2025 INVESTIGATOR MEETING & ANNUAL WORKSHOP

San Francisco, California
March 8, 2025

leap Long-Acting/Extended Release Antiretroviral Research Resource Program

ABBREVIATIONS

AE Adverse event
AI Active ingredient
ALC Absolute lymphocyte count
ANDA Abbreviated new drug application
API Active pharmaceutical ingredient
ARCH-LA Antiretroviral concentrated + highly durable LA
ART Antiretroviral therapy
ARV Antiretroviral
AUC Area under the curve
BDQ Bedaquiline
BE Bioequivalence
BIC bictegravir
bNAb broadly neutralizing antibody
CAB Cabotegravir
CD4 $CD4^+$ T lymphocytes
CDMO Contract development + manufacturing organization
CELT Centre of Excellence for Long-acting Therapeutics
CHAI Clinton Health Access Initiative
CMax Maximum concentration
CMO Contract manufacturing organization
CSA Clinical study agreement
DcNP Drug combination nanoparticles
DDI Drug-drug interaction
DMPA Depo-Provera
DOR Doravirine
DPV Dapivirine
DSD Differentiated service delivery
DTG Dolutegravir
EFV Efavirenz
EMA or EMEA European medicines agency
ER Extended release
EU European Union
FDA Food and Drug Administration
FDC Fixed-dose combination
F/TAF Emtricitabine/tenofovir alafenamide
FTC Emtricitabine
GLP Good laboratory practice
GMP Good manufacturing practice
G/P Glecaprevir/pibrentasvir
HALo Hub for Advanced LA Therapeutics
HIV Human immunodeficiency virus
HPTN HIV Prevention Trials Network
IAS International AIDS Society
1HP 1-month TB preventive
IM Intramuscular
IND Investigational new drug
INH Isoniazid
INSTI Integrase strand transfer inhibitor
IP Intellectual property
IPT Isoniazid prevention treatment
IQR Interquartile range
IR Immediate release
ISFI In situ forming implant
ISL Islatrovir
ISR Injection site reaction
IV Intravenous
LA Long-acting
LAI Long-acting injectable
LAPaL Long-acting therapeutics, patents, and licenses
LEAP Long-acting extended release antiretroviral research program
LEN Lenacapavir
LMIC Low-middle income country
LMNC Lymphomononuclear cell
LN Lymph node
LPV Lopinavir
LTBI Latent tuberculosis infection
LTZ Letrozole
M2 BDQ primary active metabolite
mAbs Monoclonal antibodies
MD Multiple dose
MDR-TB TB resistant to RIF + INH
MHRA Medicines and Healthcare products Regulatory Agency
MPP Medicines Patent Pool
MPT Multipurpose prevention technology
MSM Men who have sex with men
NDA New drug application
NCD Non-communicable disease
NGO Non-governmental organization
NHP Non-human primate
NIH National Institutes of Health
NRTTI Nucleoside reverse transcriptase translocation inhibitor
NTP National treatment program
NVP Nevirapine
PA-IC90 Protein-adjusted inhibitory concentration 90%
PBMC Peripheral blood mononuclear cell
PBPK Physiologically based pharmacokinetic
PD Pharmacodynamics
PDUFA Prescription Drug User Fee Act
PEG Polyethylene glycol
PEPFAR President's Emergency Plan for AIDS Relief
PI Protease inhibitor
PK Pharmacokinetics
PLWH People living with HIV
PoC Proof of concept
PrEP Pre-exposure prophylaxis
PSG Product-specific guidance
PY Person-year
QD Once-daily
QTc Corrected QT interval
QW Once-weekly
RCT Randomized controlled trial
RIF Rifampicin
RPV Rilpivirine
RR-TB Rifampicin-resistant TB
RTV Ritonavir
SC Subcutaneous
SHIV Simian HIV
SUD Substance use disorder
SVR Sustained virologic response
TAP Target access profile
TAB Teropavimab
TB Tuberculosis
TDF Tenofovir
TLC-ART Targeted long-acting and combination antiretroviral therapy
TLD Tenofovir, lamivudine, dolutegravir
TLE Tenofovir, lamivudine, efavirenz
TP Triphosphate
TPP Target product profile
TRP Target regimen profile
U=U Undetectable = untransmittable
ULAI Ultra-long acting
VAS Visual analog scale
VL Viral load
VS Virologically supppressed
WHO World Health Organization
3TC Lamivudine
ZAB Zinlirvimab

CONTENT

Where will we LEAP next?

On March 8, 2025,

the Long-Acting Extended Release Antiretroviral Research Resource Program (LEAP) virtually convened clinicians, investigators, developers, community advocacy groups, not-for-profit institutions, and regulatory authorities. Attendees shared their diverse perspectives and discussed updates, challenges, and future directions on the development of LA formulations. The meeting served as a forum to collectively advance the LA field. The workshop consisted of two plenary sessions and four focus groups.

OPENING REMARKS

Charles Flexner

Principal Investigator of LEAP

"Many good things are coming despite the broader challenges globally and nationally."

Dr. Flexner highlighted 2024 as a year of major progress for LEAP, marked by new collaborations and scientific milestones. He noted that LEAP convened its first Tuberculosis Working Group in Baltimore, co-sponsored a CELT workshop in Liverpool on bioequivalence and generic approvals, and participated in global access planning meetings with CHAI, the Gates Foundation, WHO, and DAIDS. The program published the first systematic review of LA/ER drugs for children, adolescents, and pregnant women, and presented new PK and modeling data to inform next-generation formulations. Looking ahead, Dr. Flexner said LEAP's five-year grant renewal will launch new cores on user preferences, translation, and communications, alongside continued support for HIV, TB, and hepatitis research and the March 18, 2025 LEAP Hepatitis B Workshop in Los Angeles. He thanked several colleagues:

- Mark Barsanti – 10 years of service; founding Executive Committee member; stepping down in June
- Bob Bollinger – foundational support at program launch; 10 years on Executive Committee; stepped down at year's end
- Sue Swindells – Vice Chair; 10-year partner; stepping down in June; staying one extra year to support TB Working Group transition
- Elaine Abrams – 3 years on Executive Committee; incoming Vice Chair; focus on children, adolescents, pregnant women
- Community representation expansion – adding two members:
    - Ronald Sunyonga (Makerere University) – joining after visa delay
    - Chari Cohen (Hepatitis B Foundation) – HBV community representative; attending HepB workshop

OPENING REMARKS

Carl Dieffenbach

Director, Division of AIDS, NIH

"The year 2024 was a pivotal one for long-acting antivirals – no doubt about it."

Dr. Dieffenbach summarized the landmark PURPOSE trial results.

Trial	Population	Key Efficacy Results	Notes
PURPOSE 1	Cisgender women in high HIV-incidence regions. Evaluate twice-yearly SC LEN vs. daily oral PrEP (F/TAF or TDF/FTC)	No HIV acquisitions in LEN arm vs. 1.69 (TDF/FTC) and 2.02 (F/TAF) per 100 PY	Near-complete protection with LEN
PURPOSE 2	MSM, transgender women, gender-diverse individuals. Assess LEN vs. TDF/FTC for HIV prevention	HIV incidence: 2.37 per 100 PY (background) vs. 0.10 (LEN) and 0.93 (TDF/FTC)	LEN significantly reduced HIV acquisition (IRR 0.04 vs. background; p<0.001)

Kelley et al., NEJM 2025

Bekker et al., NEJM 2024

He emphasized that the next phase for LA prevention must move from discovery to implementation. He noted that LEN is now being tested for once-yearly dosing and called for coordinated implementation of LEN and CAB-LA with sufficient PK for sustained coverage. Developing agents with long half-lives can transform chronic HIV care and inspire future LA cures for HBC and other diseases. Extending LEAP's collaborative model beyond HIV, he urged continued innovation, vigilance for long-term safety, and inclusion of diverse populations (children, adolescents, pregnant people, and people who inject drugs) to ensure the benefits of LA therapies reach all who need them.

Kenly Sikwese

Executive Director, AFROCAB

Community-Based Presentation

"The discussion is no longer whether people living with HIV or HBV or HCV prefer long-acting technologies. That debate is over."

High demand from PLWH to enroll in LAI-ART clinical trials

Setting / Study	Key Findings
Kampala advocates meeting	> 70% preferred bimonthly LAI for HIV prevention
AFROCAB booth (AIDS 2022)	Strong overall demand for LA options + choice
Kigali PLWH consultations	Varied priorities but consistent emphasis on access and reduced clinic burden
Fort Portal CARES Cohort (Uganda)	After 12 months of LAI-ART, 94% preferred to remain on injections; better adherence, more privacy, less stigma than oral therapy

"The demand was so strong … so many people wanted to join the study that meeting the eligibility criteria became a challenge."

Key Takeaways

- Accelerate African research (CAB, LEN studies), with stronger leadership from local investigators, institutions
- Improve industry transparency with manufacturers on regulatory pathways, product access, equitable supply
- Prioritize community voices in research, policy, implementation planning
- Define equity goals collaboratively with communities to avoid exclusionary criteria for LAI access
- Innovate DSD models: Community-based and supported self-administration options tailored to local contexts
- Mobilize resources: Strengthen funding mechanisms + partnerships for sustainable LAI delivery
- Adapt to political shifts: Address "the elephant in the room" – how programs can adjust to U.S. government funding declines, turning current challenges into opportunities for local ownership

William Spreen

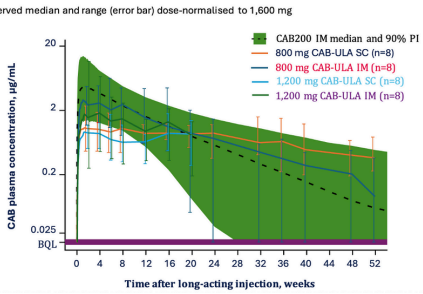
Cabotegravir Medicine Development Leader, ViiV Healthcare

Current Status of LA/ER CAB and RPV

"We've now accumulated data from more than 15,000 individuals in real-world cohorts – essentially confirming that clinical trial results are reproducible in everyday settings."

- CAB-LA continues to demonstrate high effectiveness for HIV prevention across multiple global real-world cohorts (e.g., IDWeek and HIVR4P 2024)
- PILLAR + ImPrEP presented at CROI 2025 (extending evidence to diverse populations)
  - Khan et al., CROI 2025 ; Grinsztejn et al. CROI 2025
- CAB + RPV LA: durable virologic suppression over 3-5 years + strong patient preference for LAIs vs. daily oral ART

Study	Population	Key Findings
SOLAR / CARES	Adults on oral ART	Non-inferior efficacy vs BIC/FTC/TAF; improved treatment satisfaction
LATITUDE	Individuals with adherence challenges	Superior efficacy vs oral ART
MOCHA	Adolescents	Maintained viral suppression and strong preference for CAB/RPV LA
CROWN (Ongoing)	Viremic individuals (VL 1,000-100,000)	Evaluating CAB/RPV LA every 2 months vs oral ART for label expansion



CAB ULA

- Slower absorption, extended half-life; potential every-4-month dosing
- EXTEND 4M trial (NCT06741397): PK-bridging registrational study for PrEP; 200 participants, primary endpoint at month 13
- CROWN ULA study under development for treatment; targets label expansion
- RPV ULA
- Suspension formulation (600 mg/mL); Phase 3 trial late 2025 comparing Q4M CAB ULA + RPV ULA to current Q2M regimen.

ULA formulations are the next frontier in HIV prevention and treatment, aiming to extend dosing intervals from every 2 months to > 4 to 6 months. CAB ULA and RPV ULA are progressing through registration and Phase 3 studies; EXTEND 4M trial is demonstrating promising PK that may enable regulatory approval without additional efficacy trials.

HIV Prevention: CAB ULA Q4M for PrEP: EXTEND 4M Registrational Trial (NCT06741397)

Purpose	PK bridging study to support regulatory approval of CAB ULA Q4M for HIV PrEP
Design	200 participants (100 male, 100 female); begins with CAB LA lead-in (600 mg IM ×2 doses), then transitions to CAB ULA (1600 mg IM every 4 months)
Endpoints	• Primary: CAB ULA drug levels ~ HPTN 083/084 efficacy data • Secondary: Assess safety, tolerability, treatment satisfaction
Goal	Provide sufficient PK + safety data to support NDA submission without more efficacy trials
Timeline	Study launched December 20, 2024; primary endpoint at month 13, final study completion at month 33

HIV treatment: CAB + RPV ULA Q4M for HIV Treatment: Phase 3 Starting in Late 2025

- Phase 1 trial (NCT05418868) evaluating multiple CAB and RPV ULA formulations to determine the optimal Q4M dosing
  - PK, safety, tolerability data to confirm Q4M dosing feasibility
  - Adults (18-55), HIV-negative, body weight ≥40 kg, BMI 18–32 kg/m²
- CAB ULA doses: 800-1600 mg SC or IM, < 46 participants in ongoing/future cohorts
- RPV ULA: Early cohorts (36 participants) ongoing, with final dose selection pending
- Phase 3 registrational trial late 2025: Randomized, multicenter, international, open-label study to evaluate the non-inferiority of CAB ULA + RPV ULA Q4M vs approved CAB LA + RPV LA Q2M regimen in adults and adolescents virally suppressed on ART
  - IM/gluteal administration

ULA Pipeline

Candidate	Type	Current Status	Potential Dosing
N6LS (VH109)	Broadly neutralizing antibody (bNAb)	Phase 2b EMBRACE trial; IV or SC Q4M	4 months
VH310	CAB prodrug	Preclinical; sustained levels up to 54 weeks in primates	≥6 months
VH184	3rd-gen integrase inhibitor	Phase 2 oral PoC; injectable Phase 1 ongoing	4-6 months
VH499	Capsid inhibitor	Phase 2a oral PoC; injectable in development	TBD

Key Takeaways

- Significant progress since regulatory approvals of CAB + RPV LA for HIV treatment (Jan 2021) and CAB LA for PrEP (Dec 2021)
- New real-world data in key populations reinforces transformative potential of LA formulations
- CROI 2025: > 25 presentations on CAB + RPV LA or CAB LA PrEP
- Extension phases from these trials have shown long-term, durable efficacy – including in underrepresented populations
- Toward ULA success: CAB ULA in registrational trials for PrEP; advancing toward Phase 3 for HIV treatment alongside RPV ULA
- ULA pipeline: N6LS (bNAb), CAB prodrug, VH-184 (third-generation INSTI), VH-499 (capsid inhibitor)

Luisa Stamm

HIV Section Head, Infectious Disease Clinical Research
Merck Research Laboratories

Current Status of the Merck LA/ER Pipeline

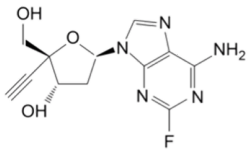
"Merck's HIV portfolio now spans long-acting programs in Phases 1 through 3."

Gilead-Merck Collaboration

ISL-LEN combination (NRTTI + first-in-class capsid inhibitor)

- Non-overlapping resistance profiles, long half-lives – potential to be first once-weekly oral regimen for virologically suppressed PLWH
- Colson A et al., IDWeek 2024

Islatravir (ISL) is a first-in-class NRTTI with multiple mechanisms of action



ISL

- Multiple mechanisms of action: translocation inhibition + delayed chain termination
- Long intracellular half-life of active triphosphate (~186 hours)
- High potency and high barrier to resistance, active against resistant HIV variants
- Programs paused in 2021 due to lymphocyte decreases; restarted in 2023

Markowitz M et al., Curr Opin HIV AIDS 2020

Protocol	Population	Design	Comparator
051 (N=553)	VS	Open-label, randomized, switch	DOR/ISL QD vs baseline ART QD
052 (N=514)	VS	Blinded, randomized, switch	DOR/ISL QD vs BIC/FTC/TAF QD
053 (N=500)	Treatment-naive	Blinded, randomized, new start	DOR/ISL QD vs BIC/FTC/TAF QD
054 (N=641)	Prior DOR/ISL (100 mg / 0.75 mg)	Open-label, single arm	DOR/ISL QD

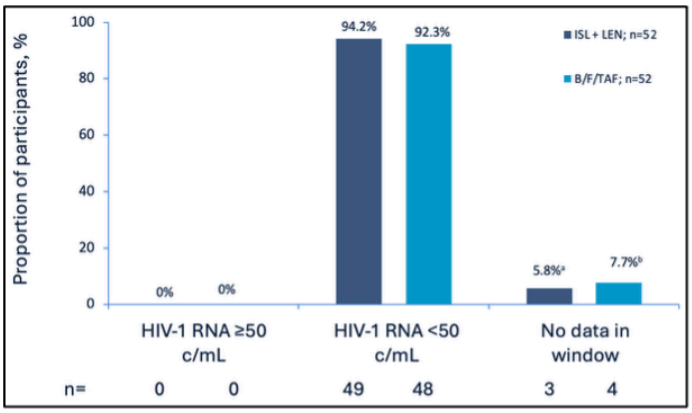
Phase 3 DOR/ISL topline reslults

ISLEND-1

- VS population
- N~600
- ISL/LEN QW vs. BIC/FTC/TAF QD
- Blinded, randomized, switch
- Enrolling

ISLEND-2

- VS population
- N~600
- ISL/LEN QW vs. baseline ART QD
- Open-label, randomized , switch
- Enrolling



HIV Pipeline Programs

Program	Mechanism	Dosing	Status
DOR/ISL	NNRTI + NRTTI	Daily oral	Phase 3
ISL/LEN	NRTTI + capsid inhibitor	Weekly oral	Phase 3
ISL/ULO* (MK-8507)	NRTTI + NNRTI	Weekly oral	Phase 2 restart
MK-8239	ISL prodrug	LAI	Phase 1
MK-8527	NRTTI	Monthly oral	Phase 2

*Ankrom W et al., AAC 2021; Schürmann D et al., JAIDS 2022, Gillespie G et al., JCP 2022

"The positive data from both the 0.25 mg daily and 2 mg weekly islatravir regimens support the continued development of NRTTI-based long-acting therapies and PrEP options."

Moupali Das

Vice President, HIV Prevention and Virology
Pediatric Clinical Development
Head, HIV Prevention
Gilead Sciences

LA HIV Treatment + Prevention Pipeline

"More than 16 million people have accessed a Gilead treatment or PrEP regimen, including in low and middle income countries."

LEN: Gilead's Core Anchor for HIV Treatment + Prevention

- First-in-class HIV capsid inhibitor (EC50 = 100 pM, long half-life)
- Multimodal mechanism, no overlapping resistance with existing ART
- Flexible dosing: weekly oral, monthly oral, quarterly injectable, twice-yearly injectable, annual formulations under development
- FDA priority review (PDUFA date of June 19, 2025)
- Filed with EMA and EU-M4All, enabling LMIC submissions
  - More global filings in progress

Developing New Options for Treatment & PrEP

Category	**Mode**	**Current Options**	**Target Dosing** (Game-changers)
Treatment	Injectable	Monthly or bi-monthly	Twice-yearly; quarterly
Treatment	Oral	Daily	Monthly; weekly
PrEP	Injectable	Monthly or bi-monthly	Once-yearly; twice-yearly
PrEP	Oral	Daily	Monthly or weekly

LA Treatment Pipeline

Formulation	Details
Once-weekly oral regimen	• ISL/LEN positioned to be first once-weekly oral ART • Phase 2: comparable viral suppression to BIC/FTC/TAF at week 48 • No significant lymphocyte changes; well-tolerated • Enabled Phase 3 I-LAND 1 + I-LAND 2 studies, now enrolling
Weekly oral INSTI + LEN prodrug (GS-1720 + GS-4182)	• First weekly oral regimen combining INSTI + capsid inhibitor mechanisms • GS-4182: ~11-day half-life and 2× higher oral bioavailability vs LEN • GS-1720: ~9-day half-life; resistance profile comparable to BIC • WONDERS phase 2/3 trials in both naïve and VS populations
Monthly oral LEN prodrug (GS-3107)	• Substantially increases oral bioavailability of LEN (4-12-fold in animals). • Preclinical studies demonstrate sustained exposures enabling monthly dosing. • Human Phase 1 trial ongoing to assess safety and PK
Quarterly injectable (LEN + GS-1614)	• GS-1614 is an ISL prodrug with >28-day half-life in nonhuman primates • Delivers therapeutic ISL-TP exposure without CD4 or ALC reductions • Comparable safety profile across SC and IM administration in preclinical models • Phase 1 study ongoing
Twice-yearly injectables	• LEN + TAB + ZAB (two bNAbs): achieved proof-of-concept in phase 1b • High-potency INSTIs (GS-1219, GS-3242) show twice-yearly PK in NHPs; Phase 1 trial ongoing

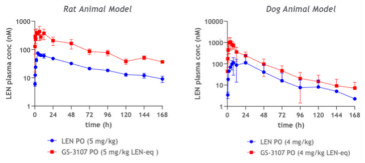
New LTZ Phase 2 Trial Data Presented at CROI 2025

Study design	Phase 2, randomized trial evaluating twice-yearly LEN + TAB + ZAB (LTZ) vs. continued daily oral ART
Population	• Suppressed (<50 copies/mL) on ART ≥1 year; CD4 ≥200 • More diverse than phase I: 80% US-based; 85% men; >1/3 Black; 1/4 Latino; median age ~51; mean CD4 749
Randomization	• 53 switched to LTZ regimen • 27 remained on daily oral therapy
Intervention	• LTZ group: oral LEN loading dose days 1-2 • LEN 927 mg SC Q6M • TAB 2550 mg IV Q6M • ZAB 2550 mg IV Q6M
Primary endpoint	Proportion with HIV-1 RNA <50 copies/mL at week 26
Efficacy	• 96% maintained suppression in both LTZ and control groups • Therapeutic bnAb + LEN levels maintained • CD4 increases similar between groups
Safety	• LTZ: no severe or serious drug-related AEs • ISRs most common (mild) • ~40% developed LEN depot nodules (minimal pain) • No infusion reactions • One oral-therapy participant withdrew due to metastatic pancreatic cancer
Interpretation	• Twice-yearly LTZ efficacy comparable to daily ART at week 26 • Study continuing to week 52
Regulatory	FDA Breakthrough Therapy designation granted in 2025 for LTZ

LA Prevention Pipeline

- Twice-yearly LEN PrEP demonstrated unprecedented efficacy in PURPOSE 1 and 2
- 96-100% reduction in HIV infections vs background incidence across diverse populations
- Majority of participants (73-93%) had never previously used PrEP
- Safety comparable across LEN, F/TAF, TDF/FTC arms
- ISRs mostly mild and decreased with successive doses
- 95% continued into open-label extension

Monthly Oral LEN Prodrug (GS-3107)



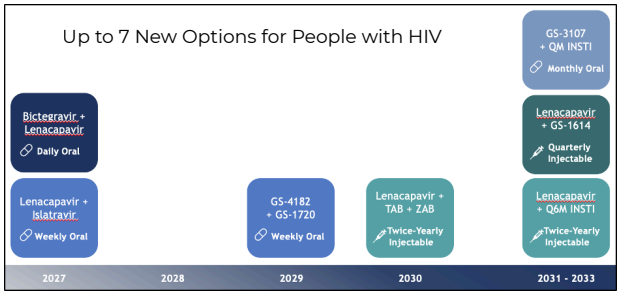
- Increased LEN oral bioavailability (4-12 fold in rats, dogs)
- Preclinical data: sustained exposures for monthly dosing
- Human Phase 1 trial ongoing to for safety and PK

PURPOSE: Update on Global Lenacapavir Regulatory Filings

- FDA accepted NDAs for lenacapavir for PrEP under priority review, with a PDUFA date of June 19, 2025.
- EMA validated Gilead's MAA and EU-M4all applications, both under Accelerated Assessment.
- EU-M4all is intended to support faster regulatory reviews outside the EU, including in low- and lower-middle-income countries.
- Gilead's global access strategy prioritizes speed and efficient regulatory pathways to expand worldwide access to lenacapavir for PrEP.
- Ongoing innovation aims to develop longer-acting injectable and oral formulations of lenacapavir for PrEP.

Twice-Yearly Injectables (LEN + TAB + ZAB)

Study design	Randomized, blinded, phase 1b proof-of-concept (11 U.S. centers)
Population	Adults with HIV-1 RNA <50 copies/mL, ≥18 months on ART, CD4 ≥500 cells/µL, susceptible to TAB and ZAB
Intervention	• LEN 927 mg SC + oral loading dose • TAB 30 mg/kg IV • ZAB 10 or 30 mg/kg IV
Participants	21 randomized; 20 treated; 86% male; age 25-61; median CD4 909 (IQR 687-1270)
Primary endpoint	SAEs through week 26
Safety results	No SAEs; 2 grade 3 ISRs (erythema + cellulitis, resolved); 85% any ISR; 60% grade 1 ISRs
Efficacy results	One viral rebound (10 mg/kg arm; resuppressed on ART); one withdrawal at week 12 with HIV RNA <50; suppression maintained through week 26
Interpretation	Regimen generally well tolerated; supports feasibility of twice-yearly long-acting ART in selected PLWH



Vivian Cox

Senior Medical Lead, TB R&D
Johnson & Johnson

Update on J&J's LA Formulations for Tuberculosis

"Dosing frequency must balance pharmacology with patient and clinic practicality – the number of injection sites per visit, visit intervals, and total injection volume."

Bedaquiline LA Formulation Phase 1 Treatment Trial

Study overview	• PK, safety, tolerability study of intragluteal BDQ LAI injections • 32 healthy participants (conducted at a European site) • Single ascending dose design • Group A: 2.5 mL (500 mg) • Group B: 5 mL × 2 injections (2 g total, 8 enrolled to date)
Safety	• Monitoring grade ≥3 AEs, SAEs • Legacy safety issues: QTc prolongation and transaminitis (from oral BDQ) • ISRs: pain, swelling, erythema, induration, nodules, abscess/necrosis • Pain assessed through VAS-A (5 min post-injection) and VAS-B at scheduled time points • Participant survey comparing daily pills vs one/two injections
PK	• Target exposure based on latent mouse model: ~0.3 µg/mL • Too early to estimate LAI bioavailability vs oral BDQ • PK sampling captures variability within and between participants • Coefficient of variation acceptable • ECG monitoring captures worst-case M2 metabolite Tmax

Draft LAI Target Regimen Profile for RR-TB disease

Target population	RR/MDR-TB in adults and children, PLWH co-morbidities
Forgiveness/adherence	Delay of injection up to 14 days does not influence treatment outcomes; dependent on number of injection visits
Number of component drugs	3-4 drugs, ≥2 are LAI and part of continuation phase
Dosing frequency	Intensive phase: 2 months hybrid oral-LAI regimen with cavity-penetrating agents • Lead-in for safety/tolerability/shift from positive to negative cultures • May allow loading to reach steady state faster Continuation phase: 2-3 drugs, once-off or monthly repeat injections • Acceptability depends on # visits • Volume ≤5 mL depending on ISR risk
Duration	2-3 months total; ≤3 LAI doses
Efficacy and safety	• Non-inferior to standard of care • Safety profile favorable for LAI development

Do different formulations (oral vs LAI) adequately deliver BDQ to lymph nodes, which are important reservoirs for TB infection?

- Uncertain BDQ/M2 penetration into LNs; lymphatic drainage pathways (popliteal vs iliac) complicate interpretation
- Comparing AUC_0-last tissue/plasma ratios for oral vs IM BDQ in tissues and draining/non-draining LNs
- Oral BDQ reaches LNs adequately; LAI BDQ may further improve LN exposure
- BDQ LAI cannot fully replace a 24 week oral treatment: oral lead-in regimen is required

Andrew Owen

CELT

University of Liverpool, UK

LEAP/CELT Workshop on BE Assessment and Generic Approvals for LA Antiretroviral Formulations

"It takes a long time between approval of innovator LA products and availability of generic versions … We have to do better."

Different regulatory authorities have different requirements; early engagement is critical.

Category	US FDA	WHO PQ
Guidance	Separate PSGs: one for CAB-LA and one for CAB oral	• July 2023 guidance on CAB-LA BE study requirements • Includes oral tablets in same guidance
Study duration	• Not reported in PSG • Single-dose parallel design recommended • FDA proactive on modeling; new ideas published	42 weeks; LAI: single-dose crossover or parallel design
Pre-submission meetings	• Depends on filing pathway (505(b)(2) vs ANDA) • Early engagement recommended for BE approach	• WHO PQ pre-submission meeting highly recommended • CSA pilot program through Research for Health also available
Device components	• Additional requirements for device constituent parts • Comparative analysis to RLD device for ANDA filings	• WHO does not have associated device component requirements • Reviews dossiers as drugs

FDA 505(b)(2) New Drug Application:

- Modification of approved product (e.g., new dosage form, strength, route of administration, formulation, or combination)
- Permits reliance on literature or FDA findings on safety/effectiveness for a previously approved product

FDA ANDA 505(j): Generic Products:

- Duplicate of approved product
- Need to determine pharmaceutical equivalence and BE

CELT Updates

- CELT is advancing nanoparticle engineering, injectables, microarray patches, scalable manufacturing
- Upcoming launch of HALo Hub (High- and Low-dose LA Therapeutics) led by Steve Rannard will expand fundamental research capacity for next-gen LA therapeutics
- CELT integrates PK modeling, preclinical systems, translational access planning

Key Takeaways

- It takes a long time between approval of innovator LA products and availability of generic versions (10-15 years)
- Need team approach and information access
- Generic manufacturers need to develop two LAI products rather than one (oral lead-in)
- Manufacturing LA products can be extremely complex
- BE studies not as straightforward as for orals
- Modelling and simulation have an important role to play
- BE may not be needed for all LA product types

Charles Flexner

Principal Investigator of LEAP
Johns Hopkins University

Accelerating Access Planning for LA HIV Treatments in LMICs (workshop overview)

"[This is an] important first step toward building a coordinated global framework for equitable access to long-acting HIV treatment in LMICs."

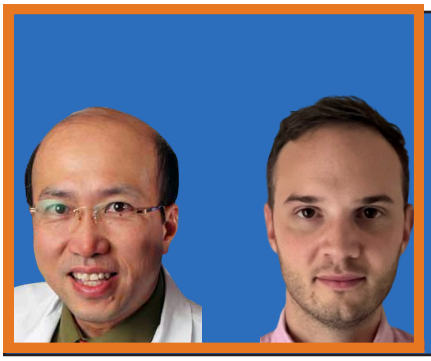
Global access meeting organized by Gates, NIH, PEPFAR, WHO, & CHAI

Goals

- Galvanize global action, momentum for LA HIV treatments in LMICs
- Align around a TAP for LA HIV treatment
- Develop shared understanding of how to accelerate the development and introduction of fit-for-purpose LA treatments for use in LMICs

Next Steps

- Establish coordinated global research agenda (working group already convened)
- Sustain multi-partner engagement to maintain momentum
- Publish a scientific viewpoint summarizing meeting outcomes (in progress).
- Publish TAP
- Develop market-sizing scenarios to guide investment, manufacturing
- Coordinate donor engagement for required studies
- Provide readout to pharmaceutical partners not present at the first meeting
- Generate new data on HIV community treatment preferences
- Investigate alternative dosing schedules, especially those not requiring oral lead-ins
- Track new LA combinations aligning with both TPP and TAP
- Explore extension of LA delivery platforms to other therapeutic areas



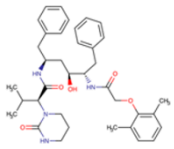
Rodney Ho & Simone Perazzolo

University of Washington

Development of Long-Acting TLD and Lopinavir and Ritonavir

"If successful, LA TLD could ultimately address the needs of the roughly 23 million people on TLD and 31 million on daily ART globally."

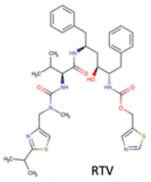
Lopinavir



LPV
Protease inhibitor

- Molecular Weight: 628.8 Da
- logP: 5.9
- pKa: 13.39
- Solubility (in water): 1.9 x 10^{-3} mg/mL

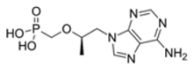
Ritonavir



RTV
Protease inhibitor

- Molecular Weight: 720.9 Da
- logP: 6
- pKa: 2.8 and 13.7
- Solubility (in water): 1.1 x 10^{-4} mg/L

Tenofovir



TFV
Nucleoside reverse transcriptase inhibitor

- Molecular Weight: 287.21 Da
- logP: -1.6
- pKa: 3.8 and 6.7
- Solubility (in water): 13,400 mg/L

TLC-ART 101 Phase 1 First-in-Human Trial (LPV/RTV + TFV)

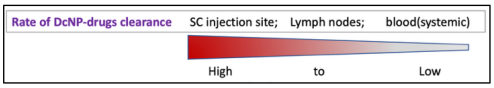
- Phase 1 study: 12 participants (1.5 mL, 3 mL, 4 mL SC injections)
- 1 injection dose to replace ~ 39g of LRT drug substances
- RTV = metabolic "booster" (potent CYP3A inhibitor)
- No excipient-only arm due to prior safety data
- All participants completed 64-day follow-up

TLC-ART Program engineers LAIs to be lymphatics-targeted and deliver three drugs simultaneously and directly into HIV target cells

- Overcome pill fatigue, stoppage, viral rebound
- Innovative approaches, early FDA input, community support (U=U now well-understood)
- TLC-ART 101: (LPV/RTV + TFV) – RTV is a metabolic "booster"

Why Target Lymphatics/Cells?

- DcNP formulations target lymph nodes and lymphocytes (where HIV resides)
- Approximately 70% of injected dose leaves injection site and distributes systemically into PBMCs (>plasma)
- High intracellular AUC in PBMCs: improved antiviral action and resistance suppression
- Cell-targeted delivery reduces local depot burden and ISRs



TLD-ART 301: LA TLD (TFV + 3TC + DTG)

- Goal: Transform daily oral TLD > once-monthly SC LAI
- Made possible by DcNP Technology
- Multi-drug matrices: synchronized delivery
- 1 injection replaces 30 pills
- IND-enabling studies underway with Unitaid support
- Formulation scalable + manufacturable
- Tech transfer to CMO

Oral vs SC LAI Pharmacology

Feature	Oral LPV/r + TFV	TLC-ART 101 LAI
Target of delivery	Plasma > PBMC	PBMC > Plasma
LPV duration	Short; booster-dependent	~2 months sustained
RTV role	Required for first-pass metabolism, CYP3A-labile	Minimal; rapidly cleared
Cell:plasma AUC	<1	>1 for all 3 drugs

Key Takeaways

- Monthly LA TLD feasible; could benefit millions globally
- Booster-free LA PIs may simplify combinations + reduce injection volume
- DcNP platform: sustained intracellular exposure + reduced drug load
- PK/PD modeling supports 3-drug dose selection
- Expansion of platform: development of LA HBV combination therapies

Andrew Owen

CELT, U Liverpool

Update from LONGEVITY

"It takes a long time to move from approval of an innovative long-acting product to approval of corresponding generics."

LONGEVITY program: LA formulations for HIV, HCV, TB prevention, other global-health priorities; nanoparticle formulation science; PK/PD modeling platforms; GMP scale-up via CELT; global partnerships; HALo Hub

LONGEVITY Target Indications

HCV Therapy	TB Prevention
Highly effective oral combinations: up to 98% SVR (randomized controlled trials)	Preventing active disease in LTBI is an essential public health intervention
Real-world SVR rates drop as low as 30-50% (observational studies)	Short-course regimens effective: 1-month RPT + INH as effective as 9-month INH (BRIEF TB trial)
Adherence challenges in daily oral regimens drive treatment failure	RPT monotherapy under study (ASTERoiD trial)
LA regimens may eliminate daily pill burden	• TB treatment: often requires complex multidrug regimens (especially DR-TB) • Single-agent regimens effective for prevention
LA therapies: test-and-cure model when paired with high-quality diagnostics	Demonstrated efficacy of shorter regimens: single-shot LAIs could be effective for TB prevention

	Research and preclinical POC	CDMO Translation	GLP Toxicology	Phase 1	Onward Licensing
LTBI (Rifapentine)	→	→	Q1 2025	2026/27	TBD
LTBI (Isoniazid-prodrug)	→		Q2 2025	2026/27	TBD
LTBI (Rifapentine / isoniazid MAPs)	→		TBD	TBD	TBD
HCV (glecaprevir / pibrentasvir)	→	→	Q2 2025	2026/27	TBD
Malaria (atovaquone / proguanil MAPs)	→		TBD	TBD	TBD

Hub for Advanced Long-acting Therapeutics (HALo)

Developing foundational physical sciences for LA formulations (Steve Rannard)

- Building industry + CDMO forums to strengthen translational ecosystems

Pharmacometrics Tools (Rajith Rajoli)

- PBPK modeling platform freely available via CELT
- Supports adult, pediatric, DDI, rat, mouse simulations

Community of Practice for Maternal & Pediatric Health

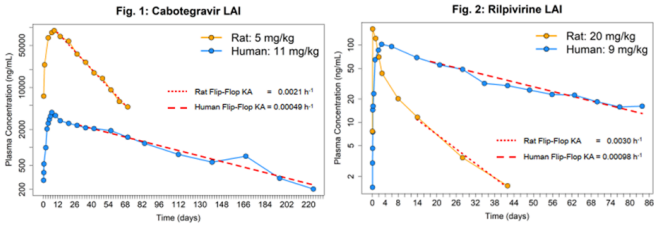
- Stakeholders: academia, clinicians, regulators, industry, patient groups
- Focus on reducing delays between adult + pediatric LAI availability
- Prioritizes LMIC needs, equitable access

Progress Snapshot

- Preclinical proof-of-concept achieved for LAIs: G/P FDC, rifapentine, INH prodrug
- Early success: microarray patches for malaria, LTBI
- GMP manufacturing across multiple formulations; GLP toxicology protocols
- Patient/provider surveys completed (strong acceptability for LAI)
- Patents filed; licensing executed with MPP
- Two pre-IND meetings with FDA; MHRA submission for LTBI filed; Phase 1 clinical protocols drafted

Vermeulen et al., IJTLD Open 2025

Preclinical Results



HCV POC	LTBI POC
LAI formulations: uniform particle size (150-200 nm)	RPT LAI: plasma concentrations > target for ~28 days (rats), ~14 days (mice)
Co-formulation: wide G/P ratios with single manufacturing process	Extended half-life expected to be longer in humans
Rodent studies: combination improves half-life for both APIs	LTBI mouse model: RPT LAI efficacy ~ to 1HP regimen
Dose proportionality maintained; liver:plasma ratios similar to oral regimens	Novel INH prodrug LAI: 15-20X extended half-life (rats)

Manufacturing Update

Formulation	Status & Key Milestones
RPT LAI	Method transfer complete; scaled to GMP; γ-irradiation terminal sterilization optimized; GLP tox batches in production
INH Prodrug LAI	Scaled synthesis from grams to kilograms; formulation robust; CDMO method transfer imminent
G/P LAI	Method transfer complete; process scaled for GMP; γ-irradiation optimization underway

Elizabeth J. Phillips

John A. Oates Chair in Clinical Research Director, Vanderbilt University

Hypersensitivity Reactions to Lipid-Based Excipients in Long-Acting Formulations

"Lipid-based excipients are common in long-acting formulations and can cause hypersensitivity reactions ranging from mild local responses to systemic effects."

Lipid-Based Excipients in Long-Acting Formulations

Excipient	Notes
PEG	Common in lipid nanoparticles; can trigger complement activation–related pseudoallergy (CARPA); example in HIV = CAB/RPV; also in COVID-19 mRNA vaccines
Polysorbates	Rare cause of true IgE-mediated allergy
Phospholipids	Generally well tolerated; rare IgE-mediated reactions

What are LA-Related Hypersensitivity Mechanisms?

Mechanism	Features	Diagnostic Information	Incidence
IgE-mediated anaphylaxis	Requires sensitization; rapid-onset severe reactions (urticaria, angioedema, bronchospasm)	↑ Tryptase (30-90 min), positive skin tests for PEG/polysorbates	Rare, more common with non-lipid PEG formulations
Non–IgE mast cell activation	Direct activation, irritant effects, or mas-related G-protein-coupled receptor X2-mediated responses	Variable markers; diagnosis often clinical	
CARPA (complement activation-related pseudoallergy)	Triggered by PEGylated or liposomal drugs; anti-PEG IgM/IgG involvement	Complement markers ↑ (5-60 min), normal tryptase in animal models as way to induce tachyphylaxis to CARPA	Uncommon, but systemic reaction

TLCA-RT-101 (LA combination of LPV/RTV/TFV using lipid nanoparticles shows similar hypersensitivity risks as liposomal anthracyclines.

In a Phase 1 trial (n=12), injection site reactions were common: 10/12 participants experienced immediate local reactions (grade 1–2).

Reaction Type	Observations
ISRs	10/12 participants; immediate grade 1-2 local reactions
Systemic reactions	5 participants had anaphylaxis, lip swelling, rash, or pruritus
Laboratory findings	Normal tryptase → non-IgE mechanism (likely complement activation)

Key Takeaways

- Lipid-based excipients can cause hypersensitivity ranging from mild ISRs to systemic reactions
- CARPA is predominant mechanism; IgE-mediated reactions remain rare
- Mitigation strategies include gradual exposure, premedication, improved excipient design, predictive diagnostics

Rahima Benhabbour

Associate Professor, UNC Chapel Hill
Founder & Director, Anelleo, Inc.

Preclinical Development of ULA Formulations

"To our knowledge, this represents the longest duration of protection ever demonstrated in non-human primates with a single injection."

The Benhabbour laboratory develops polymer-based, ULAI platforms for HIV PrEP + multipurpose prevention technologies. ISFI system enables sustained drug release well beyond currently approved LA products.

ULA HIV Prevention: Platform Technologies

- ISFIs form biodegradable depots enabling tunable drug release
- Support combination delivery of ARVs and contraceptives
- Depot removal allows rapid reversal of drug effects

Young et al., Nat Comm. 2023

ULA ARV Technologies

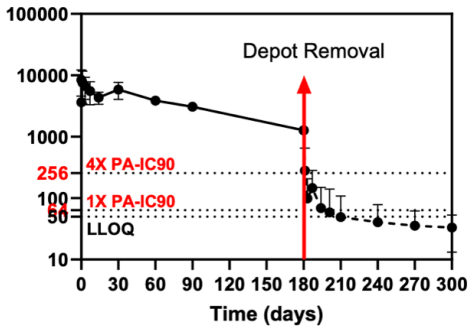
Program	Preclinical Findings
ULA CAB (ARCH-LA)	• Single CAB ISFI injection:100% protection against 38 SHIV challenges over 6 months in macaques • Longest protection ever documented from a single CAB dose
ULA DTG	• Mouse studies:>2 years sustained DTG exposure after implantation • Implant removal rapidly reduces drug levels • ~40% of depot drug remains at 6 months
Co-formulated MPT implants (ARVs + hormonal contraceptives)	CAB or DTG co-formulated with ENG (etonogestrel) or MPA (medroxyprogesterone acetate) ARV levels remained >4X PA-IC90 for ≥90 days MPA cleared within 24 hours after implant removal

LA MPTs expand preventative options, bringing choice and empowerment to women and girls, and make a global impact in women's sexual and reproductive health.

Key Takeaways

- ISFIs allow UL durations (months → years)
- Removable depots reduce pharmacologic tail
- Enable combination ARV + contraceptive MPTs

PK Tail After Implant Removal



Benson Edagwa

Community Pride of Nebraska Professor
Co-Founder, Exavir Therapeutics Inc.
and Aion Medicines Inc.

Ultra-Long-Acting Slow Effective Release Therapies

"Using this approach, we can administer a very small dose and achieve sustained drug exposure for up to four months."

Technology Platform for Scalable, Transferable Manufacturing

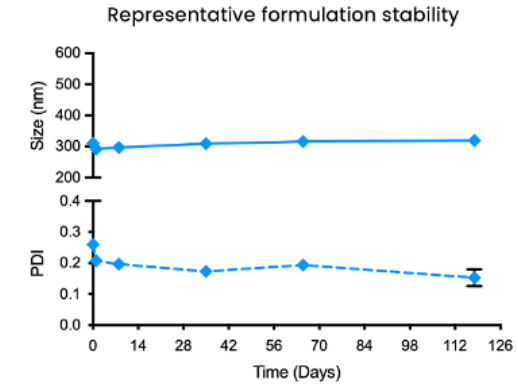
- Aqueous suspension with stabilizers
  - Long-term storage
- Scalable
- Indications: HIV, HBV, metabolic disease, addiction medicine
- Platform applied to many therapeutics
- Developed ULA GLP-1 agonist lasting 3-6 months
  - May help address weight-gain issues associated with integrase inhibitors

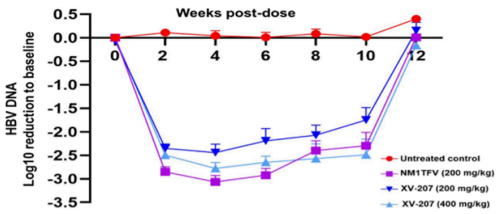
Advances in LA DTG Prodrugs

- Monomeric DTG strategy produced low DTG plasma exposure in rhesus macaques
- Solution: Dimeric DTG prodrug (XV-122) achieving ~4 months sustained higher DTG exposure with very small dose (~50 mg/kg)
- XV-122/XV-207 could support self-administration for HIV and HIV/HBV co-infection
- Uses same aqueous suspension manufacturing approach as Apretude (CAB-LA)
- Highly relevant globally, including pediatric use (for children, LA formulations not available)
- Program is being advanced by Exavir Therapeutics Inc

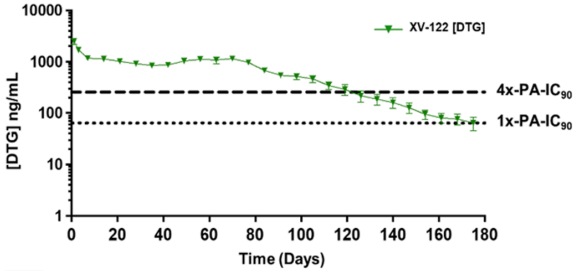
LA Tenofovir (Second-Generation to Combine with LA DTG)

- Developed high-concentration (~300 mg/mL) aqueous formulation
- Single injection of XV-207 suppresses HBV DNA for > 2 months
- Also developed prodrug of buprenorphine that sustains therapeutic drug levels in rats for up to 6 months after a single injection
- May help reduce opioid dependence and minimize HIV transmission in vulnerable populations





XV-207 has demonstrated in vivo proof of concept against HBV in preclinical models



Plasma DTG levels after a single dose of XV-122

Anil Gupta

Director of Medicinal Chemistry, Scripps/ CalibrSkaggs Institute

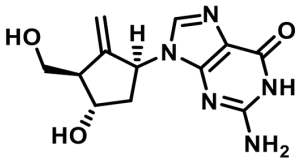
Long-acting Entecavir for the Treatment of HBV

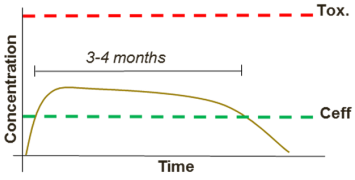
"We believe we've made significant progress in developing a viable long-acting entecavir prodrug."

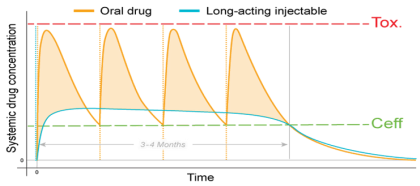
Why Pursue a LA ETV?

- Standard HBV therapies (ETV, TFV, ADV) require daily dosing; adherence is low
- LA dosing could Improve adherence and clinical outcomes
- ETV has favorable potency (IC50 0.5 nM), low clearance, low protein binding

Workflow for LA ETV







A LA ETV prodrug for chronic HBV TPP aims for 1-3 months therapeutic coverage from a single SC or IM injection. Early formulation challenges prompted a shift from oil-based ETV suspensions to a structured prodrug strategy.

ETV Prodrug Development

- 30 ETV prodrugs (esters and carbonates) synthesized
- Solubility measurement, formulation development, follow-up PK studies of selected prodrugs
- Most esters still exhibited poor solubility in oil-based vehicles
- ETV has a high melt (~298°C by differential scanning calorimetry)
- API formulation shows modest clearance, but good potency allow for low injection volumes; relatively high Cmax is an issue
- Aim to further reduce Cmax

CBR-457 is the optimized LA ETV prodrug showing stability and multi-species favorable PK.

Species	Dose	Outcome
Mouse	100 mg/kg (SC/IM)	ETV levels above Cmin for ~21 days
Dog	37 mg/kg (IM)	Exposure up to 3 months; delayed, reduced Tmax
Dog	2 mg/kg (SC/IM)	~1.5 months coverage at clinically relevant dose
All	—	No ISRs observed

Next Steps

- Finalize CBR-457 optimization
- Repeat-dose toxicology studies
- Advance to human dose projection + modeling
- Evaluate manufacturability for scalable CDMO transfer

Lobna Gaayeb (MPP) & Adeniyi Olagunju (U Liverpool)

LA Therapeutics: Digital Tools for Informed Decisions

"When we work together, we can work faster and better."

Key Features
Side-by-side LA technologies comparison tool (e-commerce style)
Filter/search by health area, type of technology, targeted age group, API, developer, disease, route, dosing interval
Export data into spreadsheets
World maps of patents coverage, clinical trial sites, global approvals
Mobile-friendly interface with QR code access

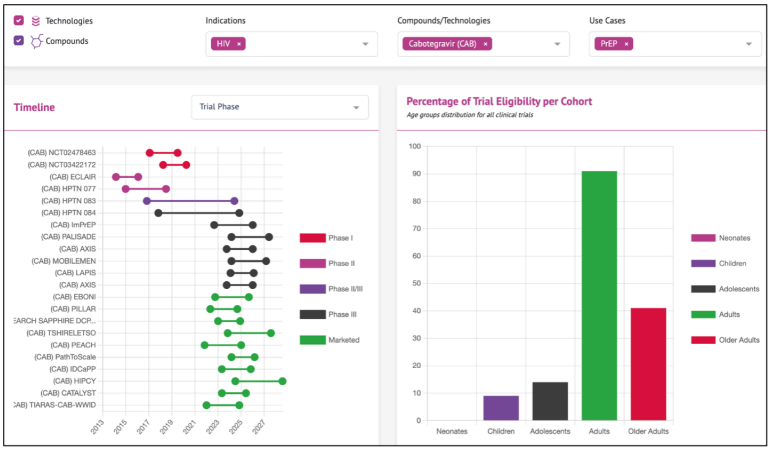
LAPaL (Long-Acting Therapeutics Patents & Licenses database) is a free, collaborative, data-driven tool that centralizes information on LA technologies, compounds, formulations, IP, clinical development, and regulatory activities for therapies that could have major impact in LMICs. LAPaL covers LA therapeutics across disease areas, development stages, and formulation types.

LAPaL

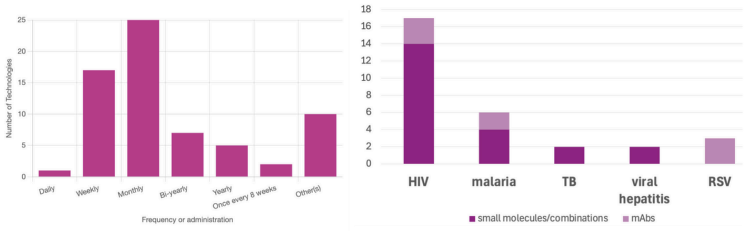
Category	Description
Health areas	HIV, TB, malaria, contraception, oncology, diabetes, mental health, pain, SUDs, other NCDs
Entry types	LA platforms, compounds; combinations with different administration routes, dosing intervals, population targets
Innovators	Universities, research institutes, startups, large pharma, nonprofits, consortia
Development stages	Preclinical to marketed products

Data Category	Examples
Formulation	Solubility, polymorphs, physicochemical profile, API compatibility
IP landscape	Global patents, licenses, enforcement status by income group
Clinical	Timelines, locations, phases, age eligibility, indications
Regulatory	Approvals, submissions, regional status
Applications	Disease areas, dosing intervals, administration routes, platform adaptability

Clinical Trials Dashboard



Dosing Intervals and Indications of Selected LA Formulations in LAPaL



People can contribute to LAPaL, co-create opportunities, and accelerate innovation in long-acting health products to address public health gaps.

What's Next?

- Integration with revamped LEAP website to create a unified communication hub
- Expansion to 30 technologies and 50 formulations by mid-2025
- Launch of stakeholder survey to inform redesign

Toward a collective agenda to advance the long-acting field.

Four 15-minute Focus Groups preceded the 2025 Annual LEAP Workshop and were intended to foster informative and provocative discussion of strategically selected topics, listed below. The highlights and recommendations from each focus group were presented. Attendance for these sessions was limited.

Focus Group 1
Self-Administration of LA Formulations

Focus Group 2
Drug Combinations for LAI Treatment

Focus Group 3
Management of Injection Site Reactions

Focus Group 4, Part 1
Update on WHO LA TPP

Focus Group 4, Part 2
TPP & TAP of LAIs for Global Use

FOCUS GROUP 1

Rapporteur

Imelda Mahaka

Pangaea Zimbabwe AIDS Trust

Co-Chairs

Raphael Landovitz

UCLA

Kenly Sikwese

AFROCAB

Self-Administration of Long-Acting Formulations: Is it a Good Idea?"

- Potential but uncertain
- Practical barriers
- Next steps

What is the landscape for self-administration?

- Mix of excitement and wariness for LAIs for HIV prevention and treatment
- Many candidates (IM, SC) nearing regulatory approvals or completed Phase 3 trials
- All approved are for healthcare provider administration
  - Requires contact with already strained health systems; variability in nurse injection skills
- Concerns about sterility, refrigeration, and self-injection competency
- Perception that injections are stronger than pills may increase acceptance
- Injection technique affects many things: tolerability, ISRs, PK

Are there specific groups that would benefit from self-administration more than others?

- Modelling can provide simulation of scenarios (dose, intervals) on how to understand feasibility
- Discrete choice experiments study people's preferences by asking them to choose between different hypothetical options that vary in key attributes

"Is self-administration of LA formulations a good idea? Our group's answer was: we're not sure yet. But with continued research and collaboration, we'll figure it out."

Participants recognized major potential benefits – more convenience, reduced clinic burden, and expanded user choice – but also noted significant concerns. Current LAIs are technically difficult to administer; even healthcare workers show inconsistent technique. Communities raised practical worries about safety, emotional readiness, storage, and sterility. Evidence from LMIC surveys showed low enthusiasm for self-injection, though alternative delivery platforms (patches, prefilled devices) may improve acceptability. Any move toward self-administration should consider better formulations, stronger support systems, user-preference data, and studies explicitly evaluating self-care.

Are there lessons learned from other therapeutic areas?

- Need for alternative self-administration methods for simple, comfortable, and safe
- LA contraception (e.g., DMPA) good example of high acceptability in LMICs
- Outside HIV, self-injection exists (e.g., interferon, heparin) but with smaller injection volumes
- PATH is advancing patches and devices; surveys show patches are acceptable after training prefilled
- Ongoing work will test whether current devices can handle LEN-level viscosity
- Weekly autoinjectors for insulin/GLP-1s increase costs in HICs
- Choice and dosing frequency will heavily influence uptake

Potential Implementation Challenges

- How to know if a person can self-inject correctly and safely before transitioning out of clinic-based care?
- How to ensure compliance? Reminders, triage to clinics, manufacturer or helplines/online support?
- How to monitor outcomes?
- Should self-administered LAIs be packaged with accompanying tests, such as STI screening, pregnancy tests?
- What is the optimal clinic visit frequency when self-administration is used?
- Provider comfort and buy-in is a big factor determining the feasibility of self-administration programs
- Past experience with self-administered DMPA shows potential resistance if providers perceive threats to their clinical role

FOCUS GROUP 2

Rapporteur

Ethel Weld

Johns Hopkins University

Co-Chairs

Cissy Kityo

Joint Clinical Research Centre, Uganda

Melynda Watkins

CHAI

Combinations for LAI Treatment: What makes a Good Partner?

- PK Compatibility
- Dosing Schedules
- Partnerships

What Makes a Good LA Drug Partnership?

Timeframe	Candidate Partners	Notes
Now	Q6mo LEN + Q2mo CAB-LA	8 injections/year; 6 visits/year; available now
Medium term (tweak dosing, add late-pipeline products)	Q4mo LEN + Q4mo CAB-ULA	6 injections/year; 3 visits/year; needs modeling
Medium term	Q4mo LEN + Q4mo CAB-ULA	5 injections/year; 4 visits/year; not aligned
Medium term	Q6mo LEN + Q3mo CAB-ULA	6 injections/year; 4 visits/year; partial alignment
Long term	Q6mo LEN + Q12mo CAB prodrug (VH310)	3 injections/year; ~2 visits/year; first-in-human study planned for 2025
Long term	LEN + ISL (NNRTTI) or LA orals	Combination of 2 injections/year + 52 pills/year possible

Selected Studies of LA Partners

Study Name	Design/Purpose	Sample Size/ Accrual	Findings/ Contribution	Comments
ISL+LEN Ph 2	**PO once weekly** ISL + LEN vs. BIC/TAF/FTC	**104/104**	HIV VL <50 c/mL (wk48): ISL/LEN 49/52 **(94.2%)** B/F/TAF 48/52 (92.3%)	Mean change from baseline in CD4+/ lymphs: **ISL + LEN** -12/µL/-0.07x 10^3/µL **B/F/TAF** -29/µL/-0.03 x 10^3/µL (P=0.88; P=0.23)
GS-1720 + GS-4182 (t1/2 9 days,11 days)	**Oral once weekly** INSTI+PO LEN prodrug vs B/F/TAF	?/675	Pending completion (est. 2030)	
Ward 86 pilot case series	**Q26wk LEN SC + Q1-2mo CAB IM**	**34** (76% male; 71% on q8wk)	HIV VL < 75 c/mL: 32/34 (94%) at 4-16 weeks	Short follow-up period 47% w **VS** at entry
Paris pilot study	**LEN SC + CAB q2mo IM**	8 (VS, RPV-R)	8/8 maintained VS	Ppts preferred to oral rx
LEN + q6mo bNAbs	**LEN + IV teropavimab** and **zinlirvimab (30 mg/kg)**	16	15/16 (94%) had VS at 26 wks.	Higher dose more effective Susceptibility to either/both
GS-1614 (ISL prodrug) + GS-6212	**NRTTI prodrug + INSTI Q3mo IM**	Phase 1b	*Pending*	
Ph 1	**CAB-ULA Q 4mos SC/IM (healthy volunteers)**	48	*Pending*	

/S=virally suppressed PNP=Postnatal Prophylaxis HEU=HIV Exposed Uninfected CK=creatine kinase ISR=Injection Site Reaction DcNP= drug combination nanoparticles y.o.'s=year-ol

bNAb Partnerships

- ENABLE trial: infants with HIV using SC bNAbs + oral ART
- Potential LA partners: CAB + N6-LS; LEN + TAB + ZAB

DDIs by Route

- SC LPV shows distinct PK; may not require RTV booster; thus fewer DDIs
- IM RPV avoids gastric pH dependency seen in oral RPV
- Injection-based DDIs differ substantially from oral formulations

Dosing Cadence

- Several LA products in development target 6-month dosing intervals
- Others aim for 4-month or 3-month intervals, with additional once-weekly oral partnerships emerging
- Studies show strong suppression with Q26-week SC LEN plus Q1-2-month IM CAB, including a Paris case series where all injection recipients remained suppressed
- RPV- related limitations of LA CAB/RPV: high baseline VL, cold-chain needs, lack of formulation stabilization, supply-chain and licensing barriers, NNRTI resistance risks
- Need LA options for people who are not virologically suppressed
- Microarray patches: high acceptability in pediatric populations
  - RPV cannot be formulated into a reasonably sized patch; ISL and LEN are other options

"In terms of number of partners, we're usually talking about two-drug regimens; we're no longer in the era of "thruples."

Discussion focused on PK compatibility, harmonized dosing intervals, and mechanistic complementarity, noting that most successful two-drug regimens include a strong INSTI. Limitations of CAB/RPV were highlighted, especially challenges with RPV. Emerging partners include LEN, ULA CAB, CAB prodrugs like VH310, and bNAbs. The group emphasized synchronizing dosing schedules, developing options for unsuppressed people, and exploring microarray patches. They also underscored the value of cross-company collaborations to align dosing intervals across HIV and other therapeutic areas.

LA Partners Need Harmonization for Dosing Schedules

Timeframe	Candidate Partners	Notes
Now	Q6mo LEN + Q2mo CAB-LA	8 injections/year; 6 visits/year; available now
Medium term (tweak dosing, add late-pipeline products)	Q4mo LEN + Q4mo CAB-ULA	6 injections/year; 3 visits/year; needs modeling
Medium term	Q4mo LEN + Q4mo CAB-ULA	5 injections/year; 4 visits/year; not aligned
Medium term	Q6mo LEN + Q3mo CAB-ULA	6 injections/year; 4 visits/year; partial alignment
Long term	Q6mo LEN + Q12mo CAB prodrug (VH310)	3 injections/year; ~2 visits/year; first-in-human study planned for 2025
Long term	LEN + ISL (NNRTTI) or LA orals	Combination of 2 injections/year + 52 pills/year possible

What's On the Wish List for the Future?

- Cross-company collaborations to create "economies of cooperation"
- Earlier, better pediatric inclusion; equity focus
- Align LA-ART with other therapeutic partners: contraception, SUD, schizophrenia, TB, HBV
- Develop LA options with fewer side effects + easier delivery systems

"The LA pipeline is moving rapidly – the future is already arriving."

Key Takeaways

- Partners now: Q6mo LEN + Q2mo CAB; complete LA regimen remains limited by RPV
- Medium-term partners: CAB-ULA, ISL-based combinations, partial interval alignment
- Long-term partners: CAB prodrug (VH310), bNAbs q6-12mo, novel platforms
- Data gaps persist across PK, pediatric use, DDIs, feasibility

FOCUS GROUP 3

Rapporteur

Rachel Bender Ignacio

University of Washington

Co-Chairs

Monica Gandhi

UCSF

Laura Waters

Gilead

Management of Injection Site Reactions

- Tolerability
- Injection Technique
- Optimizing Practices

CAB and RPV ISRs: What's the Clinical Experience?

- Pain is more common than nodules or itching; people describe it as tolerable and rarely dose-limiting
- Real-world ISRs may be more frequent due to variation in injection technique and experience
- Nurses reported clear differences in immediate vs delayed pain between RPV and CAB
- Injection site selection varies; ventrogluteal site is increasingly preferred over dorsogluteal

Person-Centric Approach Can Minimize Impact of ISRs

- Prepare people for expected ISR frequency and severity
- Ask about prior injection experiences and tailor comfort strategies
- Provide information in multiple formats
- Keep CAB and RPV on consistent sides to track ISRs
- Encourage gentle movement after injection (walking, light motion – not vigorous exercise)
- Ultrasound guidance and correct depth reduce pain and prevent SC injections
- Longer needles help ensure IM delivery and lessen discomfort
- Prefer ventrogluteal over dorsogluteal injection sites
- Adjust techniques or sites if ISRs become problematic ("one size does not fit all")

What Do We Still Not Know?

- Alternative injection sites (thigh, upper arm) may yield similar or higher LEN exposures but are not yet FDA-approved
- Need evidence on optimal injection sites for children and low-BMI individuals
- Local hypersensitivity reactions can occur with lipid nanoparticle formulations (per Dr. Phillips and TLC-ART data)
- Some implants show local skin and soft-tissue toxicity, including with TAF and ISL
  - ISL implant discontinued due to lymphopenia concerns
- Questions remain about in-situ forming implants in preclinical studies – will they be well tolerated at the injection site?
- Unclear best management strategies for significant LEN leakage
- Need data on stigma from LEN nodules

Injection Site Reactions

"Injection site reactions are extremely common, but they tend to lessen over time… Pain is by far the most frequent complaint."

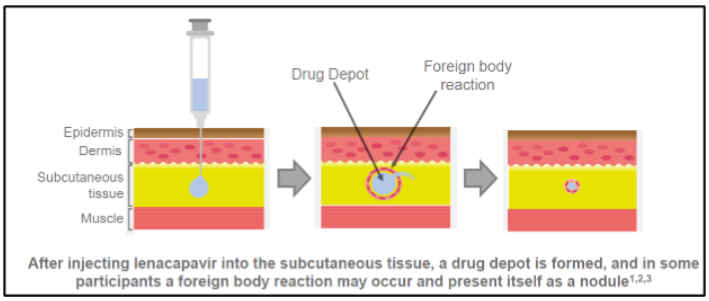
Injection-site reactions with CAB/RPV are extremely common but usually lessen over time; pain is the most frequent symptom, and technique strongly influences tolerability. Ventrogluteal injection, the Z-track method, slow delivery, site rotation, and patient preparation all improve comfort. For LEN, the palpable SC depot is expected, not pathological, and correct depth prevents burning and leakage. Supportive measures include compresses, analgesics, and consistent staffing. Outstanding questions include optimal pediatric sites, managing leakage, stigma from nodules, and sharing best practices.

Injection Site Considerations

Technique / Tool	Impact
Z-track method	Reduces leakage and ensures proper IM deposition
Slow injection speed (10 sec/ml)	Decreases pain and improves drug retention
Ultrasound guidance	Reduces likelihood of shallow/SC misadministration
Needle length optimization	Helps ensure consistent IM depth across body sizes

LEN Injection: Key Techniques

- LEN is oily and can leak without proper technique, causing burning, staining clothing, and loss of product
- Provide ice and analgesics before injection and/or topical lidocaine pre-injection
- Consistent staffing improves injection skill and patient trust
- Avoid injecting into dermis/epidermis; shallow delivery causes significant burning
- Use a true 90° angle to ensure proper SC depth + to prevent leakage during insertion/withdrawal
- Nodules are expected (a depot feature), some may persist longer than local PK; should be normalized with patients
- Bioequivalence study: similar or higher exposure (Cmax, AUC) from abdomen, thigh, or upper arm
- Alternate sites are not FDA-approved but may be considered in low-adipose individuals



After injecting lenacapavir into the subcutaneous tissue, a drug depot is formed, and in some participants a foreign body reaction may occur and present itself as a nodule[1,2,3]

Key Takeaways

- ISRs are the norm, not the exception
- Technique quality drives tolerability
- LEN depot is expected
- More data needed on alternative sites
- Set expectations for optimal adherence
- Prioritize training and standardization
- Reassurance prevents unnecessary clinical visits
- Could improve access for people with diverse body types

FOCUS GROUP 4 - Part 1

Rapporteur

Raj Gandhi

Mass General Hospital

Chair

Paul Domanico

CHAI, on behalf of Marco Vitoria

Target Product and Target Access Profiles of LAIs for Global Use

- **Products and Future Guidance**
- **Community Engagement**
- **Feasibility**

"A major focus will be capturing community voices – defining key parameters, determining how to weigh them, and prioritizing the drivers that will shape both the TPP and the TRP."

WHO is actively updating its LA ARV TPP as product portfolios mature. LA formulations bring both promise and challenges for treatment and PrEP implementation.

Domain	Considerations (Draft)
Clinical factors	High barrier to resistance; suitability for diverse populations
User perspectives	Ease of use, reduced stigma, alignment with user preferences
Pharmacologic factors	Dosing interval, durability, DDIs
Programmatic factors	Cost equivalence to current options; feasibility in LMIC settings

LA ARTs

- Key advantages: Improved adherence, fewer treatment interruptions, greater convenience, and better quality of life
- Public health impact: Reduced transmission risk and lower burden of opportunistic infections and comorbidities through sustained viral suppression
- Targeting challenges: Need to accurately identify priority populations and account for social and demographic factors influencing uptake
- Implementation barriers: Product-specific limitations, delivery logistics, and healthcare provider readiness
- Value considerations: Balancing individual preferences with system constraints and demonstrating long-term value despite higher upfront costs

FOCUS GROUP 4 - Part 2

Rapporteur

Raj Gandhi
Mass General Hospital

Co-Chairs

Paul Domanico
CHAI, on behalf of Marco Vitoria

Michael Reid
UCSF

Target Product and Target Access Profiles of LAIs for Global Use

- Prioritizing Populations
- Weighing Evidence
- Enhancing Access

Defining Priority Populations for LA Agents: Who Stands to Benefit Most?

Population	Rationale
Children & adolescents	High adherence challenges with oral ART; LA options needed
Pregnant & postpartum women	High vulnerability; adherence drops during postpartum period
People with adherence barriers	Homeless/refugee populations, people who inject drugs
Future: All PLWH	Goal is equitable access to LA therapies for all

What Don't We Know?

- Determine optimal use of LEN + CAB as LA treatment for people with viremia
- Understand interactions between LA ARVs and TB regimens (particularly rifamycins)
- Develop agents with non-overlapping resistance profiles vs. drugs used for PrEP
- Advance oral LA regimens with very infrequent dosing
- Develop safer options for pregnancy and breastfeeding
- ·Study cycling on/off LA therapy and long-term consequences
- Ensure HBV screening before switching from TFV-containing regimens

Ongoing Trials

Study	Design & Population	Research Question
PALACE (ACTG A5431)	Single-arm proof-of-concept of LA LEN + LA CAB for participants with NNRTI resistance, viremia, and adherence challenges	Does LEN+CAB achieve viral suppression in high-risk, ART-experienced individuals?
LANCET (ACTG A5433)	Phase 3 randomized trial of PLWH and viremia on TLD; compares standard care with LA LEN + LA CAB	Can LA therapy outperform enhanced adherence counseling and PI-based ART?

Key Challenges & Targets for Long-Acting ART

- DDIs with TB therapy, especially rifamycins; people developing TB on CAB need to transition to DTG-based oral ART
- Need LA agents with fewer interactions, including compatibility with TB regimens
- Need synchronized dosing schedules (e.g., weekly or monthly orals; 6-12-month injectables)
- Develop LA options safe for pregnancy and breastfeeding
- Improve usability: easy delivery, potential for self-administration, fewer ISRs
- Screen for HBV before non-TFV regimens and study long-term cycling on/off LA therapy
- Ensure post-trial access to LA therapies, especially in LMIC studies
- Ideal LA treatment agents should avoid resistance overlap with PrEP drugs (TDF/FTC, CAB, LEN)
- Precedent exists for overlapping resistance in prior regimens (e.g., EFV/NVP)
- Target: new LA agents with non-overlapping resistance profiles

"Our priority populations today are those with adherence challenges and other high-risk groups, but the ultimate goal is long-acting options for all."

Participants emphasized that those with the greatest adherence difficulties – children, adolescents, pregnant/postpartum women, and people with viremia – should be the first to benefit. Two upcoming ACTG studies of LA LEN + CAB were highlighted, along with questions about drug resistance, TB treatment interactions, pregnancy use, and oral LA options. Implementation barriers – including affordability, delivery systems, training needs, and future generic access – were discussed in addition to global funding uncertainty. Ultimately, the group called for scalable, synchronized, affordable LA regimens that can reach all people who need them.

What is the Elephant in the Room?

Global funding uncertainty and supply disruptions threaten the ability to procure and deliver essential medications. This heightens the importance of generating strong evidence for Ministries of Health on the value and impact of long-acting regimens.

Implementation and Market Access Challenges and Targets

Issue	Key Points
Cost & affordability	• LA regimens: drug costs + delivery/training costs (clinics, workforce) • Generics expected ~2027-28 may lower drug costs, but delivery costs will remain
Dosing frequency targets	• Oral ART enables 6-month dosing • Target for LA agents: dosing every ≥6 months
Safety & usability targets	• Need fewer injection-site reactions and fewer DDIs • Develop products requiring minimal training or allowing self-administration
Populations & implementation needs	• Address challenges in children, adolescents, pregnancy, and breastfeeding • Phase 3 trials required for regulatory approval of novel LA regimens
Market & manufacturing	• Need incentives for multiple generic manufacturers to produce LA regimens • Economies of scale possible with large-population use; market guarantees may help

LA Therapies: Future Directions

Target Area	Future Goal
Dosing frequency	≥ 6-12 months or longer, similar to contraceptive implant evolution
Delivery systems	Simplified administration; potential for self-administration
Drug interactions	Agents compatible with TB therapy and fewer DDIs
Formulations	Options safe for pregnancy, breastfeeding, and children/adolescents

Key Takeaways

- Priority populations
  - Now: People with adherence challenges; adolescents; pregnant + postpartum women
  - Future: LA options suitable for all populations
- Knowledge gaps & research needs
  - Now: Evaluate LEN + CAB for people with adherence barriers; expand research in children, adolescents, and pregnancy
  - Future: Develop agents with fewer interactions/side effects, longer dosing intervals, and easier delivery
- Implementation & market access
  - Ongoing: Affordability, delivery systems, workforce training, incentives for generic manufacturers remain essential for scale-up

Long-Acting/Extended Release
Antiretroviral Research Resource Program