2021 INVESTIGATOR MEETING & ANNUAL WORKSHOP

VIRTUAL
MARCH 5, 2021

leap

Long-Acting/Extended Release
Antiretroviral Research Resource Program

ABBREVIATIONS

ARV antiretroviral
ART antiretroviral therapy
BIC bictegravir
bNAb broadly neutralizing antibody
CAB cabategravir
cART combination antiretroviral therapy
CHAI Clinton Health Access Initiative
CMC chemistry, manufacturing and controls
COGS cost of goods sold
DAA direct-acting antiviral
DDI drug-drug interaction
DMPK drug metabolism & pharmacokinetics
DTG dolutegravir
ER extended-release
FDA Food and Drug Administration
FTC emtricitabine
GLAD Global Long-Acting and Drug combination products
GLP good laboratory practice
GMP good manufacturing practice
HBV hepatitis B Virus
HCV hepatitis C Virus
HIV human immunodeficiency virus
HPTN HIV Prevention Trials Network
IM intramuscular
INH isoniazid
IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials
INSTI integrase strand transfer inhibitor
ISL islatravir
LA long-acting
LAI long-acting injectable
LEAP Long-acting extended-release Antiretroviral research resource Program
LEN lenacapavir
LMIC low-to-middle income country
LPV lopinavir
LTBI latent tuberculosis Infection
mAb monoclonal antibody
MPP Medicines Patent Pool
NHP non-human primate
NRTI nucleoside reverse transcriptase inhibitor
NRTTI nucleoside reverse transcriptase translocation inhibitor
OLI oral lead-in
PBPK physiologically based pharmacokinetics
PBMC peripheral blood mononuclear cell
PD pharmacodynamics
PEP post-exposure prophylaxis
PK pharmacokinetic
PLWH people living with HIV
PrEP pre-exposure prophylaxis
RLS resource-limited setting
RPV rilpivirine
RTV ritonavir
SC subcutaneous
SIV Simian immunodeficiency virus
TAF tenofovir alafenamide
TB tuberculosis
TDF tenofovir disoproxil fumarate
TFV tenofovir
TLC targeted long-acting combination
TLD tenofovir, lamivudine and dolutegravir

CONTENTS

Where will we LEAP next?

On March 5, 2021 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 in the development of LA formulations. The meeting served as a forum to collectively advance the field.

The investigator meeting began with opening remarks from Drs. Carl Dieffenbach and Charles Flexner, which were followed by two plenary sessions comprising presentations on existing and novel LA technologies and approaches. The meeting was preceded by four 90-minute focus groups intended to foster informative and provocative discussions on strategically selected topics: 1) LA formulations for viral hepatitis, 2) Lessons learned from development of LA antiretrovirals for HIV prevention, 3) LA monoclonal antibodies for treatment and prevention of HIV and SARS-CoV-2, and 4) Advancing the inclusion of key populations in the development of LA formulations.

This report summarizes the plenary session presentations and includes highlights and recommendations from each focus group discussion.

OPENING REMARKS

Carl W Dieffenbach

Director of the Division of AIDS at the National Institute of Allergy and Infectious Diseases

Welcomed attendees, emphasizing the significant advances made within the field of long-acting antiretrovirals during the past year. Despite science "going virtual," two antiretrovirals (ARV) have been licensed, and two additional LA ARVs are forthcoming. Today's agenda will highlight updates on the development of LA ARV formulations from the pharmaceutical industry, and LEAP will continue to lead the field forward to include diseases other than HIV.

Charles Flexner

Professor of Medicine, Pharmacology, Molecular Sciences and Inernational Health at Johns Hopkins Univeristy and Principal Investigator of LEAP –

Opened the workshop with an overview of LEAP productivity during 2020, highlighting the 5-year award that will expand the program's scope to include tuberculosis and viral hepatitis. Other accomplishments include developing models of microneedles and an implant for ARV delivery; participating in a cost-effectiveness analysis of LA CAB and RPV in LMICs; conducting comprehensive reviews of LA formulations and implants for HIV, and expanding external collaborations to include the Controlled Release Society.

In 2021, LEAP expects to develop a new working group on LA formulations for HCV, HBV and HIV coinfections and will add expertise to the LEAP executive committee in pediatrics, viral hepatitis and broadly neutralizing antibodies. LEAP will continue Modelling and Simulation Core activities, including collaborations with the PATH and IMPAACT networks, and will continue to seek new funding mechanisms and expand external collaborations.

PLENARY I

William Spreen Leader of Cabotegravir Medicine Development at ViiV Healthcare –

Presented lessons learned during development of the LA ARVs, Cabotegravir (CAB) and Rilpivirine (RPV), which has resulted in several marketing approvals for HIV treatment and prevention (Canada March 2020; EU Dec 2020; US Jan 2021; and Australia Feb 2021).

Combination LA CAB and LA RPV IM is safe, tolerable, acceptable and effective to maintain virologic suppression up to 96 weeks.

- In three Phase 3 non-inferiority studies comparing LA CAB/RPV to oral antiretroviral therapy (ART) – ATLAS, FLAIR and ATLAS-2M – efficacy was non-inferior.
- LAI CAB as monotherapy for PrEP has clear, early superiority over oral ART – HPTN 083 and 084.

Oral lead-in could be optional in the future.

- No significant safety issues were observed among >90,000 CAB injections and >60,000 RPV cumulative injections
- Direct-to-inject and oral lead-in groups had similar safety, tolerability and efficacy during the Phase 3 extension of FLAIR and ATLAS-2M.

LA therapy was successfully continued during the pandemic.

- Only 7% of participants missed an injection visit from 1 Dec 2019 to 15 Sep 2020, and these patients were successfully bridged with oral ART.

Real-world data will be needed to define the risk of developing resistance during the CAB PK tail following LA CAB for PrEP.

- HPTN 083 and 084 data from three incident tail-phase HIV infections are encouraging (data to be presented at CROI 2021).

Future of LA CAB development.

- Microarray patch for LA HIV PrEP (in collaboration with the PATH organization).
- Double-strength formulation to reduce injection volumes and allow self-administration (NCT04484337).
- CAB implant (in collaboration with Northwestern University).

Jay Grobler Executive Director of Infectious Diseases and Vaccines at Merck & Co, Inc –

Provided an update on Islatravir (ISL), a first-in-class nucleoside reverse transcriptase translocation inhbitor (NRTTI) as monotherapy for LA oral HIV prevention, and MK-8507, a novel nuceoside reverse transcriptase inhibitor (NRTI) for co-administration with ISL for LA oral HIV treatment.

ISL has high potency against HIV-1, a long half-life and physical properties that allow low-dose oral administration with flexible dosing intervals.

- Anticipated dosing intervals include daily, weekly or monthly administration as well as the potential for yearly administration via a subdermal implant.

Pre-clinical studies in NHPs suggest efficacy of ISL for HIV PrEP and PEP at concentrations that extrapolate to low oral doses in humans and the potential for single-dose oral ISL for PEP.

- Extrapolating to humans, a simulated single 60 mg oral ISL dose achieved PBMC drug concentrations 1-2 fold higher than the lowest concentration that was completely protective in the NHP PEP study (no evidence of viral RNA, pro-viral DNA or antibodies to SIV).

Phase 2 studies (P016) support the safety, tolerability and favorable PK of monthly oral ISL (60mg and 120 mg).

- Plasma ISL concentrations remained above the target exposure threshold (determined via translational PK/PD modelling) throughout the dosing interval.

Simulated PK of MK-8507 supports weekly oral dosing as combination therapy for HIV treatment.

- MK-8507 was well-tolerated at all doses tested, and single doses as low as 40 mg reduced viral load in treatment-naïve PLWH for up to 7 days.

Future directions for ISL and MK-8507.

- Phase 3 PrEP studies of monthly oral ISL (60 mg) will initiate this year. Phase 2 HIV treatment studies of weekly oral MK-8507 in combination with oral ISL (20 mg) will initiate soon in 2021 (NCT04564547).

PLENARY I

Martin Rhee Executive Director of Virology Clinical Research at Gilead Sciences –

Summarized the pre-clinical and clinical data on Lenacapavir (LEN, GS-6207), a first-in-class LA HIV Capsid Inhibitor. These data support an indication for LAI LEN as monotherapy for HIV treatment among heaily ART-experienced patients with multi-class resistance.

LEN inhibits multiple steps in the HIV replication cycle, has high in vitro potency and is fully active against major mutants.

- EC50 = 50pM in PBMCs and non-overlapping in vitro resistance profile.

Phase 1 studies support potent antiviral activity, and PK supports SC administration every 6 months starting with an oral lead-in (OLI).

- Viral load significantly declined (-1.3 to -2.3 log10 copies/mL) over a 10-day period following single-dose LEN SC.
- After a single dose of the PK-optimized formulation (309mg/mL), LEN half-life was 7 to 11 weeks, and plasma concentrations were 6-fold above the EC95 at 6 months and remained detectable for 56 weeks, but were not high enough during the first 4 weeks.
- Oral LEN tablets are bioavailable and have a long half-life (12 days).

Proposed dosing is predicted to maintain plasma LEN concentrations 6-fold higher than the plasma EC95.

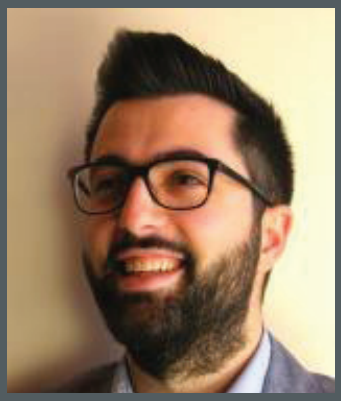
- Proposed dosing comprises a 14-day oral lead-in (600 mg tablet on Day 1 and Day 2, then 300 mg on Day 8) followed by LEN SC (927mg) administered every 6 months starting on Day 15.

Ongoing Phase 2/3 studies in heavily ART-experienced PLWH achieved its primary endpoint by demonstrating antiviral activity of LEN during the functional monotherapy period (CAPELLA study).

- 88% in LEN arm (oral LEN plus failing ART regimen) vs. 17% in placebo arm (placebo plus failing ART regimen) achieved viral load reduction ≥0.5 log10 copies/mL after 14 days of functional monotherapy period (to be presented at CROI 2021).

Future development of LEN.

- Looking forward to CAPELLA study results – LEN has potential for LA HIV treatment and prevention.



Marco Siccardi Associate Professor of Pharmacology and Therapeutics at Univ of Liverpool –

Provided an overview of the LEAP Modelling and Simulation Core, focusing on the principles, strategies and applications.

Modelling allows investigators and developers to understand the mechanisms of LA formulations, simulate new formulations or clinical scenarios and rationalize selection of LA candidates.

- Experimental, preclinical or clinical data are integrated to predict/simulate PK elements by accounting for formulation characteristics (release rate, stability, geometric representation), drug characteristics (DMPK data), animal data (extrapolate key formulation characteristics to humans), and patient variability (including patient sub-populations).

Models use a set of equations to describe different body compartments and movement through the body.

- The relationship between PK and PD can then be used to simulate scenarios, including virtual design of novel formulations, different routes of administration and dosing frequency, and predict tissue penetration and PK/PD in virtual populations.

LEAP modelling experience reflects a range of technological platforms, drug delivery strategies, disease areas, and populations.

- Special populations have included neonates and children, the elderly, pregnant women, breastfeeding women, and pharmacogenetics.
- Recently published work includes an ARV implant (TAF) model and a bNAb model (both based on pre-clinical data) to support bridging to humans and to identify an administration strategy.

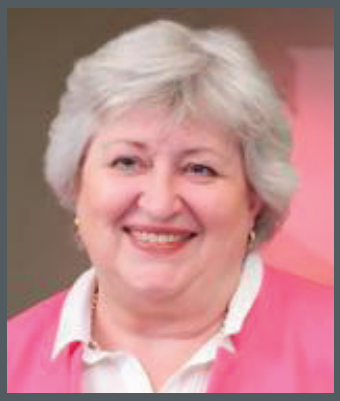
Overview of the LEAP Modelling and Simulation Core process.

- Requests for potential use (via LEAP website or email) are approved by the LEAP executive committee.
- Developer/investigator provides input data (in vitro DMPK data; pre-clinical data; PK/PD); The Modelling and Simulation Core provides a flexible, open source environment for simulation, model qualification and PBPK-PD, then prediction and simulation (different routes of administration, identify optimal formulation characteristics, complexity related to clinical scearios); Constructive feedback are provided to inform novel studies.

Key characteristics of the LEAP Modelling and Simulation Core.

- Flexibility (new/personalized modeling modules); no cost to investigators (NIH-funded); confidentiality of provided data.

PLENARY I



Susan Swindells Professor of Infectious Diseases at University of Nebraska Medical Center –

Provided an update from the LEAP TB Working Group, including prioriy targets and approaches to developing LA formulations for TB prevention and treatment.

Length of standard TB treatment and characteristics of existing TB agents pose major challenges for the development of LA TB formulations.

- Standard TB treatment comprises a 6-month regimen of TB drugs, which are dissimilar to successful LA formulations developed for other diseases (i.e. half-life, target concentration, water solubility, daily oral dose and lipophilicity).

LTBI treatment will be the first LA target.

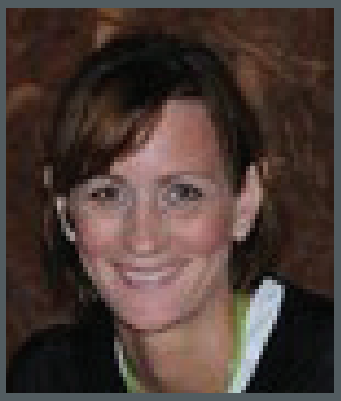
- The global LTBI burden is enormous, LTBI treatment completion rates are sub-optimal, and LA LTBI treatment is potentially achievable, as regimens are shorter (1 or 3 months vs 6 months) and incorporate fewer drugs (1-2 drugs vs 4 drugs) than standard treatment for active TB.

Approach towards LAI 1HP-RPT (1-month of isoniazid plus rifapentine) includes development of a novel isoniazid prodrug.

- Newer TB drugs developed for drug-resistant TB have more promising profiles for LA treatment.
- Optimal dosing of LA rifapentine will be determined using a mouse model (Nuermberger-Ammerman laboratory at JHU).
- A novel isoniazid prodrug is under development to achieve lower water solubility than the current formulation (Caren Myers, Department of Pharmacology and Molecular Sciences at JHU).

The LONGEVITY program research consortium will facilitate development of LA TB prevention.

- The program aims to repurpose key medicines as LAI formulations for malaria prevention, tuberculosis prevention, and HCV cure and includes infrastructure for sustainable translational capacity and a roadmap to market.
- The research consortium comprises Johns Hopkins University, University of Nebraska Medical Center, University of Liverpool, Clinton Health Access Initiative, Medicines Patent Pool, Treatment Action Group, and Tandem Nano, LTD.



Erika Englund Lead of Chemistry, Manufacturing and Controls (CMC) at US FDA –

Highlighted chemical studies and tests that investigators could consider during development of extended-release (ER) injectables, focusing on development of formulations with a low-solubility active pharmaceutical ingredient (API) or ER properties attributed to the excipient (microparticles).

Common quality concerns warranting early consideration.

- Changes in physical properties during storage
- Risk of incomplete dosing (needle clogs, product viscosity, difficulty withdrawing correct volume, withdrawn volume has correct dose)
- Unequal dispersion
- Location of injection (different length needles could be needed).

Product quality tests to consider.

- Physical stability over time; in-use stability according to preparation labelling; confirmation of delivered dose; in vitro drug release test; particulate matter (USP<788>), visible particles (USP<790>) and particle size distribution; delivery device performance tests; and leachable/extractable studies to confirm compatibility of product with the primary closure system (USP<1663>, USP<1664>) and other components in contact with the formulation.

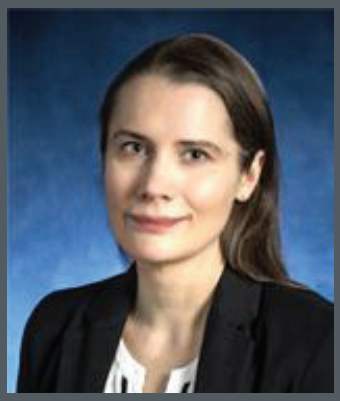
Other development issues to consider.

- Are clinical batches representative of proposed commercial batches?
- What is the risk of dose dumping (leaking into the vein or rapid release due to change in properties)?
- What is the location of injection?
- Are there novel excipients? Supportive data are similar to active pharmceutical ingredient?
- If the product will be supplied in a kit, are components of the kit 510K cleared? Human factors studied could be requested.

General recommendations.

- Refer to FDA guidelines for general CMC recommendations early and throughout development.
- Request a dedicated CMC meeting towards the end of phase 2 studies if an LAI suspension is being developed.
- Request evaluation of the proposed in-vitro release test method from the Division of Biopharmaceutics Reviews, as the review may take three months.

PLENARY II



Nicole C Ammerman Center for Tuberculosis Research at Johns Hopkins Univeristy –

Discussed the potential role of recombinant hyaluronidase to modify injection volumes of long-acting injectable (LAI) formulations.

Achieving an effective dose and exposure profile with a tolerable total injection volume is a key limitation in development of LAIs.

- Subcutaneous (SC) administration is preferred over intramuscular (IM), as the SC route involves less discomfort and allows for repeat dosing via self-administration.
- Small SC injection volumes do not support most LAIs, including CAB and RPV.

Hyaluronic acid limits SC injection volumes.

- Hyaluronic acid prevents fluid dispersion through the extracellular matrix and resists compressive forces created by the LAI drug depot.
- Hyaluronidase temporarily depolymerizes hyaluronic acid and promotes fluid dispersion.

Hyaluronidase allows larger SC injection volumes, but may impact PK.

- Studies of LAI paliperidone palmitate (PP-LAI) co-administrated with hyaluronidase in a rat model suggest that granuloma formation around the LAI drug depot may affect plasma exposure.

A pilot study of PP-LAI is underway in mouse (JHU) and rat models (University of Liverpool).

- The study aims to document the host inflammatory response and release kinetics of PP-LAI co-administered with hyaluronidase.
- Endpoints are the histology surrounding the PP-LAI drug depot in muscle tissue and blood sampling up to 4 weeks post injection.

Future implications of the pilot study.

- If there is no impact on drug release, then other LAI formulations will be tested and ultimately compared with other antimicrobial formulations.

Edmund V Capparelli Pediatrics Pharmacology Laboratory and Host-Microbe Systems and Therapeutics at UCSD –

Reviewed LA modifications of monoclonal antibodies (mAb) with a focus on aspects relevant to the development of LA antiretrovirals (ARV).

Modifications of the antibody Fc region can protect the antibody from metabolism, lengthen the product half-life and impact tissue distribution.

- In previous studies of VRC01, the LS version of the Fc region (VRC01-LS) binds more tightly to FcRn than VRC01, VRC01-LS has a longer half-life than VRC01, and high VRC01-LS concentrations were maintained in serum, vaginal tissue and rectal tissue.

PK studies of LS-modified broadly neutralizing antibodies (bNAbs) require non-standard approaches – population PK modelling can be helpful.

- Traditional noncompartmental PK studies (single-dose washout and dosing to steady state) require observation over at least three half-lives and are impractical.
- Population PK modelling can use non-steady state concentrations and truncated washout data to provide information on half-life and simulate dosing, and data can be combined across study arms, but with limited ability to assess PK covariates (dose effect, HIV status, drug combinations and patient weight).

HIV status is a key PK consideration for bNAbs.

- PK studies of the mAbs, 10-1074 and VRC01, indicate a shorter half-life and more rapid elimination among PLWH. There are limited data that this is also seen in the LA bNAb, VRC01-LS.

Recent PK data on VRC01-LS, VRC07-523LS and VRC01.

- PK data indicate the half-life of VRC01-LS is 4- to 5-fold longer than VRC01 in adults (71 days vs 15 days). A slightly smaller increase in half-life was observed among newborns (41 days vs 21 days), partly due to significant growth early in life. Data are not available for other bNAbs with LS and non-LS forms.

Future directions of LA bNAb development.

- Combination therapy with different targets; early intensification; assessment of tissue distribution; characterization of dosing regimens needed to reach specific targets for HIV treatment and prevention; effects in specific populations (acute infection, virologically suppressed HIV with ARVs, highly resistant HIV, infants); and dosing strategies (e.g. SC co-administration with hyaluronidase) due to the volume required for bNAb dosing.

PLENARY II

Andrew Owen Centre of Excellence in LA Therapeutics (CELT) at University of Liverpool –

Provided an overview of the LONGEVITY program and its activities during the past 12 months, with a focus on developing LA formulations for tuberculosis (TB) and hepatitis C virus (HCV).

CELT was launched in January 2021, and in collaboration with LONGEVITY partners, will run development programs for LAI malaria prophylaxis, TB prevention, and HCV therapy.

- For each target, advancement from formulation development through early clinical studies will proceed in parallel with GMP translation of manufacturing, GLP toxicology studies (depot site toxicology), patient and provider surveys to assure alignment with interest and needs, cost of goods sold (COGS) and pricing. All development will include ongoing engagement with regulatory bodies and stakeholders.

LONGEVITY partners.

- Johns Hopkins University, University of Nebraska Medical Center, University of Liverpool, Clinton Health Access Initiative, Medicines Patent Pool, Treatment Action Group, and Tandem Nano, LTD.

Atovaquone (malaria chemoprophylaxis), rifapentine/isoniazid (TB prevention) and glecaprevir/pibrentasvir (HCV cure) will be targeted for development as LAI formulations.

- Drug selection was based on physiochemical and pharmacokinetic similarities to drugs present in other successful LAI formulations.
- Target Formulation Profiles (TFP) were compiled for malaria, HCV and TB targets and are generally similar. Minimally acceptable characteristics include: volume enabling a monthly IM injection; 12-month shelf life as a powder with no cold chain required; manageable injection site reaction; and cost ≤ oral therapy plus technology costs for LAI contraceptive products available in LMICs.

LONGEVITY has made progress over the past year despite delays due to SARS-CoV-2.

- Confirmed compatibility of several target drugs; initiated isoniazid prodrug synthesis; completed bioanalytical validation and advanced PK model development for several candidate drugs; secured GMP drug donations for malaria and TB programs; obtained IRB approval of patient and provider survey; submitted pre-IND to FDA to gain regulatory insight for malaria program; and established external advisory board with disease and development expertise.

Rodney Ho co-Principle Investigator of the TLC-ART GLAD Project at Univ of Washington –

Discussed the Global Long-Acting Drug combination development (GLAD) project, which is using innovative drug combination nanoparticle platform (DcNP) technology to develop and transform oral into long-acting injectable (LAI) TLD (tenofovir, lamivudine and dolutegravir) for targeted all-in-one HIV treatment in LMICs.

GLAD project leverages DcNP technology and public-private partnership to accelerate novel product development to market.

- DcNP technology accelerates R&D to transform current oral TLD to LAI TLD. Public-private partnership accelerates product release to market. Timeline: pre-clinical studies (2020-2023) – Unitaid; clinical development (2024-2027) – seeking public/private partnership; regulatory and commercialization (2027 global launch target) – partnership established with CHAI and MPP.

DcNP technology can integrate ≤4 current HIV drugs with disparate physical properties into a single injectable suspension, avoiding time-consuming prodrug synthesis and associated costs.

- GLAD selected 3 existing, safe, potent short-acting HIV drugs with different physical properties. DcNP process allowed TLD co-solubilization and controlled solvent removal to make a solid (powder) intermediate – a stable nano-sized TLD is made as a subcutaneous injectable suspension.

First demonstration project shows DcNP targets cART to HIV host cells with potential for long-lasting viral suppression.

- Human oral dose vs. NHP SC injection of DcNP LPV/RTV/TFV
- DcNP created a LA form of all 3 drugs (2-week duration) with higher drug levels in lymphocytes vs plasma (AIDS 2017).
- DcNP LPV/RTV/TFV was quickly loaded in lymph nodes during first-passage. It is estimated that all 3 drugs remained associated in the lymphatic and blood systems – 70% remained in lymph nodes for enhanced exposure in lymphocytes, and the excess (30%) went to the plasma.

Technical readiness of DcNP validated in NHPs – significance of targeted all-in-one TLD dosing and potential impact in LMICs.

- DcNP platform can assemble TLD into DcNP injectable formulations, and a TLD dosage (PIs plus NRTI) appears safe in preclinical studies – dosage is fixed, but requires one injection vs two separate injections of LA-CAB and LA-RPV, and the LA product is projected to be price competitive.
- DcNP results in more drug in lymphoid tissue: Early projections from CEPA (Unitaid) predict 2.3% increased viral suppression in PLWH, suggesting significant impact if clinical trials find evidence of improved outcomes.
- Exemplifies new paradigm, public-private partnership, to accelerate next-generation products to LMICs (key stakeholders provide funding and implementation support to top innovative teams).

Future development. Advance LAI TLD to proof of concept; secure support for clinical development; address risk of DTG clinical issue (substitute other INSTI for safety)

PLENARY II

Lobna Gaayeb Project Manager of LA Technologies at Medicines Patent Pool (MPP) –

Provided an overview of MPP, the first and only existing patent pooling mechanism, and their collaborative approach towards eliminating gaps in access to LA formuations for LMICs by focusing on voluntary licensing and patent pooling.

Intellectual property protections pose a major barrier to access of LA technologies in LMICs – main conclusions from the 2018 Unitaid-MPP Intellectual Property Report on LA technologies.

- Multi-layered protections exist on the molecule, formulation, delivery device and manufacturing process, adding years of exclusivity. Patented platform technologies can be applied to multiple products. Geographical coverage of patent filings vary by product and technology, but key manufacturing countries are often covered.

MPP aims to avoid gaps in access to LA formulations (availability, affordability, quality, acceptability and adaptability) through voluntary licensing.

- MPP negotiates public health driven licenses with patent holders then sublicences drugs to generic manufacturers within a large network of vetted companies. Competition among generic manufacturers produces cheaper, high quality medicines and accelerates development of formulations better adapted for RLS.

Common features of MPP licenses.

- Focus is bespoke licenses tailored to a specific product and context. Terms are negotiated with each patent holder, but all are public health driven and aligned with MPP principles. Common features: wide geographic scope; non-exclusive (promotes competition); transparency (published on MPP website); quality-assured; complementary; license management (monitor compliance); and technology transfer (to accelerate development of generic versions).

Strategic partnerships accelerate development and broaden access to LA technologies – the focus is shifting to earlier stage products.

- MPP collaborates with innovators (seeks access commitment) and leverages partnerships with diverse LA stakeholders (scientific groups, funding agencies and investors, industry, developers, generic manufacturers, and advocacy groups) to facilitate development and affordable access (via licensing and access to a wide network of manufacturers). MPP services span license management to end-user support, including regulatory issues and roll out, market analysis and prevention of stock outs (by ensuring adequate competition).

LA Patents and Licenses (LA PaL), open-access online database, is under development to facilitate information sharing – version 1 expected late 2021.

- Intended to complement scientific, clinical and community engagement – will ensure information transparency and facilitate matching of drugs and technologies, with a focus on patents and licenses. Product identification cards and profiles are in development.

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

Each focus group was convened virtually and lasted 90 minutes. Participants represented diverse perspectives, including clinicians, academia (some with links to industry), pharmaceutical industry, regulatory authorities, community advocacy organizations, and not-for-profit research and implementation institutions. Individual groups are at different points in the collective conversation, but each engaged in a crucial dialogue intended to inform how to collaboratively and strategically advance the LA field amidst a continually evolving landscape.

Focus groups were facilitated by two discussion leaders. Assigned rapporteurs presented their summaries of the discussions and conclusions during the investigator meeting.

FOCUS GROUP 1
LA formulations for viral hepatitis

FOCUS GROUP 2
Lessons learned from development of LA antiretrovirals for HIV prevention

FOCUS GROUP 3
LA monoclonal antibodies for treatment and prevention of HIV and SARS-CoV-2

FOCUS GROUP 4
Advancing the inclusion of key populations in the development of LA formulations

FOCUS GROUP I

Craig McClure Leader of the Viral Hepatitis Program at Clinton Health Access Initiative –

Summarized discussions among the newest LEAP group, the Viral Hepatitis Working group. The goal was to develop an agenda for 2021. Discussions were structured around the following questions: What is needed? What is possible? What is being done? How do we strategically advance the field?

DISCUSSION LEADERS

Dave Thomas
Professor of Medicine at Johns Hopkins University School of Medicine

Andrew Owen
Professor of Pharmacology & Therapeutics and co-Director of CELT at Univ of Liverpool

HCV cure and HBV treatment were identified as priority targets, both requiring development of Target Product Profiles (TPP) to identify what is possible, guide research and development, and build consensus in the field.

- The ideal for HCV is a “one-stop cure”: HCV diagnosis and treatment with a single device – one injection, implant or other technology – in one clinic visit.
- For HBV, improving treatment adherence is an achievable, short-term target and may have value for pregnant women or pediatrics.

Possible approaches for LA HCV cure include: existing direct-acting antivirals (DAA) on the market; reformulating existing DAAs not on the market; or development of new compounds – potency limits candidates, even in combination.

- glecaprevir/pibrentasvir is the only existing DAA candidate for LAI using clinically proven approaches. A high cure rate is achieved for all HCV genotypes with oral therapy for 8 weeks, but doses are large and PK may not be favorable – treatment for 4 to 6 weeks may be adequate, but regulatory uncertainty exists if efficacy is lower.
- The potential to reformulate other DAAs for LAIs is limited due to the large volumes required, but oral dosing may not be the best surrogate for injectables. There may be an opportunity to improve the bioavailability of sofosbuvir, and biodegradable implants were considered.

- Developing a new compound would require government/public investment, as industry has largely exited the field.
- The bar is high – existing daily short-course oral therapy with DAAs have minimal side effects and high cure rates, even with suboptimal adherence. However, the potential impact expected with single-visit test and cure is also high given the markedly reduced implementation in low- and middle-income regions and correctional facilities.

Ongoing approaches for LA HCV cure.

- Ongoing approaches include LONGEVITY and ultra-long acting oral formulations (enteric Lyndra approach).

LAI formulation is achievable for HBV treatment due to the potency of existing drugs.

- Could consider a product that uses an existing nucleos(t)ide analogue as a backbone (e.g. tenofovir, entecavir or associated prodrug) administered alone or in combination with a capsid assembly modulator.

Ongoing approaches for LA HBV treatment include optimization of entecavir for LAI formulation and potential to leverage work with tenofovir (TAF) in HIV.

- Some TAF implants have been associated with necrosis – injectable TAF may be a simpler pathway, but safety is unclear.
- DDIs may be a challenge with LA TAF and/or entecavir. Entecavir dosing is amenable to an enteric approach.

Strategic agenda.

- Develop TPP for HCV and HBV as a collaborative process – position papers could move the agenda forward.
- Comprehensively identify and review ongoing approaches to LA HCV cure and HBV treatment.

FOCUS GROUP 2

Andy Kaytes co-Chair of Community Advisory Board at UCSD Antiviral Research Center –

Summarized the discussions surrounding HPTN 083 and 084 trials of LAI CAB for HIV PrEP. The session was structured around the following questions: What have we learned from HPTN 083 and 084? What do we need to learn next? What to do about the "tail"? How do we avoid using oral formulations at the end of LA PrEP strategies?

DISCUSSION LEADERS

Raphael Landovitz
Professor of Medicine at UCLA and co-Director of CHIPTS

Beatriz Grinsztejn
Physician and researcher at Evandro Chagas National Institute of ID

Overview of HPTN 083 and 084 – LA CAB (5 weeks of oral CAB, then LA CAB IM every 8 weeks, then oral TDF/FTC to cover tail) vs daily oral TDF/FTC.

- Both trials were unblinded early due to superiority of LA CAB arm.
- HPTN 083 (cisgender men and transgender women who have sex with men) had 52 incident HIV infections (LAI CAB 13 vs oral TDF/FTC 39; 66% risk reduction), and HPTN 084 (cisgender women in sub-Saharan Africa) had 40 incident HIV infections (LAI CAB 4 vs oral TDF/FTC 36; 89% risk reduction).
- Incident HIV infections were classified into letter groups A to D; D were puzzling cases where HIV was acquired despite CAB arm and receiving every dose on time.

Lessons learned from HPTN 083 and 084.

- LA CAB appears to have an advantage over oral agents for HIV PrEP.
- There was no significant toxicity, hypersensitivity or discontinuations associated with CAB in the trial setting – oral lead-in (OLI) will be optional in the open-label extension.
- HIV diagnostics are delayed in oral PrEP and could be at least as challenging for LA formulations, making it difficult to determine the timing of HIV acquisition.
- Determining oral adherence at study visits is limited – adherence monitoring via plasma, dried blood spots, saliva, urine, and hair assays may be alternatives.
- Implementation challenges exist.

Lingering questions about the risk of developing resistance from breakthrough infections (D cases) and during the PK tail and whether the OLI should be obligatory.

- Resistance data are limited, but encouraging (to be presented at CROI 2021). Concerns were raised about scenarios where the tail is not covered – If there is an HIV exposure during the CAB PK tail, would drug concentrations be high enough to select for resistance? What are the implications for global TLD use or BIC or DTG-based regimens in high-income countries to treat LA PrEP breakthrough cases?
- The group discussed whether the trial data give enough confidence to remove OLI in the context of HIV prevention – numbers are small, and safety may not be generalizable. Risk/benefit analysis is more stringent for prevention than treatment. Is there a period of vulnerability with direct-to-inject – cannot yet accurately determine the time-to-protection after first injection, as current understanding of the correlates of protection and PK variability is incomplete. In contrast, could OLI be considered a liability due to sub-optimal adherence to oral PrEP? Is there any scenario where you would cover the "nose" – double-dose TDF/FTC or TAF/FTC as in IPERGAY study?

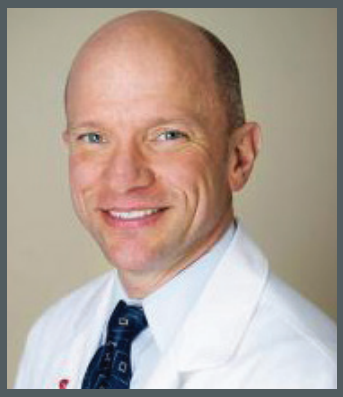
Implications for pregnant and breastfeeding women, considerations for LMICs and real-world acceptability.

- Data remain limited in pregnant and breastfeeding women – women who become pregnant on protocol will be given the option to remain on LAI CAB in the open-label extension.
- In LMICs, the OLI would add complexity and costs to care – ViiV Healthcare plans to make LA CAB available in LMICs and RLS, but what are the mechanisms and pricing structure?
- Given that the LA approach is Q8 weeks vs 4 times per year for oral PrEP, will LA CAB be acceptable, particularly among youth, transgender, and other key populations that have not seen benefits from existing oral PrEP?

Strategic agenda.

- Need mechanisms for interrogating the PK tail more systematically and should leverage knowledge about PK variability from other LA nano-crystalized formulations.
- Real-world data are needed to understand resistance implications, either via surveillance conducted with demonstration projects or relegate assessment to a location with a national healthcare system – will need to identify strategies to minimize resistance to INSTIs if break-through infections are seen.
- Are more robust HIV diagnostics needed, and what are the implications for RLS?
- More data are needed in pregnant and breastfeeding women.
- Real-world implementation: need to understand how to generate product demand and acceptability outside of clinical trials and how to access specific populations who stand to benefit most, including youth, Black, Latinx, and transgender females.

FOCUS GROUP 3



Trip Gulick Chief of Division of Infectious Diseases at Weil Cornell Medicine –

Summarized the discussions concerning the development of LA monoclonal antibodies (mAb) for prevention and treatment of HIV and SARS-CoV-2. The group considered each virus separately and focused on identifying the advantages and disadvantages of applyng mAbs to each therapeutic context.

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Katharine Bar
Director of Virus and Reservoirs Core at UPenn

Marina Caskey
Professor of Clinical Investigation at Rockefeller University

Advantages of HIV mAbs.

- HIV mAbs have potent antiviral activity.
- Clinical experience exists with HIV treatment (pilot data) and prevention (Phase 2/3), and many studies are underway. HIV mAbs are generally safe and well-tolerated, have long half-lives and low potential for DDIs.
- Target concentrations are rapidly reached with IV administration, and there is potential for SC dosing.
- Reducing the size of the HIV reservoir (a step towards HIV cure) is a theoretical benefit.

Disadvantages of HIV mAbs.

- Current standard of care for HIV treatment and prevention are excellent.
- Main challenge for mAbs is resistance due to changing HIV envelope diversity, which will require monitoring of circulating strains (HIV prevention) and standardized resistance testing (HIV treatment).
- CNS penetration of mAbs is low, and high target concentrations are needed for prevention.
- Data are lacking among children and pregnant/breastfeeding women.
- Use is also complicated by the cold chain requirement, the need for community education and high cost (particularly for LMICs).

Advantages of SARS-CoV-2 mAbs.

- Current standard of care for outpatients is limited to supportive treatment – there is a unique opportunity. Can leverage the experience with HIV.
- SARS-CoV-2 mAbs demonstrate virologic activity (more potent in combination vs. monotherapy). In Phase 2/3 studies of high-risk patients, monotherapy and combinations can prevent hospitalization and death, and emerging data for prevention show decreases in transmission in nursing homes and among household contacts.
- Generally well-tolerated, have a long half-life, and target concentrations are rapidly achieved with IV administration.
- Administered as a single IV infusion for treatment or prevention, and other modalities are being investigated (SC, IM, inhaled).

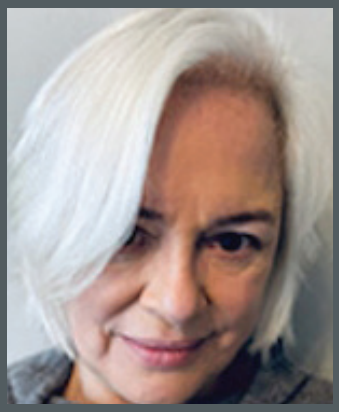
Disadvantages of SARS-CoV-2 mAbs.

- Resistance of certain epitopes is the main concern.
- Vaccines are the current standard of care for prevention.
- Immunocompromised hosts could benefit, but also have prolonged viral excretion and could select resistance.
- Data are lacking among children, pregnant/breastfeeding women, and immunocompromised populations.
- Use in people with active SARS-COV-2 infection is complicated by infection control issues, the need for community education and high cost (prohibitive in LMICs).

Next steps in development of mAbs for HIV and SARS-Cov-2.

- Develop combination regimens for HIV (e.g. HIV mAb administered in combination with ART).
- Studies of LA IV and SC formulations for HIV with dosing every 6 months to 12 months and additional formulations for SARS-CoV-2 mAbs (SC, IM and inhaled).
- Novel HIV cure studies.
- Studies in children and pregnant/breastfeeding women (HIV and SARS-CoV-2) and immunocompromised populations (SARS-CoV-2).

FOCUS GROUP 4



Polly Clayden co-Founder of HIV i-Base –

Summarized the discussion on how to accelerate inclusion of infants, children and pregnant women in studies of LA formulations. The session was structured around the following topics: current studies in key populations; implications of new LA ARV recommendations for key populations; approval status of LA CAB for prevention and implications for youth and women in high prevalene settings; products in development that should be prioritized for pediatrics.

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Elaine Abrams
Professor of Epidemiology and Pediatrics at Columbia University

Mark Mirochnick
Professor of Pediatrics and member of Division of Neonatology at Boston University

Six studies of LA ARV formulations are underway or in development in children and pregnant women.

- Four studies of LAI CAB and RPV in children:
  - MOCHA and Crème (IMPAACT) – Phase 1/2 studies in ages 12-18 y and 2-12 y.
  - IMPAACT CS5024 – feasibility and acceptability among non-adherent youth.
  - LATA – Phase 3 study in ages 12-19 y.
- Two studies of LA CAB in pregnant women:
  - European Pregnancy and Pediatric HIV Cohort Collaboration [EPICC]) – pooled analysis of maternal/fetal outcomes, vertical transmission and viral suppression using prospectively collected data in women who become pregnant on CAB-containing ART or had ≥1 LA CAB injection during the 12 months prior to conception.
  - Open-label extension of HPTN 083 (LAI CAB for HIV PrEP) – PK sampling with continued dosing among women in the LA CAB arm who become pregnant and agree to remain on LA CAB during pregnancy.

Trial strategies for LA formulations in children are the most complex.

- There are <5 pediatric LA formulations. Younger children represent a smaller market and pose a substantial challenge due to weight changes over short intervals.
- PK and PD of LAIs can be anticipated using modelling, but the potential for under- or over-dosing is concerning, particularly given the delay in data return.

First LA ARV regimen FDA-approved in January 2021, but guidelines are restrictive – no history of virologic failure and not for use in women who are pregnant or planning to become pregnant.

- Adolescents: Criteria make it difficult to offer LA CAB/RPV to adolescents, particularly never having failed. Concerns that non-adherence to oral ART could translate to failure to attend injection visits and risk for developing INSTI resistance during the PK tail. Monthly dosing and administration as two separate injections may impact acceptability. Data from the IMPAACT study among non-adherent youth will be important.
- Adolescents and women of childbearing potential: Women are still being left out of the drug development process. Study drugs were stopped in pregnant women (changed to oral arm), but this makes little sense for LA/ER formulations, as the half-life is long, and represents a lost opportunity to learn more about how to use these formulations during pregnancy. EPICC will collect outcome data, but there is nothing like this in the US – anyone who becomes pregnant should be followed carefully or enrolled in a protocol.

Adolescents and young women in high prevalence LMICs are without data on LA CAB for HIV prevention (HPTN 083 and 084).

- FDA submission is anticipated in the first half of 2021. Will there be contraceptive requirements? How to monitor consequences during the tail? What if women decide to stop LA PrEP – what should be used to "cover" the PK tail?
- LA CAB is substantially more effective in women, but do we use it in people we think will not show up for injection appointments? (individual benefit vs population). Implementation aspects should be considered in parallel with development – self-injection would obviate the need for an injection clinic visit.

LA products in the pipeline.

- Microneedle patch for pediatrics is in the R&D stage (defining user needs/developing target product profile). A patch could be cut to adjust dosing for infants. Implants are well-suited for adolescents (e.g. hormonal contraceptive implants). Removal is the main issue, but reversibility is an option (i.e. if become pregnant) if implant is removed before the tail phase. Industry may be willing to develop products for younger patients, but guidance is needed – implants are very scalable.

Summary.

- Call to action: Concern and frustration prevail as the first-in-class LA ARV is being rolled out. Old habits die hard and continue to limit the care of children and pregnant women. LA CAB/RPV and the COVID-19 vaccine exemplify what happens when we leave pregnant women and children out of development. We need to think beyond LA CAB/RPV.
- Dose finding among infants and young children is challenging and complicated, but innovative approaches are needed to accelerate these studies – could begin by including a dose among children and infants already receiving ART to build understanding of PK in addition to leveraging PK and PD modelling.
- LA drug delivery methods under development: excitement exists about the potential for microneedle patches and implants across populations.

ANNEX A FOCUS GROUP PARTICIPANTS

Name	Affiliation
FOCUS GROUP 1	
Terrence Blaschke	Stanford University School of Medicine
Bob Bollinger	Johns Hopkins University School of Medicine
Jordan Feld	University of Toronto
Charles Flexner	Johns Hopkins University School of Medicine
Bryn Gay	Treatment Action Group
Leah Johnson	RTI International
Craig McClure	Clinton Health Access Initiative
Andrew Owen	University of Liverpool
Marco Siccardi	University of Liverpool
Kimberly Struble	US Food and Drug Administration
Mark Sulkowski	Johns Hopkins University School of Medicine
Susan Swindells	University of Nebraska Medical Center
David Thomas	Johns Hopkins University School of Medicine
Giovanni Traverso	Harvard Medical School and MIT
FOCUS GROUP 2	
Jared Baeten	Gilead Sciences
Terrence Blaschke	Stanford University School of Medicine
Diana Brainard	AlloVir, Inc.
Ann Collier	University of Washington
Keith Crawford	NIH NIAID
Lut Van Damme	University of Washington
Paul Domanico	Clinton Health Access Initiative
Charles Flexner	Johns Hopkins University School of Medicine
Gerardo Garcia-Lema	US CDC
Beatriz Grinsztejn	Evandro Chagas National Instutute of ID
Rodney Ho	University of Washington
Thomas Hope	Northwestern Feinberg School of Medicine
Jeffrey Jacobson	Case Western Reserve University
Courtney Jarrahian	PATH
Jeremiah Johnson	Treatment Action Group
Andy Kaytes	Community Advisory Board, UCSD
Maggie Kilbourne-Brool	PATH
Raphael Landovitz	University of California Los Angeles
Mark Mirochnick	Boston University School of Medicine
Jean-Michel Molina	University of Paris
Malek Okour	GlaxoSmithKline
Andrew Owen	University of Liverpool
Kimberly Scarsi	University of Nebraska Medical Center
Kimberly Struble	US FDA
Susan Swindells	University of Nebraska Medical Center
Kati Vandermeulen	Janssen
FOCUS GROUP 3	
Elaine Abrams	Columbia University
Katharine Bar	University of Pennsylvania
Maria Beumont	Janssen
Terrence Blaschke	Stanford University School of Medicine
Marina Caskey	Rockefeller University
Paul Domanico	Clinton Health Access Initiative

Name	Affiliation
FOCUS GROUP 3 - cont'd	
Charles Flexner	Johns Hopkins University School of Medicine
Trip Gulick	Weil Cornell Medicine
Jacobson	Case Western Reserve University
Andy Kaytes	Community Advisory Board, UCSD
Daniella Livnat	NIH NIAD
Mark Mirochnick	Boston University School of Medicine
Randall Tressler	NIH NIAD
Virginia Sheikh	US FDA
Luisa Stamm	Assembly Biosciences, Inc
Kimberly Struble	US FDA
Raju Subramanian	Gilead Sciences
Susan Swindells	University of Nebraska Medical Center
Marci Vitoria	World Health Organization
Ying Zhang	JH Bloomberg School of Public Health
FOCUS GROUP 4	
Elaine Abrams	Columbia University
Kimberly Adkison	ViiV Healthcare
Nicole Ammerman	Johns Hopkins University
Mark Baker	ViiV Healthcare
Marc Baum	Oak Crest Institute of Science
Terrence Blaschke	Stanford University School of Medicine
Fazila Bunglawala	Univeristy of Liverpool
Diana Clarke	Boston University School of Medicine
Pollly Clayden	HIV i-Base
Paul Domanico	Clinton Health Access Initiative
Veerle Van Eygen	Janssen
Joe Fitzgibbon	NIH NIAID
Charles Flexner	Johns Hopkins University School of Medicine
Lorna Gaayeb	Medicines Patent Pool
Peter Havens	Medical College of Wisconsin
Bill Kapogiannis	NIH NICHD
Andy Kaytes	Community Advisory Board, UCSD
Linda Lewis	Clinton Health Access Initiative
Andrew Lloyd	University of New South Wales
Margaret Louey	Clinton Health Access Initiative
Christine Malati	US Agency for International Development
Elena Martinelli	Northwestern Feinberg School of Medicine
Mark Mirochnick	Boston University School of Medicine
Sharon Nachman	Stony Brook University
Eric Nuermberger	Johns Hopkins University School of Medicine
Anthony Podany	University of Nebraska Medical Center
Manjari Quintanar	PATH
Elizabeth Rhee	Merck & Co.
Theodore Ruel	University of California San Francisco
Marco Siccardi	University of Liverpool
Kimberly Struble	US FDA
Susan Swindells	University of Nebraska Medical Center
Anna Turkova	University College London

ANNEX B LEAP PARTNERSHIPS

Centre of Excellence in Long-acting Therapeutics (CELT)
https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/

Adult Clinical Trials Group (ACTG)
https://actgnetwork.org/

HIV Prevention Trials Network (HPTN)
https://www.hptn.org/

International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT)
https://www.impaactnetwork.org/

Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)
https://atnweb.org/atnweb/

JHU Center for AIDS Research (CFAR)
https://www.hopkinscfar.org/

HIV i-Base
https://i-base.info/

Unitaid
https://unitaid.org/

U.S. Food and Drug Administration (FDA)
https://www.fda.gov/

Bill and Melinda Gates Foundation
https://www.gatesfoundation.org/

Clinton Health Access Initiative (CHAI)
https://www.clintonhealthaccess.org/

Medicines Patent Pool (MPP)
https://medicinespatentpool.org/

Treatment Action Group (TAG)
https://www.treatmentactiongroup.org/

Controlled Release Society (CRS)
https://www.controlledreleasesociety.org/

leap

Long-Acting/Extended Release
Antiretroviral Research Resource Program

For more information:
www.longactinghiv.org