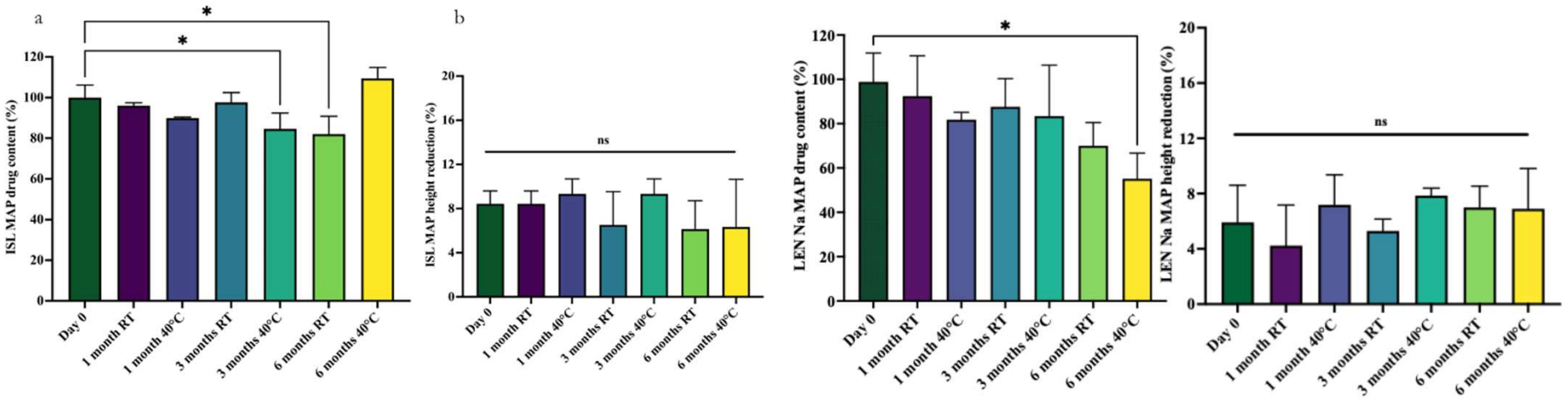
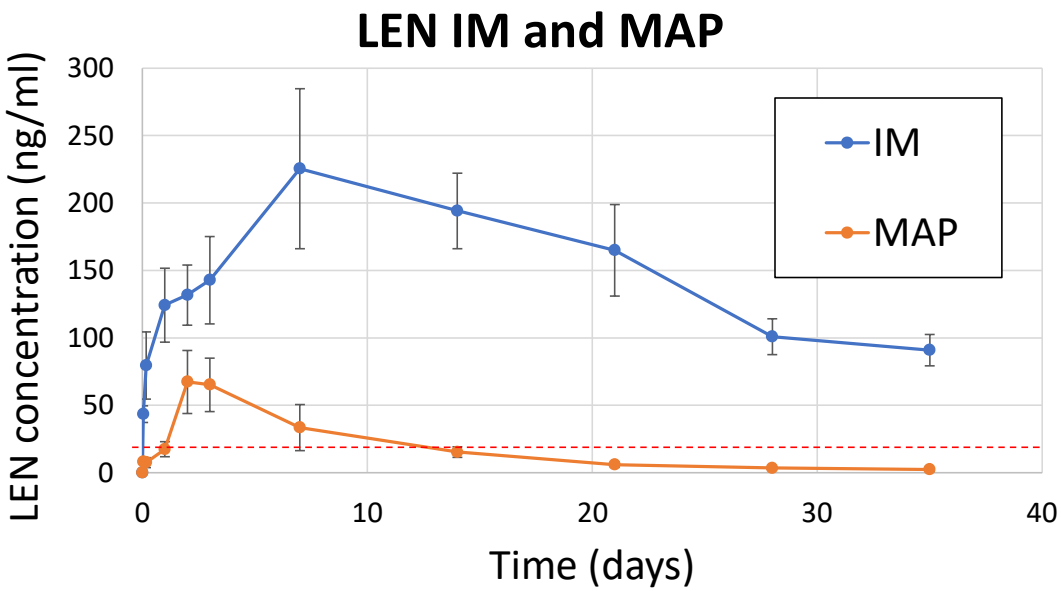
ISL and LEN MAP stability testing



Stability study of ISL and LEN MAPs over 6 months at 25°C/0% relative humidity (with desiccator) or 40°C/75% relative humidity measuring drug content and MAP height reduction after 32 N compression as an assessment of mechanical strength.

Lenacapavir: rat pharmacokinetics

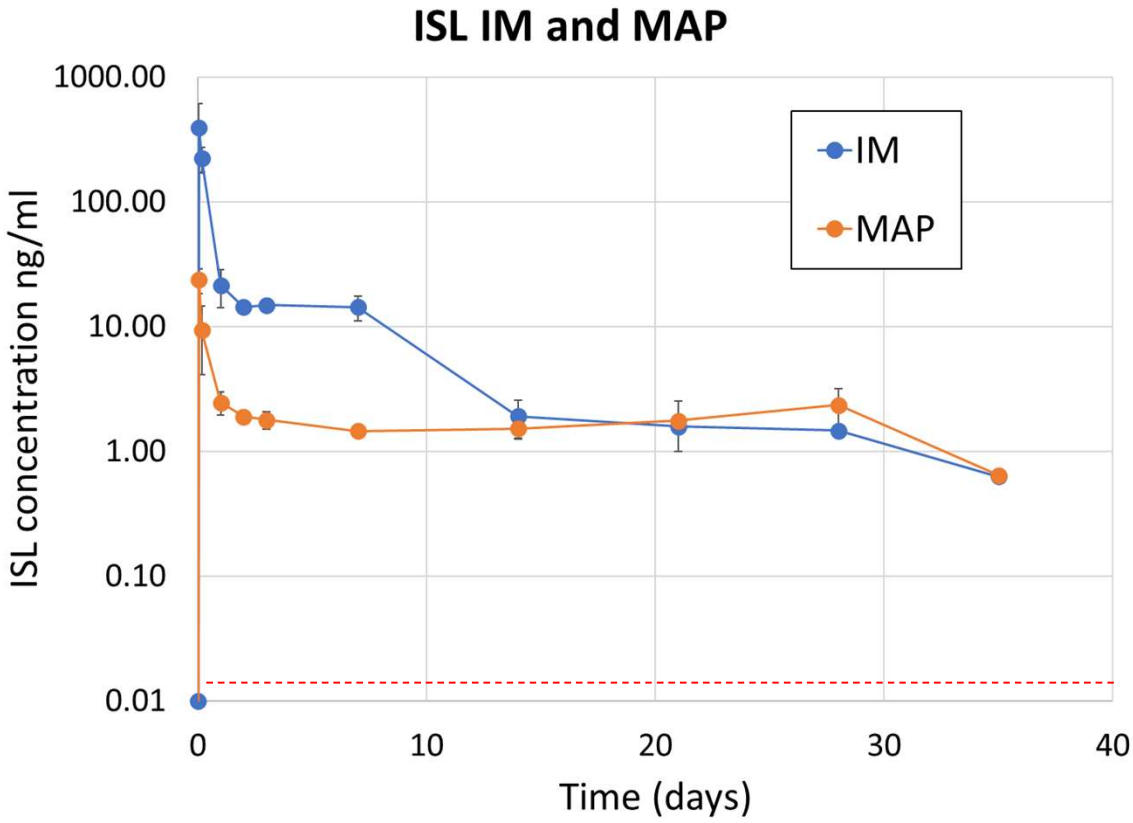
- Dosing: IM, 4 mg; MAP 10.4 mg applied, 1.8 mg delivered
- Data are mean ± SD (n=3 for first day and n≥5 on subsequent days)
- Red dotted line indicates target therapeutic concentration of 15.5 ng/ml (4x $paEC_{95}$)



Abbreviations: IM, intramuscular; LEN, lenacapavir, $paEC_{95}$, protein-binding adjusted 95% effective concentration; SD, standard deviation.

Islatravir: rat pharmacokinetics

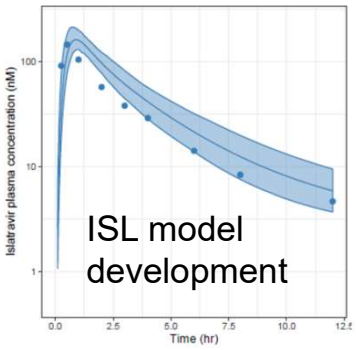
- Dosing: IM, 4 mg; MAP 10.6 mg applied, 2.4 mg delivered
- Data are mean ± SD (n=3 for first day and n≥5 on subsequent days)
- Red dotted line indicates target therapeutic concentration of 0.017 ng/ml

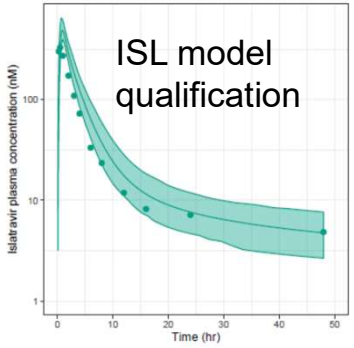


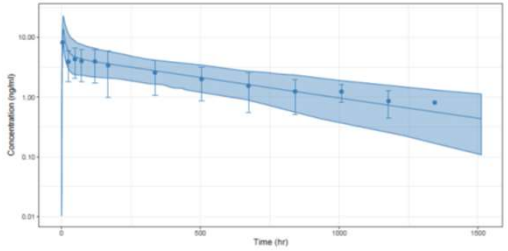
Abbreviations: IM, intramuscular; ISL, islatravir; SD, standard deviation.

LEN and ISL PBPK model development and qualification

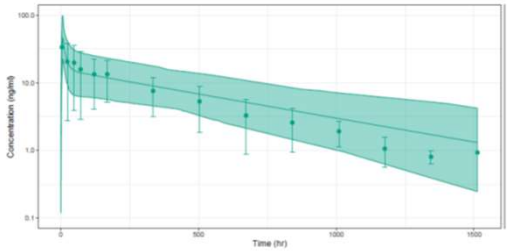
Drug	Study population	Dose/route/regimen	Sampling	Reference
ISL	24 healthy adults	5 to 400 mg PO, single and multidose	Up to 39 days	Matthews 2021 Clin Transl Sci
ISL	36 healthy adults	0.25 to 5 mg PO, multidose	Up to 42 days	Matthews 2021 J AIDS
ISL	12 healthy adults	20 mg PO, single dose	Up to 96 hours	Rudd 2021 Clin Pharmacol Drug Dev
LEN	40 healthy adults	50 to 1,800 mg PO, single dose	Up to 63 days	Begley 2020 CROI
LEN	10 healthy adults, 10 with hepatic impairment	300 mg PO, single dose	Up to 92 days	Jogiraju 2021 CROI







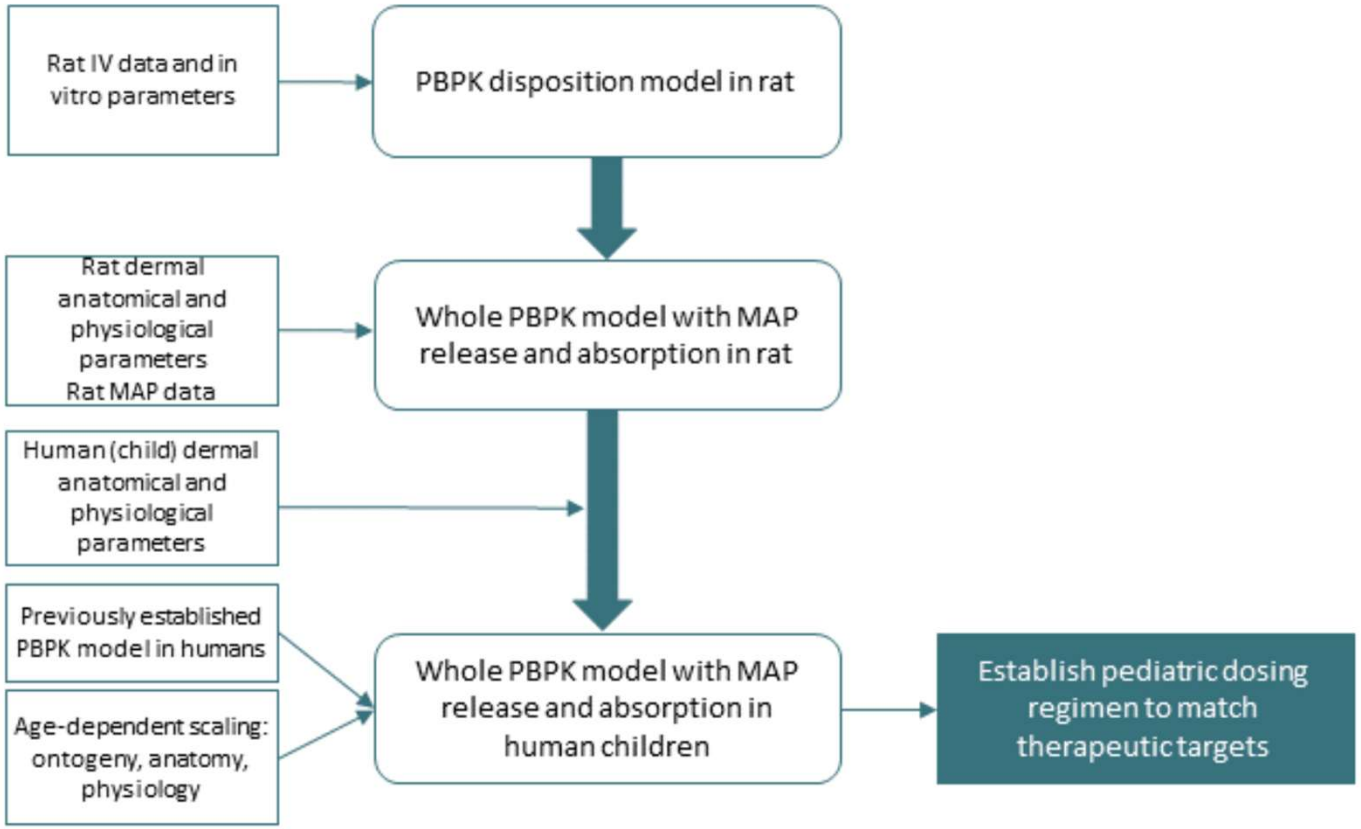
LEN model development



LEN model qualification

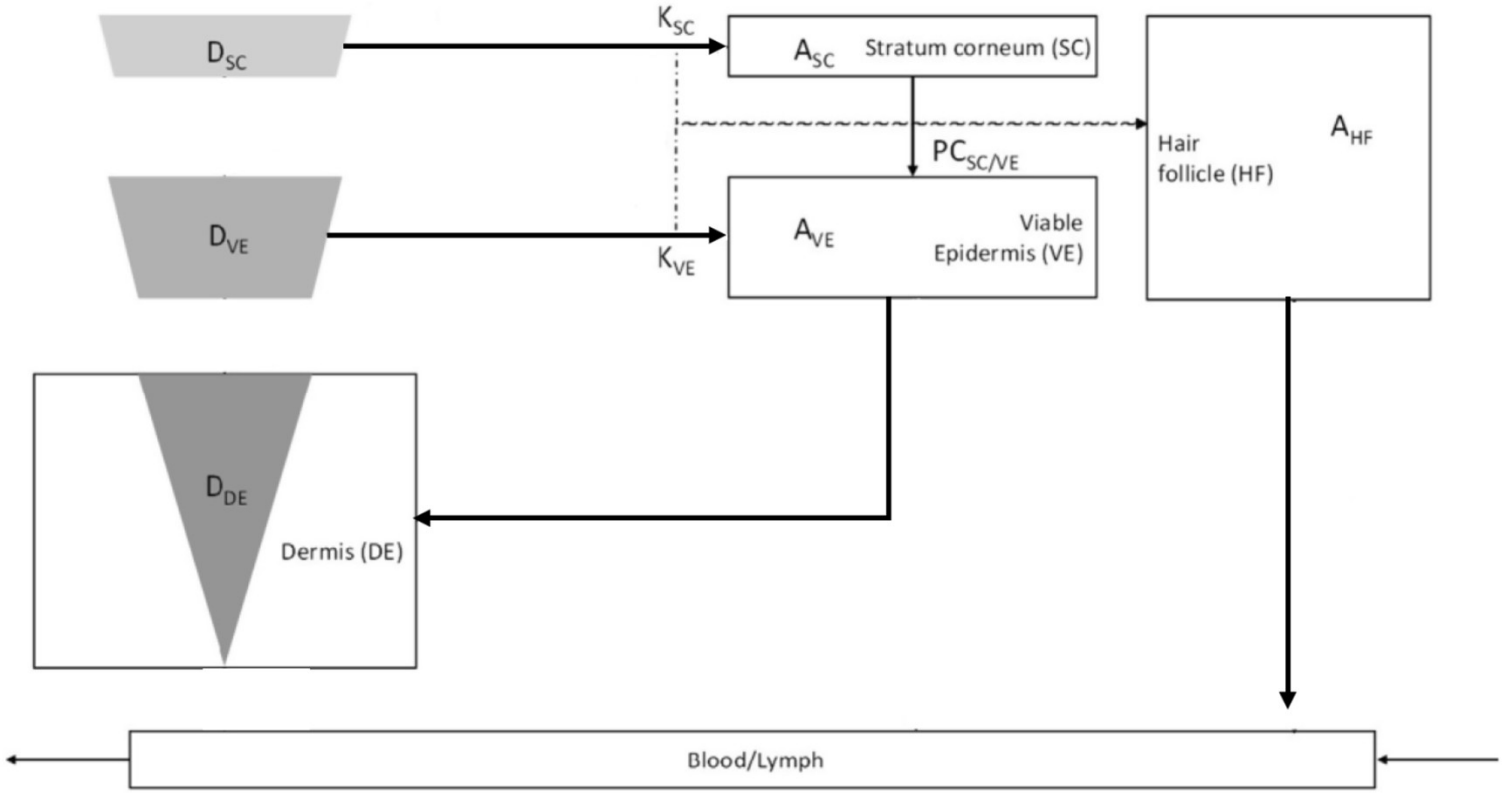
Abbreviations: ISL, islatravir; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetic; PO, per oral.

PBPK model development and qualification

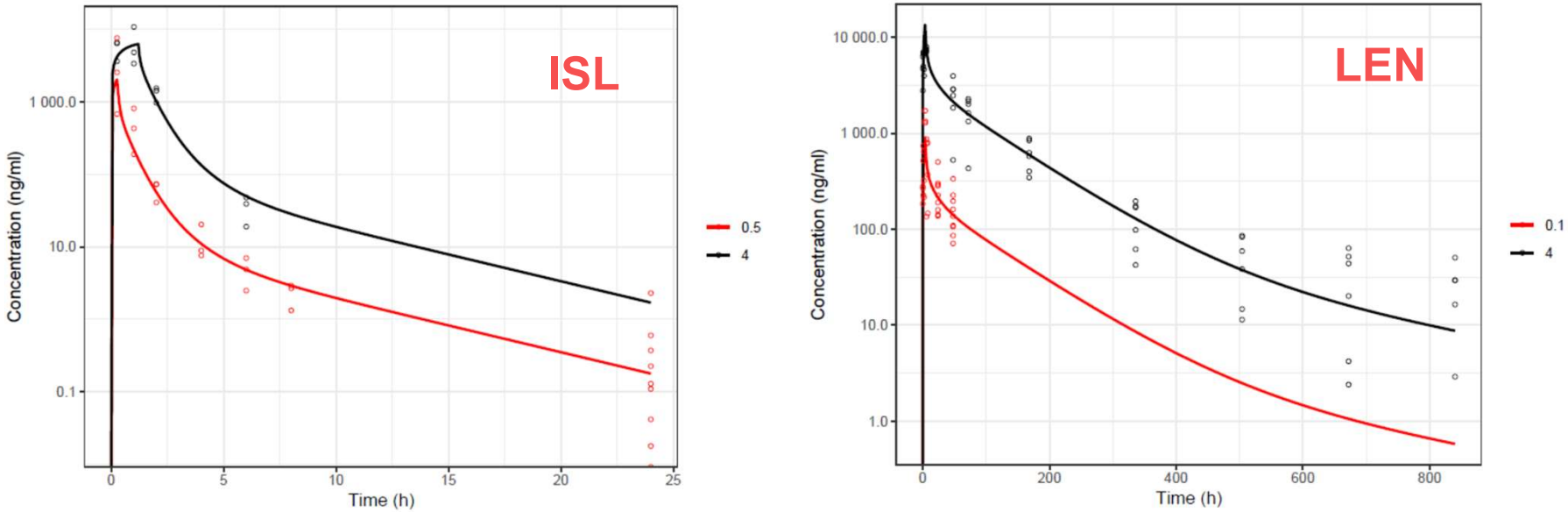


Abbreviations: IV, intravenous; PBPK, physiologically-based pharmacokinetic.

Schematic of dermal model



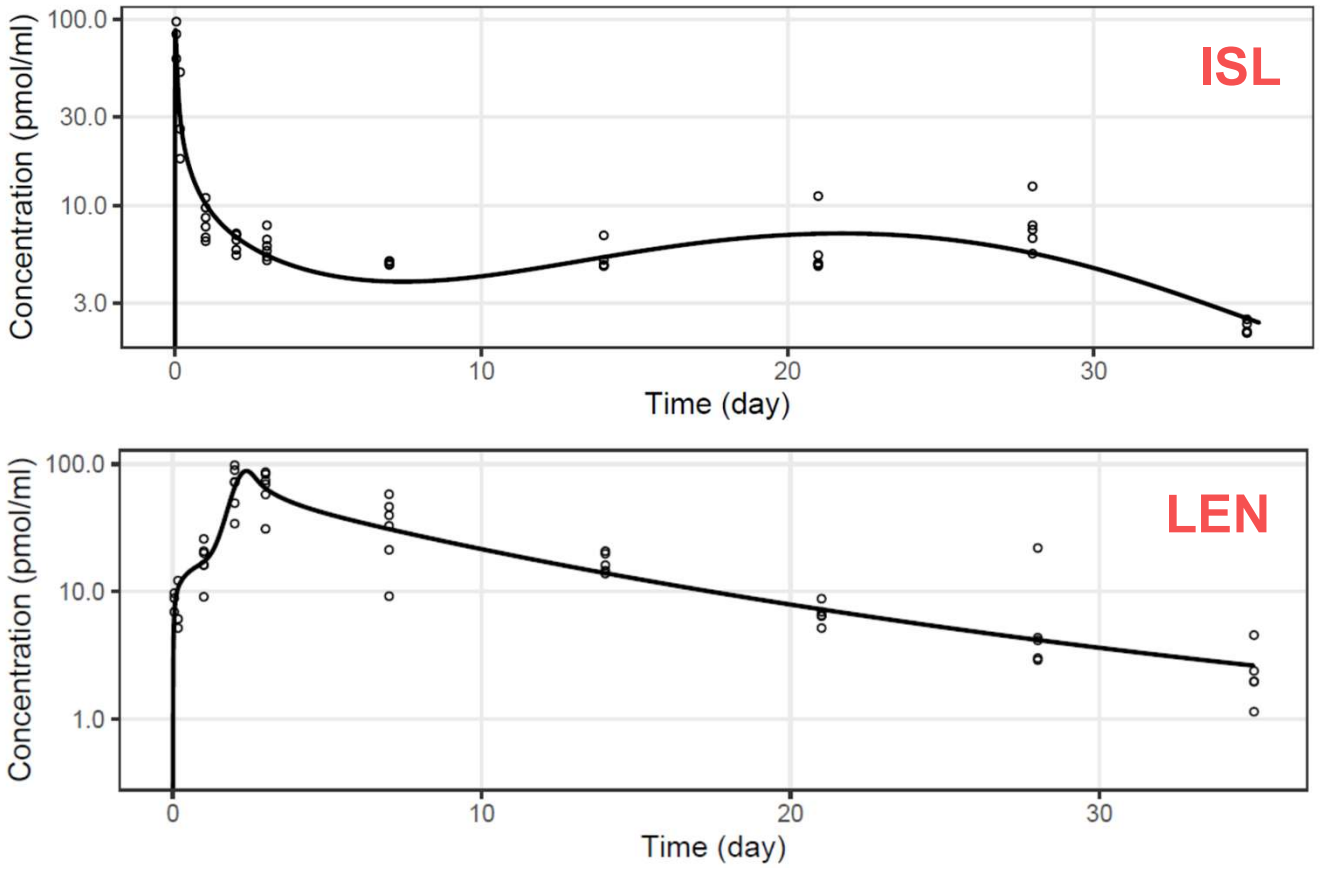
Rat intravenous pharmacokinetic data



- Rat intravenous pharmacokinetic data used to inform antiretroviral dispositions in MAP models
- Open circles: observed data; solid lines: modeled

Abbreviations: ISL, islatravir; LEN, lenacapavir.

Rat antiretroviral MAP pharmacokinetic data

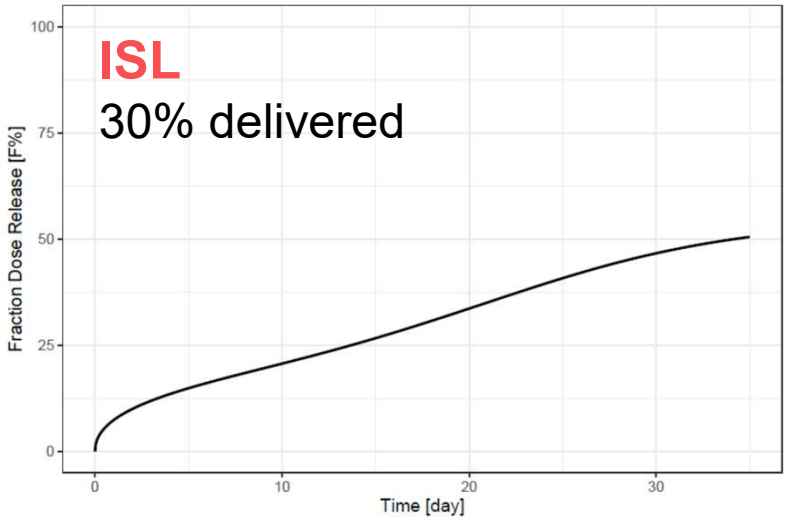


Open circles: observed

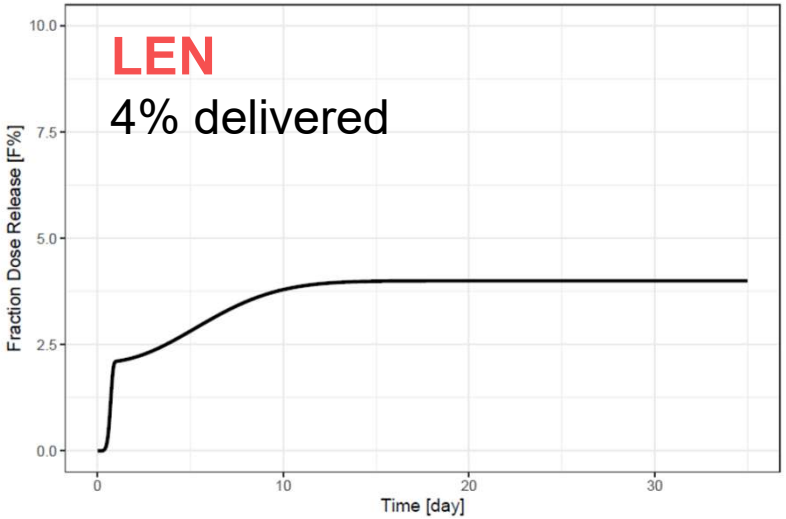
Solid lines: modeled

Abbreviations: ISL, islatravir; LEN, lenacapavir.

Rat antiretroviral MAP dissolution simulated profiles



Cumulative release (%) of administered dose from MAP to the system up to the last observation (35 days).



Cumulative release (%) of administered dose from MAP to the system up to the last observation (35 days).

- Rat LEN data insufficient to inform translation to human
- Substituted human subcutaneous LEN profile (Gilead data)

Abbreviations: ISL, islatravir; LEN, lenacapavir.

Modeling of human pediatric islatravir and lenacapavir plasma levels

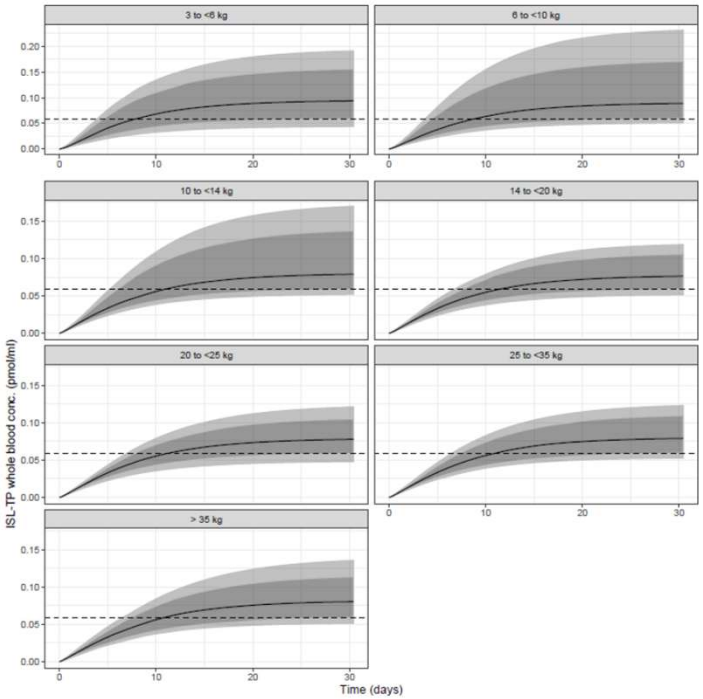


Figure 18: Islatravir-TP whole blood concentration-time profiles after application of MAP to children in different weight bands. Solid line, dark shaded area and light shaded area represent the simulated geometric mean, the 10-90% quantiles and the 2.5-97.5% quantiles of the PBPK model for a virtual population (n=200). Dotted line indicates therapeutic target concentration of 0.0585 pmol/ml of blood.

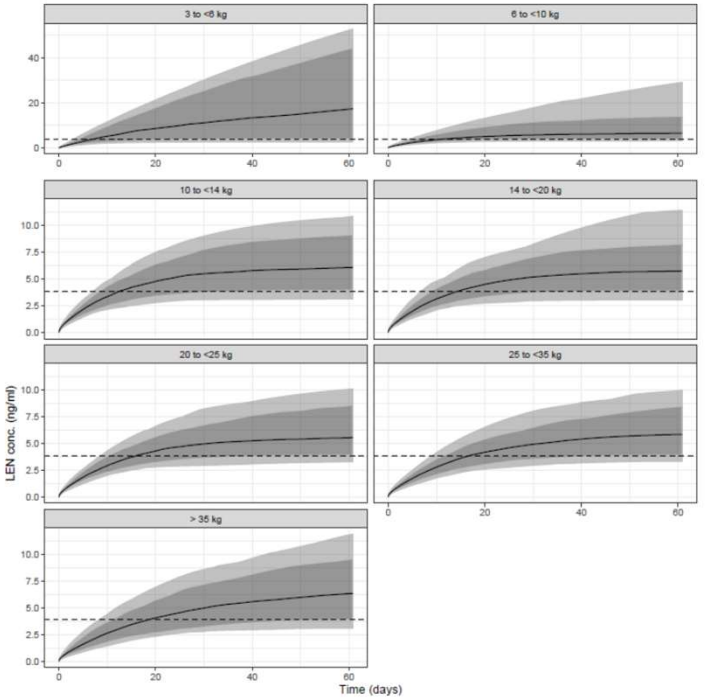


Figure 19: Lenacapavir plasma concentration-time profiles after application of MAP to children in different weight bands. Solid line, dark shaded area and light shaded area represent the simulated geometric mean, the 10-90% quantiles and the 2.5-97.5% quantiles of the PBPK model for a virtual population (n=200). Dotted line indicates therapeutic target concentration of 3.87 ng/ml.

Islatravir: Translation to human pediatric monthly dosing

Weight band (kg)	Dose (mg)	# MAPs
3 to 6	1.6	1
6 to 10	3.5	3
10 to 14	5.1	4
14 to 20	6.7	5
20 to 25	8.8	6
25 to 35	11.4	8

- All weight bands treatable with an acceptable number of MAPs
- Projected to achieve target plasma concentration in 5 days

Lenacapavir: Translation to human pediatric monthly dosing

Weight band (kg)	Dose (mg)	# MAPs
3 to 6	86.8	31
6 to 10	177.1	64
10 to 14	248.3	89
14 to 20	319.8	114
20 to 25	427.2	153
25 to 35	543.7	194

- Projected doses not feasible to achieve with MAPs alone
- Oral loading dose may enable feasibility

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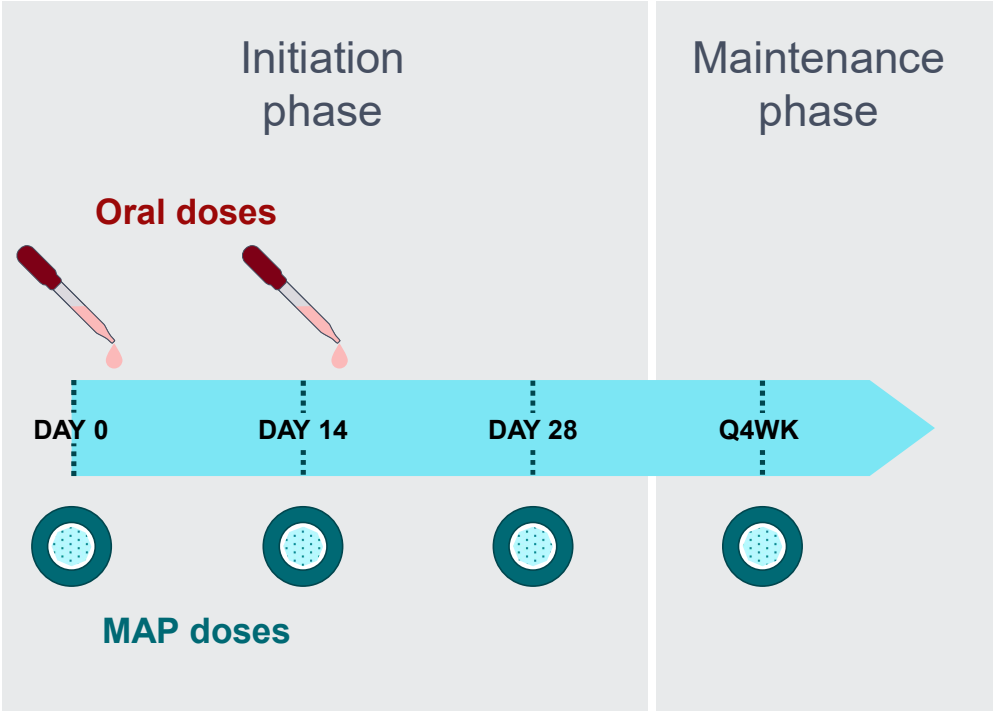
Dosing regimen: Oral lead-in increases feasibility of LEN MAPs



Weight band (kg)	LEN oral dose (mg)	LEN MAP dose (mg)	# LEN MAPs
3 to 6	21.3	26.5	2
6 to 10	41.6	54.3	4
10 to 14	68.9	69.4	6
14 to 20	67.4	88.4	7
20 to 25	86.2	110	8
25 to 35	98	119	9

PATH

Macaque pharmacokinetic/antiviral efficacy study design

- Adult rhesus macaques
- Stage 1: Pharmacokinetics
  - LEN and ISL MAPs
  - IV and MAP PK to support modeling
  - LEN oral loading dose
- Stage 2: Antiviral suppression
  - SHIV-RT infection
  - Suppress with standard regimen
  - Switch to MAPs

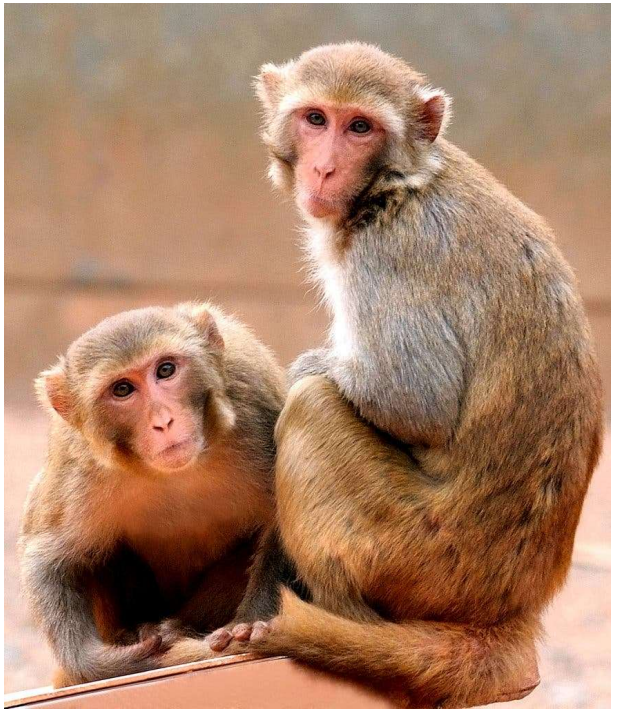


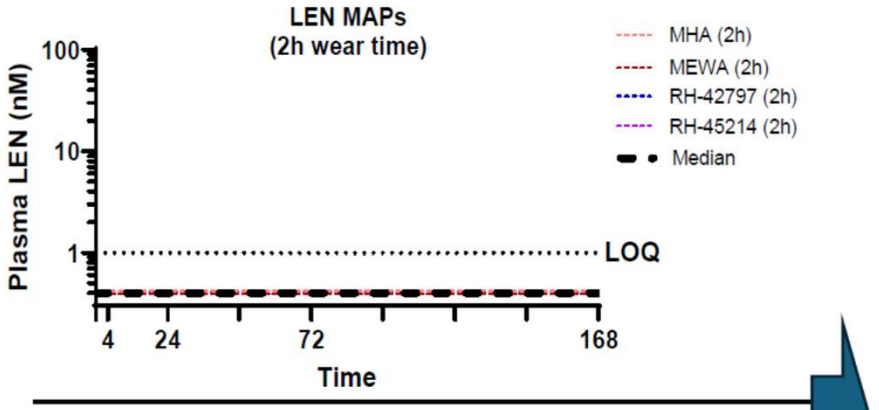
Image: National Primate Research Center

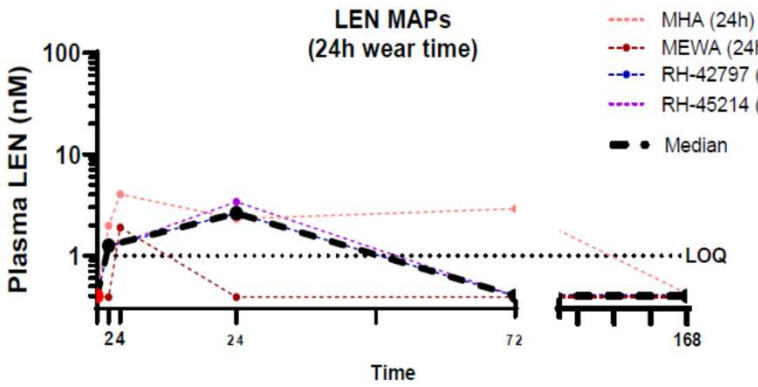
Abbreviations: ISL, islatravir; LEN, lenacapavir; IV intravenous; MAP, microarray patch; PK, pharmacokinetics; SHIV-RT, simian human immunodeficiency virus-reverse transcriptase.

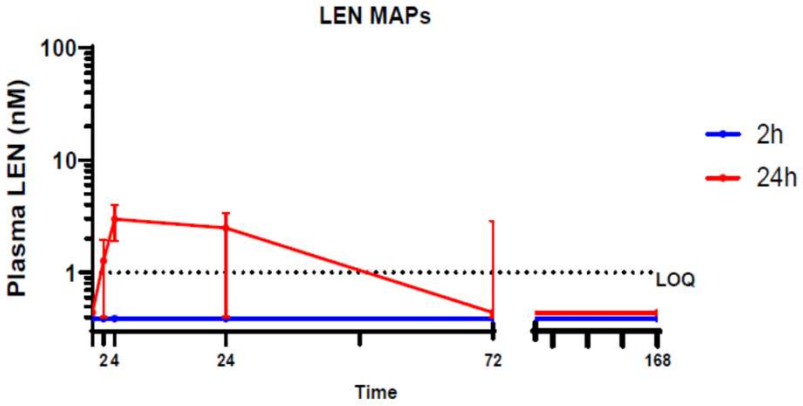
Macaque MAP application methods optimization

- Limitations:
  - Maximum sedation period
  - Animals removing MAPs
- Surgical glue/tape not effective for securing MAPs
- Jackets prevent animal access to MAPs

Macaque LEN pharmacokinetics results

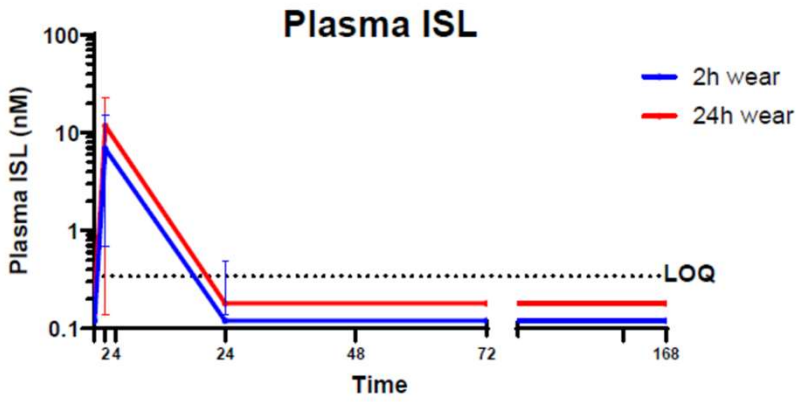




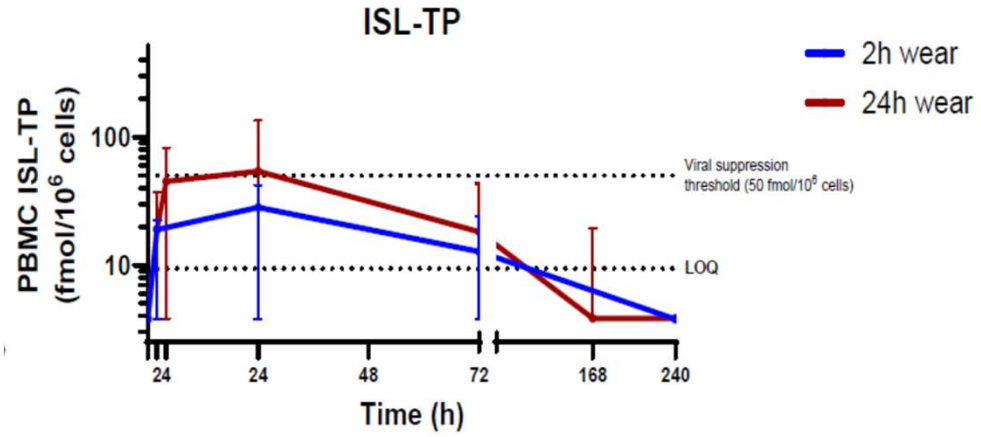


	2h	24h	fold-change
Plasma ISL C_{max} (nM)	0	2.9	
$AUC_{0\text{-}168h}$	N/A	230.5	

Macaque ISL/ISL-TP pharmacokinetics results



	2h	24h	fold-change
Plasma ISL C_{max} (nM)	7.4	11.5	**1.6**
$AUC_{0\text{-}168h}$	113.9	160.3	**1.4**



	2h	24h	fold-change
Plasma ISL C_{max} (fmol/million cells	25.6	61.7	**2.4**
$AUC_{0\text{-}72h}$	1,412	3,125	**2.2**

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Macaque ISL and LEN pharmacokinetics results

Pharmacokinetic Parameters	ISL MAPS		LEN MAPS	
Wear time (h)	**2**	**24**	**2**	**24**
Plasma Tmax (h)	2	2	—	4
Plasma Cmax (nM)	**7.42** ± *6.5*	**11.5** ± *9.3*	<LOQ	**2.95** ± *0.63*
Plasma AUC0–168 (nMol*hr/mL)	**113.9** ± *72.5*	**160.3** ± *102.6*	<LOQ	**230.5** ± *75.8*
Intracellular PBMC Tmax (h)	24	24	—	4
Intracellular PBMC Cmax (fmol/10^6 cells)	**25.6** ± *15.9*	**61.7**± *58.3*	—	—
Intracellular PBMC AUC0–72(fMol*hr/10^6 cells)	**1,412** ± *475.7*	**3,125** ± *1,612*	—	—

Wear time (h)	ISL mg applied	ISL mg delivered	ISL % delivered	LEN mg applied	LEN mg delivered	LEN % delivered
2	22.9	n/a	-2.0 ± 17.4	25.9	1.4	5.5 ± 6.6
24	28.3	5.7	19.2 ± 5.9	26.1	4.8	20.0 ± 11.4

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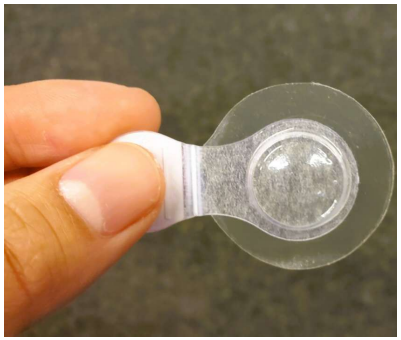
Macaque pharmacokinetics conclusions

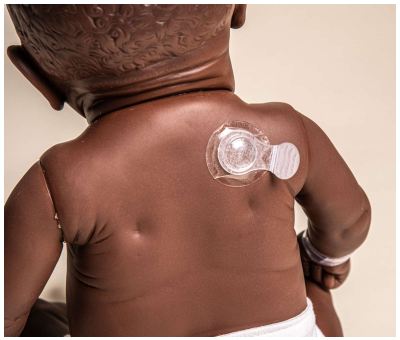
- Amounts delivered increased with extended wear time
- ISL-TP briefly reached therapeutic target
- LEN did not achieve therapeutic target
- Delivery efficiencies comparable to rats
- Decision not to progress to Stage 2 (antiviral suppression)
- PBPK modeling using macaque data predicted an unacceptably high number of MAPs needed for human dosing
- Further optimization of MAP formulations required

Pediatric antiretroviral MAP indicator development

MAP inside primary packaging, sealed.

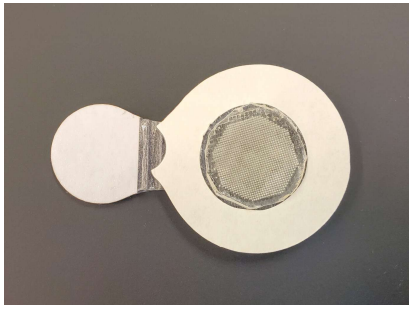


Top view: MAP with feedback indicator, pull tab (for device handling), and exposed skin adhesive.

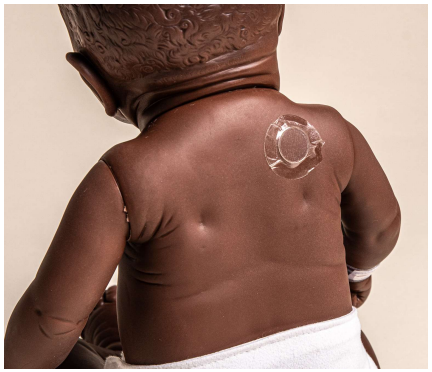


MAP applied to manikin using feedback indicator. The “dome” is pressed to deploy the array’s microneedles into the skin.

MAP inside primary packaging, opened.



Bottom view: MAP with feedback indicator, pull tab, skin adhesive with protective covering, and drug-containing array.



Once pressed, the feedback indicator is removed. MAP remains on the skin for a targeted **20 minutes or less** wear time before removal.

- Increase user confidence
- Requires specific force
- Visual, audible cues

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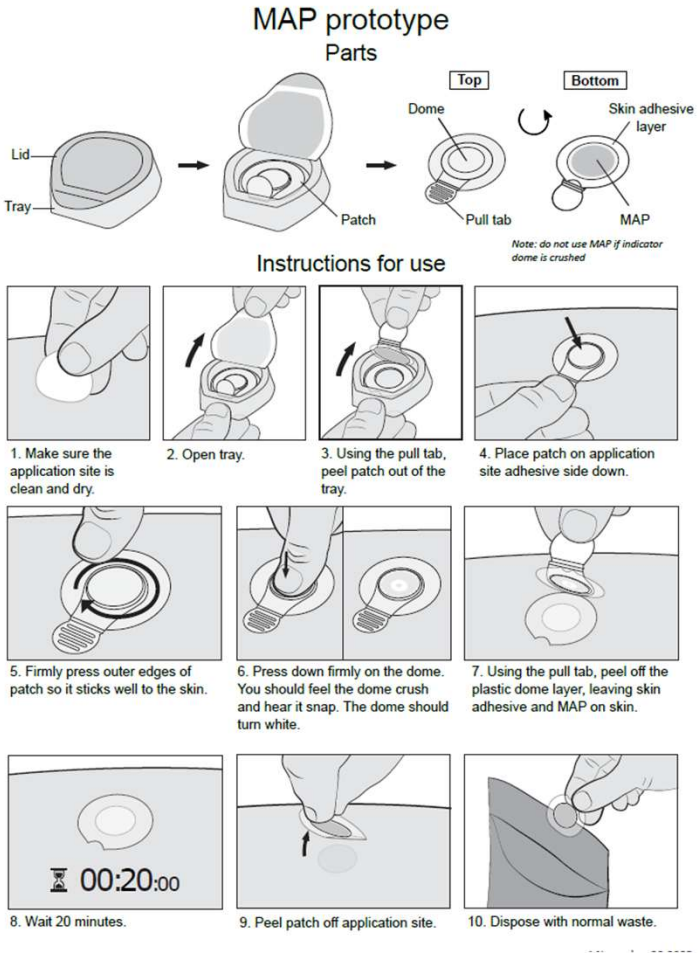
Instructions for use and video demonstration of MAP application using feedback indicator



The current version of the instructions for use is shown on the left-hand side.

Steps 1–3 and 8–10 are omitted from the video demonstration, although they would normally be completed in an actual use scenario.

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Stakeholder acceptability/usability study of pediatric MAP prototype

Methods

- Qualitative study of simulated prototype use, direct observation, and in-depth interviews.
  - Identification of use errors/difficulties
  - Acceptability, ease of use
  - Suggested improvements
  - Implementation feasibility
- Reviewed and approved by:
  - Mildmay Uganda Research Ethics Committee
  - Uganda National Council of Science and Technology
  - University of KwaZulu-Natal Biomedical Research Ethics Committee

Stakeholder type	n
Country decision-makers	9
Health care providers	14
Community health workers	8
Caregivers of pediatric HIV patients	17
Total	**48**

Images: PATH.

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Results: high acceptability and usability of ARV MAPs

- All 48 participants said MAPs were acceptable because:
  - Convenient to apply once weekly or monthly
  - Easier and more comfortable than administering daily oral medication
  - Prevents vomiting
  - Likely would improve adherence
- All 17 caregivers preferred MAPs over daily oral administration.
- Majority of 39 simulation participants:
  - Easily completed all steps
  - Felt confident about use
  - Recognized indicator cues

Usability study in Uganda. Image: PATH; permission obtained.

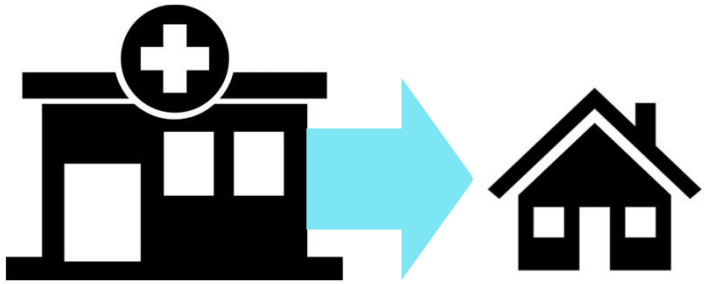
"This MAP will make the lives of the caregivers much easier."

- Country decision-maker in South Africa

Results: programmatic fit per country decision-makers

Pediatric ARV MAPs use cases: postnatal prophylaxis or maintenance treatment.

- Initial application at health facility by nurse or adherence counselor to train the caregiver.
- Future administration at home by caregiver.
- Weekly or monthly schedule acceptable to health systems if administered by caregivers.



"The weekly patch will be preferred. It's such a challenge to give a child the oral medicine. The child is crying, not happy, you cannot get it to swallow anything. It is a nightmare. The patch will simplify administration. There might be a bit of discomfort on the skin but that might be OK."

- Country decision-maker in South Africa

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Conclusions

- ARV MAPs represent a highly acceptable approach for pediatric HIV treatment and postnatal prophylaxis.
- PBPK modeling is critical for dose level estimation and translation.
- Adult macaque studies indicate further optimization is needed.
- User study provided key indicator design feedback for next iteration.
- Advanced manufacturing and clinical data needed to progress and validate platform.

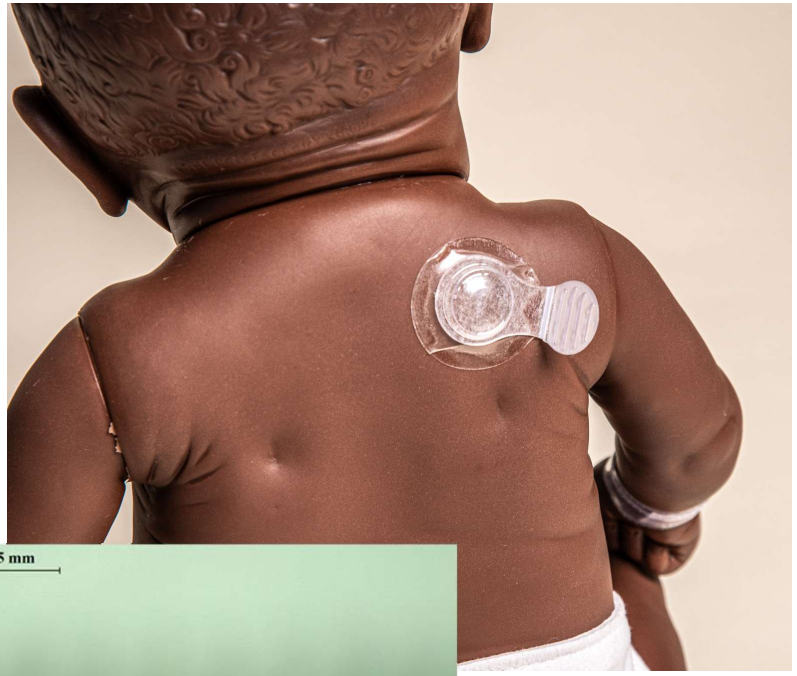

Image: PATH

Image: Queen's University Belfast

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Next steps

- Formulation development/optimization
- Good Manufacturing Practice process development, scale-up
- Juvenile animal toxicology studies
- Juvenile macaque PK and efficacy studies
- Clinical: Phase 1 in adults, then descending age studies in children


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