2022 INVESTIGATOR MEETING & ANNUAL WORKSHOP

VIRTUAL
FEBRUARY 12, 2022

leap Long-Acting/Extended Release Antiretroviral Research Resource Program

ABBREVIATIONS

ADMET Absorption, distribution, metabolism, elimination, toxicity
AE Adverse event
AIDS Acquired immunodeficiency syndrome
ANC Antenatal care
API Active pharmaceutical ingredient
ART Antiretroviral therapy
ARV Antiretroviral
ATLAS Antiretroviral Therapy as Long-Acting Suppression
B or BIC Bictegravir
bNAb Broadly neutralizing antibody
CAB Cabotegravir
CADO Conference on Antiretroviral Drug Optimization
Calibr California Institute for Biomedical Research
cART Combination antiretroviral therapy
CDMO Contract Development and Manufacture Company
CELT Centre of Excellence in Long-acting Therapeutics
cGLP Current good laboratory practices
cGMP Current good manufacturing practices
CHAI Clinton Healt Action Initiative
CMC Chemistry, Manufacturing and Controls
COGs Cost of goods
DAIDS Division of AIDS
DcNP Drug Combination Nanoparticles
DDI drug-drug interaction
DHA Docosahexaenoic acid
DMPK Drug metabolism and pharmacokinetics
DOR Doravine
DSMB Data and Safety Monitoring Board
DTG Dolutegravir
EC50 Effective concentration 50%
eDMC external Data Management Committee
EMA European Medicines Agency
ER Extended Release
ETR Etravirine
ETV Entecavir
FDA Food and Drug Administration
FDF Final dosage form
F or FTC Emtricitabine
GLAD Global Long-Acting Drugs project
HBV Hepatitis B virus
HCV Hepatitis C virus
HIV Human immunodeficiency virus
HPTN HIV Prevention Trials Network
IC50 Inhibitory concentration 50%
IC90 Inhibitory concentration 90%
ID Intradermal
IM Intramuscular
IMPAACT International Maternal, Pediatric, Adolescent AIDS Clinical Trials
IND Investigational New Drug
INH Isoniazid
INSTI Integrase strand transfer inhibitor
IRB Institutional review board
ISL Islatravir
ISR Injection site reaction
IV Intravenous
JHU Johns Hopkins University
LA Long-acting
LAI Long-acting injectable
LaPaL Long-acting technologies Patents and Licences database
LARC Long-acting reversible contraception
LEAP Long-acting Extended-release Antiretroviral research resource Program
LEN Lenacapavir
LMIC Low-middle income country
LPV Lopinavir
MALDI Matrix-Assisted Laser Desorption Ionization
MAP microneedle array patch
MBPK Mechanism-based pharmacokinetic
MN microneedle
MOCHA More Options for Children and Adolescents
MPP Medicines Patent Pool
MTCT Maternal to Child Transmission
NARTI Nucleoside analog reverse transcriptase inhibitor
NHP Non-human primate
NRTTI Nucleoside reverse transcriptase translocation inhibitor
NTAF Nanoformulated TAF
OBR Optimized background regimen
OLI Oral lead in
PADO Paediatric Antiretroviral Drug Optimization
PAIC90 Protein-adjusted inhibitory concentration 90%
PBMC Peripheral blood mononuclear cell
PBPK Physiological-based pharmacokinetic
PD Pharmacodynamic
PK Pharmacokinetic
PLGA Polylactic-co-glycolic acid
PLWH Person living with HIV
PMTCT Prevention of maternal to child transmission
POC Point of care
PPPY per person per year
PrEP Pre-exposure prophylaxis
R&D Research and development
RLS Resource limited setting
RPV rilpivirine
RTV rotinavir
SAE serious adverse event
SC subcutaneous
SD subdermal
SSA sub-Saharan Africa
TAF Tenofovir alafenamide
TAG Treatment Action Group
TB Tuberculosis
TDF Tenofovir disoproxil fumarate
TFV Tenofovir
TFV-DP Tenofovir diphosphate
TFV-MP Tenofovir monophosphate
TK Toxicokinetic
TLC Total lymphocyte count
TLC-ART Targeted Long-acting Combinational ARV Therapeutic
TLD Tenofovir, lamivudine, dolutegravir
TNL Tandem Nano Ltd
UNMC University of Nebraska Medical Center
VL Viral load
WHO World Health Organization

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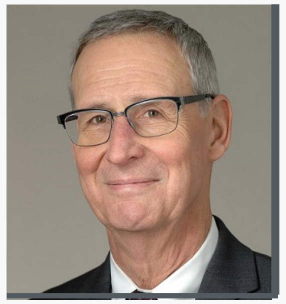
Where will we LEAP next?

On February 12, 2022 clinicians, investigators, developers, community advocacy groups, not-for-profit institutions and regulatory authorities convened virtually for the annual LEAP Investigator Meeting and Workshop. Opening remarks from Drs Carl Dieffenbach and Charles Flexner were followed by two plenary sessions comprising updates on existing technologies and presentations on novel technologies and approaches. Presentations were 10 minutes and followed by Q&A. Four focus group discussions were held in advance of the meeting. These 90-minute sessions are intended to foster informative and provocative discussions on timely topics strategically selected to help collectively advance the long-acting field. This report summarizes the plenary session presentations as well as each focus group discussion.

Keynote

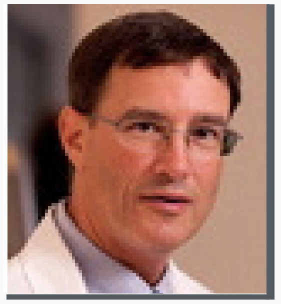


Carl W. Dieffenbach Director of DAIDS, NIAID at NIH

"Seeking to foster innovation in this field, let us continue the principles of LEAP - serving as a resource, to share knowledge, to create a robust pipeline of concepts for HIV, and in so doing, help advance LA concepts to meet the unmet medical needs in HIV and other fields of medicine."

Dr. Dieffenbach expressed excitement about recent advances and growth in the LA field, citing FDA approval of the first injectable HIV regimen and the first injectable option for HIV PrEP as well as numerous emerging development programs from Industry. He reminded attendees of our collective goal: to address the weakest link in drug-based strategies for chronic diseases – patient adherence. LA/ER formulations have great potential to eliminate pill fatigue, forgetfulness, missed doses, and stigma, yet development is slow, costly and high risk, and there is still much work to be done. Optimizing patient satisfaction, and ultimately success, will require expanding delivery solutions, improving pharmacological profiles with fewer side effects, and expanding development activities outside of HIV. Looking forward, he emphasized the value of learning from every success and failure, the need for collaboration, and LEAP's critical role in centralizing investigator resources and the growing knowledge landscape to facilitate development.

Welcome



Charles Flexner Principal Investigator of LEAP

"We are going to be talking about important developments in long-acting products for HIV and related diseases, and we will be hearing about some of the knowledge gaps and controversies that you will be helping us to solve in coming years."

2021 was a productive year for LEAP. Highlights include: two systematic reviews on LA formulation developmentand implementation, a cost-effectiveness analysis for LA CAB and RPV in LMICs (*Lancet Global Health*) and a survey of patient preferences for LA formulations for HCV (*Clinical Infectious Diseases [CID]*); a LEAP-sponsored symposium at the Controlled Release Society Annual Meeting (July 2021); and a new collaboration with Unitaid and Medicines Patent Pool (MPP) to conduct a landscape analysis of LA products and formulations (LaPaL) for HIV, viral hepatitis and TB. LaPaL will serve as an information repository for LA products/formulations in clinical and advanced preclinical stages and will include related intellectual property and patent status.

In 2022, LEAP expects to sponsor a journal supplement in CID (2022) and publish the first systematic reviews of LA/ER ARVs for children, adolescents and pregnant women and for HIV. We also plan to develop new face-to-face meetings focused on viral hepatitis and TB in the next 12-18 months. LEAP will continue to advance the LA field through ongoing collaborative projects, including: LEAP modeling and simulation core activities (led by Andrew Owen at Univ of Liverpool and in collaboration with PATH and IMPAACT); LaPaL development (LEAP-Unitaid-MPP); Unitaid programs developing LA products for TB prevention and HCV cure (LONGEVITY at Univ of Liverpool) and HIV (GLAD at University of Washington); and expand biobehavioral research activities in collaboration with Tia Morton and Theresa Senn (NIH).

Ryan Donnelly Chair of Pharmaceutical Technology at Queen's University Belfast

"Update on transcutaneous microneedles for ARV drug delivery"

Provided an overview of microneedle (MN) technology and shared the results from preclinical pharmacokinetic studies of antiretroviral drugs.

"Microneedles have great potential for HIV drug delivery"

MNs are a minimally invasive alternative to standard injection for LA ARV delivery.

- MAP formation – A nanoformulated ARV (typically water-soluble nanocrystal) is loaded into an aqueous gel at high concentration, cast into a mould and dried to form MNs. Border adhesive and an occlusive backing layer are added to stick to the skin.
- MNs painlessly penetrate the outermost skin barrier, deposit drug in viable skin layers (for sustained release), and drug depot is absorbed into the rich dermal microcirculation. Dissolving MNs shorten MAP wear time and optimize amount of drug delivered.
- Potential to offer sustained drug delivery and co-administration of several drugs (HIV treatment and prevention) with enhanced safety and patient acceptability (low risk vs standard injection, painless, and no needle phobia) and self-administration.

Rat studies demonstrate sustained mono- and co-delivery of CAB and RPV via MNs and the safety of repeated MAP application.

- RPV nanocrystal MAP performed as well as RPV IM. Plasma levels remained above IC90 (12ng/mL) for 56 days.
- CAB MAP formulations sustained plasma levels above 4xIC90 (664 ng/mL), but below CAB IM/ID for 28 days (CAB nanocrystal, micronized NA salt and FA MAP).
- CAB/RPV co-delivery via MAP (19x19 cm^2 vs 16x16cm^2) sustained plasma RPV above IC90 for 70 days (outperformed IM/ID) and plasma CAB above 4xIC90, but below IM/ID for 28 days.
- CAB/RPV MAP application Q14days (with and without initial IM bolus) yielded similar plasma RPV and CAB levels among cohorts after 14 and 28 days, respectively, with no adverse events.

Translation to humans suggests weekly CAB/RPV MAP application for adult HIV treatment.

- MNs had lower efficiency of delivery than IM/ID injection in preclinical studies (30% vs ~80%).
- Allometric scaling and basic PKPB modeling suggest patch sizes of 25-30cm^2 (RPV) and 30-40 cm^2 (CAB) would provide 7-day coverage for an adult.

***in-vivo* animal studies demonstrate sustained delivery of Etravirine (ETR), Bictegravir (BIC) and Tenofovir alafenamide (TAF) via MNs.**

- ETR and BIC (hydrophobic compounds) were studied using micro-suspension and engineered nanosuspension MAP formulations.
  - ◊ Dissolving ETR MNs sustained plasma levels for one month vs 10 days for IV delivery.
  - ◊ BIC MNs outperformed IM delivery, but with lower efficiency of delivery (similar to CAB and RPV) – weekly MAP is most likely for adult humans.
- TAF (more hydrophilic compound) was studied using prodrug-loaded dissolving MNs (made a high-density hydro-form as the MN tips) and implantable PGLA tips to control drug release.
  - ◊ Both MAP approaches outperformed IM, but plasma levels fell below therapeutic after 7 days (even with PGLA system).
  - ◊ Translation to a weekly patch may be possible.
  - ◊ Potential for co-administration with BIC MAP for HIV treatment (collaborating with Univ of Liverpool to combine TAF and BIC).

Summary and Next Steps.

- Mono- and co-delivery of ARVs is feasible – the ARVs studied are suitable for a weekly patch in adults with potential for a monthly patch in smaller children.
- More potent drugs could accomplish longer duration of action or smaller patch size.
- Next steps include macaque studies and clinical trials.
- Scalable manufacturing is needed to have real-world benefit for patients.

William Spreen Vice President and Medicines Development Leader at ViiV Healthcare

"Current Status of LA/ER CAB and RPV, including a pipeline report on novel CAB formulations"

Shared the significant progress with long-acting cabotegravir (CAB) and rilpivirine (RPV) over the past year.

CAB LA approved by FDA for HIV PrEP in December 2021 (Apretude).

- HIV incidence reduced by 69% and 90% vs TDF/FTC in HPTN 083 and HPTN 084, respectively.
- US label highlights: optional oral lead in (OLI); dosing used in registration trials (CAB 600 mg IM Q2mo, after 2 doses Q1mo); HIV-1 RNA testing recommended at initiation and during CAB-LA PrEP (to identify infection and resistance).
- CROI 2022 presentations.
  - ◊ HPTN 083 – results from 1-year follow up (Landovitz et al) and time course of drug resistance among seven CAB-LA participants with HIV infection using integrase genome sequencing (Eshelman et al).
  - ◊ HPTN 084 – estimates of CAB LA efficacy vs counterfactual placebo rates in women (Donell et al) and CAB-LA safety and PK among pregnant women (Delaney-Moretlwe et al).

CAB LA + RPV LA regimen for HIV treatment continues to evolve following initial approval.

- Regulatory approvals: Canada (March 2020); EMA (Dec 2020); US FDA (Jan 2021); GB,UK,CH, CL, HK, TW; 10+ additional submissions completed and more in process.
- Supplied as co-packs (Cabenuva) and single packs of Vocabria (CAB LA) and Rekambys (RPV LA) and tablets Vocabria (CAB) and Edurant (RPV).
- Anticipate expansion of the US indication (2022) to include Q2mo dosing, optional OLI (EMA approval Sept 2021), and adolescents aged ≥12y and ≥35kg (EMA TBD).
- CROI 2022 presentations.
  - ◊ ATLAS-2M – 3-year follow up of 1mo vs 2mo dosing (Overton et al).
  - ◊ MOCHA – safety and PK in adolescents (Bolton Moore et al) and adolescent and parent experiences with LAI (Lowenthal et al).
  - ◊ Effect of I741 polymorphism on fitness of HIV-1 subtype A6 resistant to CAB (Hu et al).

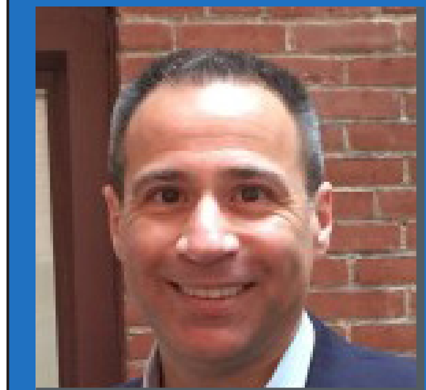
New LA opportunities.

- Double-concentrated CAB formulation in Phase I Clinical Trials (NCT04484337, results Feb 2022).
  - ◊ Safety and PK of CAB 400 mg/mL vs CAB 200 mg/mL via multiple dosing routes (IM and SC) and schedules (Q1mo and Q3mo) following 30-day OLI.
  - ◊ Two cohorts added to assess: 1) impact of a topical steroid or NSAID on ISRs; and 2) safety and PK of co-dosing CAB + Halozyme recombinant human hyaluronidase PH20 (rHuPH20).
- Co-dosing ARVs with Halozyme rHuPH20 to achieve longer dosing intervals.
  - ◊ Injection of hyaluronidase PH20 (a natural component of the extracellular matrix) allows temporary expansion of the SC space for 24-48 hours. This may enable larger injection volumes and an opportunity to extend dosing intervals beyond Q3mo.
  - ◊ PH20 is currently co-dosed with multiple approved biologics.
  - ◊ We aim to extend this approach to small molecular ARVs – ViiV has exclusive use of Halozyme rHuPH20 for INSTIs, NRTTIs, capsid inhibitors and bNAbs to CD4-binding site of gp120.
- ARV delivery via MAP (external collaboration).

Summary and Next Steps.

- Initial FDA approvals and launch of CAB + RPV LA (HIV treatment) and CAB LA (HIV PrEP).
- Additional opportunities with the LA CAB + RPV regimen are being evaluated (ViiV and Janssen), and CAB 400 formulation is in clinical trials.
- ViiV-Halozyme collaboration may enable novel LA regimens with other clinical candidates.

"We are at the beginning of the application of LA HIV therapeutics for both HIV treatment and prevention … we'll continue to look for new approaches to innovate in the LA area with much more to come"



Jay Grobler Associate Vice President of Infectious Diseases and Vaccines at Merck & Co.

"Update on ISL Development"

Focused on safety information emerging from clinical trials of islatravir (ISL).

"We remain committed to fully understanding the potential paths forward for islatravir."

Overview of Merck ISL Development Program.

- ISL is a potent NRTTI with a differentiated resistance profile and PK properties supporting the potential for extended-duration dosing.
- HIV treatment **(prior to 18 Nov 2021)**.
  - ◊ Internal program: daily oral ISL+DOR (P3) and weekly oral ISL+MK-8507 (P2)
  - ◊ Merck-Gilead program – weekly oral ISL+LEN (P2) and Q3mo LAI ISL+LEN (in development).
- HIV PrEP **(prior to 18 Nov 2021)**.
  - ◊ Q1mo oral ISL (P3) and Q1y implantable ISL (P2).

Emerging safety information for ISL and MK-8507 during a Phase 2b stable switch trial.

- Oral ISL+MK-8507 for HIV treatment among adults virologically suppressed on BIC/FTC/TAF.
- Routine, blinded medical monitoring observed downward trends in TLC and CD4+ count among a majority of participants at week 12 and 24
- Reductions appeared to be proportional to the MK-8507 dose, but still observed in the lowest dose.

Mean % Change from Baseline at Week 24 (n=79)				
Parameter	MK-8507 100mg	MK-8507 200mg	MK-8507 400mg	Control
TLC	-17%	-26%	-30%	+0.11%
CD4+ Count	-11%	-23%	-30%	-0.25%

* External data management committee (eDMC) recommended Merck stop dosing and monitor participants. Dear Investigator Letter sent to trial sites on 18 November 2021.

Results from Merck internal review of hematological parameters from all ISL or MK-8507 trials (across indications and dosing intervals)

- ***HIV treatment –***

Stable switch Phase 3 trials of daily oral ISL+DOR in virologically suppressed participants showed <1% mean reduction in CD4+ counts at week 48 with no clinical AEs related to infection.

Mean % Change in CD4+ from Baseline at Week 48		
Protocol	ISL+DOR	Control
017	-0.7%	+8.7%
018	+0.9%	+12.8%

* eDMC recommended Merck continue trials as currently designed.

- ***HIV PrEP –***

Phase 2 study of oral ISL (60mg vs 120mg vs placebo) in low-risk HIV-uninfected people showed dose-dependent reductions in TLC that were within normal limits and no increased clinical AEs related to infection.

Mean % Change in TLC from Baseline at Week 24			
Protocol	ISL 60mg	ISL 120mg	Placebo
016	-21%	-36%	+4%

* eDMC recommended Merck continue ISL PrEP trials as currently designed (based on above Phase 2 trial data and Phase 3 trial data reviewed on 07 Oct 2021).

FDA places clinical holds on studies under the following IND applications (13 Nov 2021).

- Full clinical hold (stop dosing, increase monitoring and no further enrollment) – oral and implantable ISL for PrEP and injectable ISL for HIV treatment and PrEP.
- Partial clinical hold (continue dosing those on study; stop screening/enrollment) – oral ISL+DOR for HIV treatment.

Summary and Next Steps.

- Per FDA, most ISL development programs have been impacted to some degree as of 27 Dec 2021.
- Continue to monitor participants receiving ISL.
- Investigate the underlying mechanism that led to the observed decreases in lymphocyte counts.
- Evaluate the PK, safety and hematology data from our clinical studies to understand the PK/PD relationship for this effect.

Martin Rhee Director of Clinical Research at Gilead Sciences

"Lenacapavir (GS-6207): A First-in-Class Long-acting HIV Capsid Inhibitor"

Shared the late-stage clinical data presented at various scientific meetings over the past year in heavily experienced and treatment-naïve people living with HIV.

Review of Lenacapavir (LEN) and ongoing clinical studies for HIV treatment.

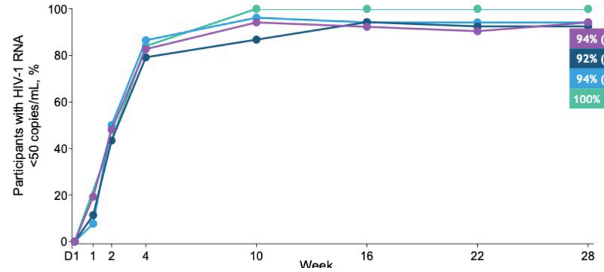
- LEN is a potent ARV (EC50 50-100pM) due to multiple HIV replication targets (nuclear transport, capsid assembly and virus assembly and release)
- Capella Phase 2/3 study among heavily treatment-experienced PLWH with multi-drug resistance or failing current ARV regimen (n=72).
  - ◊ Eligibility: resistant to ≥2 ARVs from 3 of 4 main classes and ≤2 fully active agents from 4 main classes or viral load (VL) ≥400 copies/mL on current ARV regimen.
  - ◊ Functional monotherapy period (14 days) then Maintenance period (26 weeks).
  - ◊ Randomized cohort – oral LEN (n=24) or placebo (n=12) + failing ARV regimen, then LEN SC Q6mo + OBR.
  - ◊ Non-randomized cohort – LEN oral + OBR, then LEN SC Q6mo + OBR (n=36).
- Calibrate Phase 2 open-label, randomized study among treatment-naïve PLWH (n=182).
  - ◊ Eligibility: VL ≥200 copies/mL and CD4 count ≥200 cells/µL.
  - ◊ Induction period (26 weeks) then Maintenance period (26 weeks).
  - ◊ Treatment Groups (TG): **TG 1 and TG 2** LEN SC Q6mo + oral F/TAF, then LEN SC Q6mo + TAF or BIC; **TG 3** oral LEN + F/TAF x 52 weeks; **TG 4** – B/F/TAF x 52 weeks.

LEN led to viral suppression by 26 weeks and was well-tolerated in a treatment-experienced population with advanced HIV and heavy ARV resistance (Capella).

- Study population: 64% had a CD4 count ≤200 cells/µL, and multidrug-resistance was common (NRTI, 99%; NNRTI, 97%; PI, 81%; and INSTI, 69%).
- 26-week outcomes in the randomized cohort, n=36.
  - ◊ >80% had VL<50 copies/mL with robust CD4 recovery (mean +81 cells/µL).
    - * VL decreased nearly 2-fold in the LEN group by day 14 (-1.93 vs Placebo -0.29, p<0.0001).
  - ◊ 11% had emergent LEN resistance – all were at high risk (2 had no other fully active agent and 2 had poor adherence to OBR)
- Safety in overall population, n=72.
  - ◊ No SAEs; <10% with clinical AEs related to LEN.
  - ◊ 13-25% with ISR – swelling, erythema, pain, nodule and induration were most common (most grade 1 and lasted days; nodules lasted weeks to months).

LEN may achieve rapid viral suppression with low emergence of resistance in treatment-naïve PLWH (Calibrate).

- > 90% of LEN TGs had VL <50 copies/µL at 6 months (TG1 94%, TG2 92% and TG3 94% vs B/F/TAF 100%).
- LEN performed as well as B/F/TAF over the first few weeks (B/F/TAF is known to achieve fast virologic suppression).



- One participant in TG2 developed LEN resistance at week 10 (testing performed if VL ≥50 copies/mL and <1 $\log_{10}$ reduction from Day1 to week 10).
  - ◊ Plasma LEN concentrations were consistently within target range.
  - ◊ Mutations in CA (HIV capsid protein, Q67H+K70R) were preceded by those in RT (reverse transcriptase, M184M/I), suggesting ***poor adherence to F/TAF likely led to LEN resistance.***

Summary and Next Steps.

- As part of a combination regimen, LEN was well-tolerated and led to high rates of viral suppression in treatment-experienced (LEN +OBR) and treatment-naive (LEN + F/TAF) PLWH.
- Capella and Calibrate are ongoing – one-year data will be presented at CROI 2022 (Ogbuagu O et al one-year Capella data; Gupta S et al one-year Calibrate resistance data).
- Phase 3 studies of LEN for HIV PrEP are ongoing – Purpose-1 and Purpose-2.

Andrew Owen Professor of Pharmacology and Therapeutics at University of Liverpool

"Pharmacokinetic Modeling for Long-acting Medicines"

Demonstrated how modeling can be used to support development of long-acting medicines using three examples from the LEAP Modeling and Simulations Core.

PBPK modeling and other pharmacometrics approaches aid development of LA medicines.

- Potential roles span all phases of development.
  - ◊ Assess compatibility with LA delivery (using *in-vitro* drug disposition data).
  - ◊ Inform dose selection for preclinical and Phase 1 studies (*in vitro-in vivo* extrapolation).
  - ◊ Supplement animal data to provide insight into mechanisms.
  - ◊ Guide clinical management and optimization (special populations, DDIs, dose optimization and genetics).
  - ◊ Assess exposure-response relationships across development.
- Confidence in model outcomes is proportional to the quality of input data (increases across development and as understanding of the medicines grows).

PBPK modeling to inform development – CAB MAP in rats and humans.

- Existing, unqualified base model of MAP for LA ARVs.
  - ◊ Describes MNs and drug release into the striatum corneum, viable epidermis and dermis.
  - ◊ Examined drug penetration and partition coefficient from each site into blood and lymph compartments of simulated population.
- Qualified the base model using empirical CAB PK data.
  - ◊ Rat CAB MAP qulification – single- and multiple-dose.
  - ◊ Human CAB LAI qualification.
  - ◊ ***Good fit between empirical PK data and simulated CAB performance generates confidence in the modeling.***
- Predicted CAB MAP performance in humans.
  - ◊ Simulated different CAB doses (75mg, 150mg and 300mg) delivered via MAP (unpublished) to generate expected PK performance in humans ***based on everything that has been qualified about the model***.

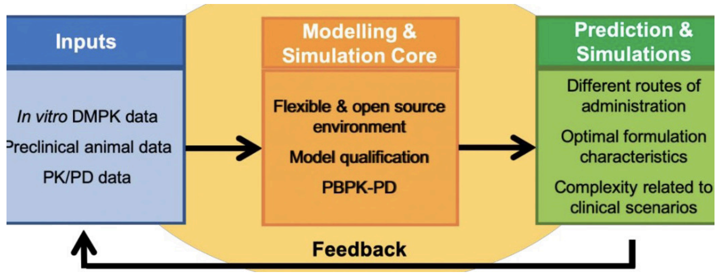
PBPK modeling to inform deployment – Dose prediction for LAI CAB in neonates.

- Model qualified against adult human LAI CAB PK data.
- Adjusted model parameters based on known differences in neonatal populations.
  - ◊ Can simulate LAI CAB performance in neonates with reasonable confidence (i.e., in mechanisms and formulation performance described by model), recognizing residual uncertainty exists.
- Simulated neonatal exposures across different CAB IM doses, ***assuming adult release kinetics***.
  - ◊ Regimen 1 (CAB 20mg IM): plasma CAB concentrations above 4xPAIC90 are achievable, but neonatal simulation unveiled a delay in CAB absorption not seen in adults.
  - ◊ Regimen 2 (CAB 20mg IM + CAB 0.8mg oral): target plasma CAB concentrations can be achieved within the first day by adding a single, oral CAB dose at Day 0.

Pharmacometrics approaches to rationalize mechanisms – A CELT LAI development project.

- Mechanistic knowledge underlies PBPK modeling, but remains limited for many LA technologies, particularly drug absorption.
- A simple PBPK model fitted to empirical animal PK data for the API achieves exposures up to 28 days and shows dose linearity across 50, 100 and 200 mg/kg.
- A pharmacometrician de-convoluted the available IV and IM PK data to derive an *in-vivo* release profile for each dose.
  - ◊ Predicted release kinetics unveiled bi-exponential release, supporting a parallel fast and slow input from the depot into the systemic circulation.
- A more advanced model was constructed that achieved a better fit to the empirical PK data.
  - ◊ Describes the drug depot with: 1) direct release into the systemic compartment (early, fast release); and 2) a two-compartment transit model into the systemic compartment (longer duration, slow release).
  - ◊ ***Modeling cannot elucidate mechanisms***, but does fits with rapid absorption of the soluble component of the formulation and slower release of the solid.

LEAP Modelling and Simulation Core is a resource for the LA research community.



- Our template submission form details the input data needed for us to engage with you.
- https://logactinghiv.org/files/Modeling-Core-Submission-Form.docx

Lynn Bertagnolli Clinical Pharmacology Fellow at Johns Hopkins University

"LEAP Systematic Review of Long-acting Formulation use in Pediatrics and Pregnancy"

Provided an overview of findings from existing studies of LA injectable and implant formulations in infants, children, adolescents, youth and pregnant and post-partum women.

Studies of LA/ER formulations across various use indications show improved outcomes and high patient acceptability.

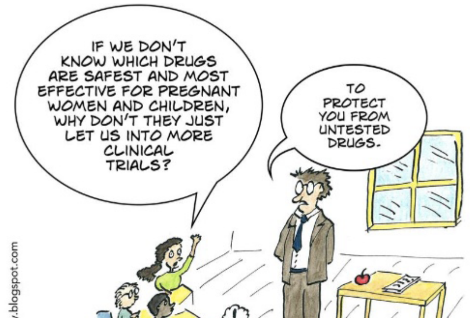
- LA/ER drug strategies exist for hormonal contraception, osteoporosis, chronic schizophrenia, HIV and pain control.
- Lower relapse rate for chronic schizophrenia observed with LA vs oral risperidone.
- High demand for LA/ER contraception – 70% of young participants (n=5086 women) chose LA reversable contraception over another formulation.
- Acceptability of LA HIV products – 61% of patients with HIV were likely or very likely to choose a LA formulation when available.

Theoretical benefit of LA drug strategies.

- Chronic diseases – adherence to lifelong, daily oral medication is a struggle for many.
- Stigma – patients may not want others to know they take pills daily.
- Periods of transition – LA strategies could bridge points of vulnerability (Infancy, childhood, youth up to 24y, pregnancy and postpartum, periods of injection drug use or incarceration).

LA formuations could have crucial roles in HIV and TB prevention among infants/children.

- 32,000 children develop drug-resistant TB each year, yet only 23% of child household contacts aged <5y received TB preventive therapy in 2017.



- >90% of children with HIV in developing countries were infected via MTCT during pregnancy, birth or breastfeeding – many infants and women fall out of care during this period.

Systematic review of existing data (up to 2018) on the safety and efficacy of LA IM and implant formulations in special populations.

- Definitions: LA/ER (once monthly or less frequent), infants (birth-1 year), adolescents (10-19y) and youth (15-24y).
- Exclusion criteria: vaccines, insulin or anesthesia/ analgesia (not IM injections); studies with no specific focus in adolescents or children; non-english articles; articles without an abstract.
- Among 27,227 unique abstracts identified, 2770 full articles were assessed for eligibility, and 97 studies were included in the analysis.
- Most studies were conducted among infants, children or youth.
  - ◊ Infants and children (n=46); youth (n=40); mixed children and adolescents (n=5); Pregnant women (n=3); postpartum women (n= 3, 2 were in adolescents)
- Five indications were studied.
  - ◊ Contraception (n=21) or other hormonal therapies (n=51); other (n=11); antibiotics (n=10); and anti-psychotics (n=4).

Conclusions.

- Despite the demand and potential benefits, clinical data on LA/ER formulations remain scarce in special populations, particularly among pregnant and postpartum women (only 6 studies).
- There is also a lack of diversity among indications studied (contraception and other hormonal therapies comprise the majority).

"There is an urgent need to reverse the neglect of long-acting research in special populations."

PLENARY I

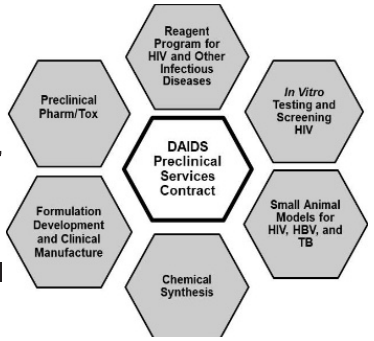
Keith Crawford Health Scientist Administrator at Division of AIDS, NIAID, NIH

"DAIDS Preclinical Services Program to Accelerate Drug Development"

Provided a program overview with a focus on available services under two technical task areas.

The DAIDS Preclinical Services Program a resource for investigators developing next generation therapeutics for HIV and related co-infections.

- High priorities include LA ARVs, novel targets and inhibitors, and novel immune-based therapies.
- Fills critical product development and resource gaps to advance promising therapeutics toward clinical trials.
- Investigators receive products, data and specialized expertise from NIAID contractors at no cost (not funding).
- Services fall under 6 technical task areas spanning product development – from initial drug discovery and lead optimization to preclinical development, including IND-directed studies and activities required for regulatory submissions and clinical trials.



Example task area 1 – Formulation Development and Clinical Manufacture (all studies cGMP compliant).

- Develop new formulations to enhance product solubility or bioavailability
- Develop alternative dosage forms (different strength or route of administration).
- Develop and validate analytical assays to determine identity, strength, quality, purity, stability and drug release methods.
- Develop manufacturing processes and procedures.
- Prepare reports to be included in the Chemistry, Manufacturing and Controls (CMC) section of regulatory submissions.

Example task area 2 – Preclinical Pharmacology and toxicology (directed toward meeting requirements for IND submission – all studies cGLP compliant).

- IND-enabling studies – characterize *in-vitro* properties (ADMET, protein binding, bioavailability and bioequivalence, potential drug interactions); pharmacology in animals; toxicology (acute, repeated dose and chronic toxicity), safety analyses in different organ systems.
- Develop bioanalytical methods and perform studies.
- Prepare all required study reports for the IND package.

How to access services. (www.niaid.nih.gov/research/daids-services-program-accelerate-drug-development)

- Submit a written request for services (specific needs, data package to support the request, overall product development plan)
- Internal evaluation by a team of expert scientists:
  - ◊ 1) matches NIAID priorities; 2) soundness of development plan; 3) investigator commitment (preliminary data, concurrent studies, communications with FDA); 4) ability of NIAID contract resources to fulfill requested services; and 5) availability of funds.
- Material Evaluation Agreement issued, and NIAID coordinates transfer of products and data between investigator and NIAID contractor.
- Resources and services listed on NIAID website.

Past projects.

- Clinical Dosage Forms and Manufacture – novel formulation, delivery system or route of administration of an approved product that alters the PK.
  - ◊ Repackaged nevirapine tablets into blister packs with a 48-month stability study.
  - ◊ Manufactured methotrexate capsules and placebo with a 60-month stability study.
  - ◊ Process development and GMP manufacture of a proprietary lipid-based product (manufactured a lipid nanoformulation).
- Preclinical Pharmacology and Toxicology.
  - ◊ Pharm/tox studies of proprietary ARV nanoformulation for IND filing.
  - ◊ Safety and pharmacology studies (GLP and non-GLP) of novel formulations of existing drugs (injection, oral, and inhaled delivery in rats and dogs).
  - ◊ 6-month tox/TK study of sutezolid for mycobacterial infection.
  - ◊ Repeat toxicity and TK studies of a novel ARV formulation in mice.
  - ◊ Reproductive tox studies of a clinical-stage ARV in rats (GLP, segment I/II).
  - ◊ *In-vitro* mitochondrial tox studies.

PLENARY II

NOVEL APPROACHES

Marc Baum Senior Faculty of Organometallic & Environmental Chemistry at Oak Crest Institute of Science

"Tenofovir implants and local toxicity: what have we learned to date?"

Shared findings from preclinical studies and perspectives on this debated topic.

Oak Crest and Northwestern University (NWU) have developed TAF implants with conflicting local tissue safety.

- TAF (a potent TFV prodrug) is one of few candidates with enough potency to be formulated and delivered via subdermal implant.
- Both reservoir devices are filled with tablets containing the API, but differ among API formulation, mechanical design, material and resulting local drug exposure.

Parameter	Northwestern Implant*	Oak Crest Implant
API	TAF hemifumarate	TAF (free-base)
Mechanical		
Sheath Material	Polyurethane	Silicone
Local TFV/TFV-DP Exposure	Low-no (macaques & rabbits at 4 weeks)	High

Preclinical dose-ranging studies of the Oak Crest implant suggest the target human dose (TAF release rate 0.25mg/d per implant) should only lead to an expected foreign body response.

- Very mild inflammation observed at <1mg/day over 14 or 30 days in dogs (significant inflammation at TAF >1mg/day and worsened at TAF >1.5mg/day).
- Mild inflammation and capsule formation observed across a range of doses in mice (TAF ≤ 0.6mg/d for 28d) and sheep (TAF ≤ 0.3mg/d for 14d).

Placebo-controlled studies of the NWU implant in macaques suggest concerning local toxicity, possibly due to a drug effect.

- Each animal served as its own control (active and placebo implants were placed contralaterally).
- Unacceptable inflammation and cases of severe necrosis observed at TAF 0.13mg/day over 30 days (n=2) or 90 days (n=4).
- No local toxicity observed around placebo implants.

TFV/TFV-DP exposure in tissues surrounding Oak Crest and active NWU implants suggest local toxicity may be more than a drug effect.

- Used existing Oak Crest and NWU preclinical datasets to compare tissue concentrations of TFV and TFV-DP at the implant site.
- Oak Crest implant – high local TFV/TFV-DP exposure in mice and sheep (TFV-DP ~100-fold lower than TFV).
- Active NWU implant – low-no local TFV/TFV-DP exposure in rabbits at 4 weeks and macaques, and a wide range of TFV exposure (spanning Oak Crest values) with no TFV-DP exposure in rabbits at 12 weeks.

What else could be present and be causing toxicity at the NWU implant site?

- API formulation, device shape, and device material are different than the Oak Crest impant.
- Several intermediate compounds are produced during TAF metabolism and were not previously measured.
- Recent Oak Crest MALDI mass spectrometry studies.
  - ◊ All intermediate compounds (metabolite Y, metabolite X, TFV, TFV-MP and TFV-DP) are present in tissue sections collected at the implant site, and their distribution around the implant varies.

Next Steps.

- Continue to investigate why research groups are seeing differing local toxicity.
- Continue Phase 1/2 clinical trials of the Oak Crest TAF implant for HIV prevention in women (CAPRISA 018).
  - ◊ Phase 1 ongoing (dose and duration escalation among low-risk women in South Africa) – most women have had implant for 6 months; 3 safety reviews completed; and DSMB recommends trial continuation.
  - ◊ Phase 2 component planned (extended safety, tolerability and acceptability) – randomized 1:1 TAF SD implant + oral placebo vs placebo implant + oral TDF/FTC.

"TAF still has a lot of potential, especially as the list of potent ARV drugs that are useful for implants is dwindling ... We really do need to give TAF the full benefit of scientific investigation"

Arnab Chatterjee Vice President of Medicinal Chemistry at Calibr, Scripps Research

"LAI HBV Therapy – LA NARTI for the treatment of HBV"

Shared progress in the development of long-acting parent entecavir (ETV) and ETV prodrugs for parenteral HBV treatment.

LA HBV treatment is an unmet need.

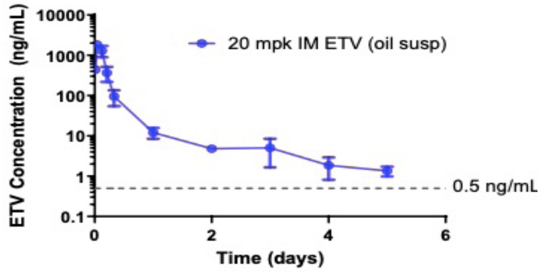
- Approved oral NARTIs carry minimal risk of resistance, achieve >99% viral suppression and are well-tolerated, but require lifelong daily dosing for viral suppression.
- Convenience and access issues make patients susceptible to missed treatment and disease relapse.
- Calibr develops LAI medicines using a broad approach
  - ◊ Integrated platform between solid-state chemistry and formulation development.
  - ◊ In-house molecular and pharmacology resources.
  - ◊ Team can quickly pivot and optimize a drug candidate (e.g. alter the structure or generate a different solid-state form for IM and SC injection).

Development of LAI ETV for chronic HBV treatment.

- Optimal characteristics from TPP include: Q6mo dosing, dose volume ≤1ml for self-administered SC injection, low viscosity for smaller needle (27G), and low cost for use in LMICs (COGs $100/treatment).
- ETV has reasonable properties as a low-dose oral drug: IC50 0.5nM, low plasma protein binding (13%) and low clearance.

Suspension-based depot strategy for parent ETV (20mpk IM ETV oil suspension).

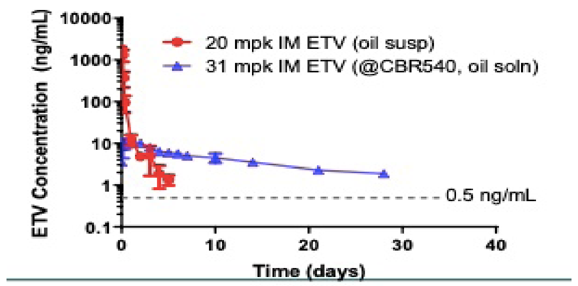
- ETV is a good LAI candidate
  - ◊ High melting point, solubility in various excipients (oil solubility allows easy passage through 27G needle), and API formulation shows modest clearance and good potency to enable low injection volumes.



- Observed high peak to trough levels with relatively high C_{max}, even with IM oil-based suspension.

Solution-based depot strategy for ETV prodrugs.

- >30 ETV prodrugs synthesized (esters and carbonates).
  - ◊ narrowed candidate selection via solubility measurement, prodrug functionality evaluation (turnover studies in plasma, hepatocytes and microsomes), and PK modeling in animals.
- Bis-DHA compound (CBR540) provides the most favorable PK profile.
  - ◊ Lower C_{max} and extended exposure after a single CBR540 oil solution injection vs parent ETV oil suspension (in rats).



  - ◊ Production of ETV and intermediate metabolites enable slow release.
- Mono-DHA compound (CBR261) is likely a good candidate for suspension – many candidates were crystalline (advantageous from GMP perspective).

Summary and Next Steps.

- Generated a series of prodrugs that provide sustained ETV release after a single IM injection
- CBR540 – low injection volumes achieve >150-fold lower C_{max} and prolonged exposure relative to parent drug.
  - ◊ Predicted human dose volume <500 mL for 1-month coverage.
  - ◊ ISRs were not observed in animals (no histology).
- Complete detailed ISR studies and preclinical toxicology studies to better understand the safety of intermediate metabolites of CBR540.
- Examine the role of SC administration for self-administration.
- Perform detailed human dose projections as dose-escalating PK data are generated.

Benson Edagwa Associate Professor of Pharmacology and Experimental Neuroscience at UNMC

"Novel Long-Acting ProTides of Approved ARVs"

Shared progress using the prodrug approach to develop long-acting formulations of integrase inhibitors and Tenofovir alafenamide.

Overview of the prodrug approach and formulation advantages.

- Creating a prodrug (ARV + promoiety) allows the ARV (active drug) to be formulated as a nanosuspension (prodrug nanocrystals).
- Once injected, the ARV half-life depends on the rate of prodrug release from the nanosuspension and subsequent slow hydrolysis (generates the ARV and a non-toxic promoiety).
- ARV prodrug formulations are very stable (particle size, homogeneity and stability of API within the formulation and at various temperatures) and readily syringeable via a 28G needle after several months of storage.

Preclinical studies suggest novel integrase inhibitor prodrug formulations of CAB, DTG and BIC are well-tolerated locally and could potentially enable a once-yearly injection.

- A single injection of NM2CAB (45mg CAB eq/kg in rats), NM2DTG (45mg DTG eq/kg in rats) and NM2BIC (45mg BIC eq/kg in mice) sustained plasma ARV levels >PAIC90 for up to 12 months.
- High tissue levels of M2DTG (prodrug) and DTG were detected in monkeys for up to 7 months (after a single injection).
  - ◊ Secondary storage in liver, lung, kidney, spleen, muscle and lymph nodes extends the ARV half-life (prodrug undergoes hydrolysis to sustain therapeutic concentrations of active drug in the tissues).
- Histology and imaging at the injection site (NM2DTG-injected vs saline injected vs uninjected) show expected histiocytic infiltration followed by macrophages (carry drug from the injection site to peripheral tissues).

Applying the prodrug approach to TFV creates a stable, LA ProTide that suppresses HBV infection for up to 3 months in a mouse model.

- TAF is potent and inherently long acting, yet unstable within the prodrug formulation (susceptible to hydrolysis), whereas TFV ProTide formulations (NM1TFV and NM2TFV) are stable for months.
- Preclinical PK studies indicate that NM1TFV and NM2TFV readily convert to TFV-DP (active metabolite) *in vivo*, have no advantage over nanoformulated TAF (NTAF) in PBMCs, but lead to higher TFV-DP levels in tissues.
  - ◊ A single injection of NM1TFV, NM2TFV or NTAF provides TFV-DP exposure > EC90 in PBMCs for 56 days.
  - ◊ TFV-DP levels in rectal tissue and parenchymal cells differ by formulation – NM1TFV > NM2TFV > NTAF up to 2 months following a single injection (study will continue for >6mo to assess duration of this effect).
- A single injection of NM1TFV (lead candidate) suppressed HBV infection (HBV DNA) for up to 3 months in humanized mice infected with HBV, whereas NTAF was ineffective.
  - ◊ The model was validated using serial human albumin levels (human hepatocytes remained stable) and liver histology (NM1TFV – liver cells only showed staining of human hepatocyte marker; NTAF and no treatment – liver cells showed staining of human hepatocyte marker and HBV markers, HBcAg and HBsAg).

Summary and Next Steps.

- Prodrug and formulation manufacture is scalable.
- Preclinical PK studies support the potential for once-yearly dosing of CAB, DTG and BIC prodrug nanocrystals.
- TFV can be transformed into a LA ProTide that can suppress HBV replication for over 3 months in a mouse model.
- Exavir Therapeutics, Inc. has licensed the LA antiviral agents and has several pipeline programs to address HIV, HBV and HIV-HBV co-infection.
- We continue to look for partners to accelerate development of prodrug formulations.

Andrew Owen Professor of Pharmacology and Therapeutics at University of Liverpool

"Update from LONGEVITY"

Focused on the progress in the Centre of Excellence in Long-acting Therapeutics (CELT) and the TB prevention and HCV cure programs under this Unitaid-funded grant.

Challenges and opportunities related to LA medicines for malaria, tuberculosis (TB) and hepatitis C virus (HCV).

- >400 million people are affected worldwide with combined annual mortality >2 million persons per year.
- Deploying affordable LA medicines in LMICs may equitably bridge healthcare gaps across all 3 diseases.
- LONGEVITY grant includes activities to mitigate anticipated patent-related challenges in development, commercialization and access to LA medicines.
- Aiming for price parity with treatments currently being deployed in LMICs.

Potential long-term impacts of LAI medicines and LONGEVITY.

- LAIs almost universally result in lower doses relative to oral comparators – success expected to decrease net doses required for effectiveness.
- LAIs promise to improve treatment completion rates and decrease transmission – success expected to decrease treatment failure and influence the emergence of drug resistance.
- LAIs for HIV have been associated with reduced stigma in qualitative studies.
- LONGEVITY aims to deliver interventions in LMICs focused on LAI malaria chemoprophylaxis, TB prevention (products targeting latent TB infection), and HCV cure (aiming for one-shot treatment).

LONGEVITY TB and HCV programs.

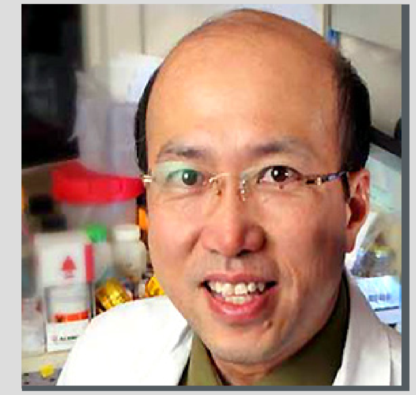
- CELT established at University of Liverpool.
- Development programs mirror one another, except the TB program includes prodrug development focused on INH (JHU and CHAI).
- Patient and provider needs assessments are conducted in parallel with formulation development and preclinical studies and GMP translation of manufacturing (series of surveys lead by UNMC and TAG).
- COGs and pricing activities (CHAI) are conducted in parallel with safety studies (focused on excipients and depot toxicology) and Phase 1 clinical trials (characterize PK in human populations).
- Regulatory engagement (CHAI) and stakeholder engagement and communications (CELT and consortium partners) are conducted in parallel to all programs.

Progress in research and development through year 2.

- Malaria chemoprophylaxis program.
  - ◊ Initiated research to define transmission of drug-resistant parasites; confirmed formulation compatibility for several target drugs; completed bioanalytical validation and PK model development for candidate drugs; achieved preclinical proof of concept for several target drugs in small animals; completed CDMO engagement and initiated GMP translation of LAI atovaquone.
- TB Prevention program.
  - ◊ Initiated INH prodrug synthesis and early preclinical evaluation for a number of candidates.
- Secured GMP drug donation for malaria (Hetero Drugs Ltd.) and TB (Sanofi) programs.

Progress in supportive activities.

- Established lab infrastructure and web resources for CELT at University of Liverpool.
  - ◊ website is fully operational (www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/).
  - ◊ Teoreler software will soon enable users to conduct basic PBPK modeling via CELT website (beta testing planned Q2, 2022).
- UNMC obtained IRB approval for interests and attitudes survey and initiation for malaria program is imminent.
- Completed pre-IND with FDA for malaria program (CHAI, UofL, and JHU).
- Published advocacy literature (TAG, UNMC, and UofL). –
  - ◊ Illustrated glossary for LA technologies
  - ◊ Pipeline report for LA technologies for malaria and HCV (www.treatmentactiongroup.org/hcv/long-acting-technologies-resource-compendium/).
- Contracted GLP toxicology consultant to initiate protocol development for malaria (CHAI, U of L).
- Executed MPP license on LONGEVITY candidate LAI technologies (MPP, TNL, U of L).



Rodney Ho Professor of Pharmaceutics and Adjunct Professor of Bioengineering at University of Washington

"Targeted Long-acting Combinational Anti-Retroviral Therapeutic (TLC-ART) Program – Update"

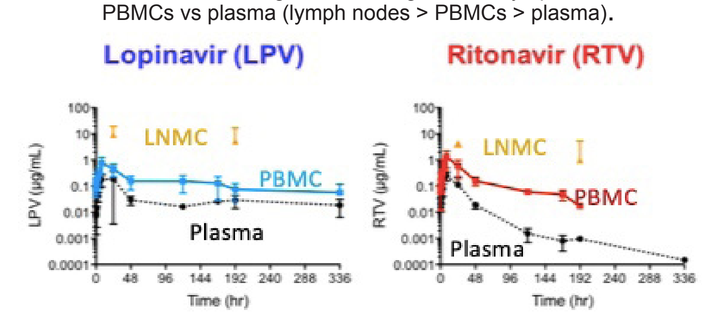
Reviewed the Global Long-Acting Drugs (GLAD) project and shared progress on study outcomes and global implications.

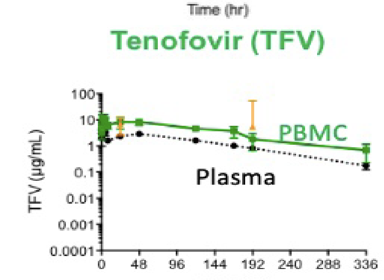
The GLAD project aims to transform daily oral TLD into once-monthly LAI-TLD for global health impact.

- TLC-ART's enabling DcNP technology accelerates R&D (combines up to 4 existing drugs with disparate properties into a single injectable suspension).
- Private-public funding (Unitaid-NIH) accelerates preclinical development to first-in-human studies.

Why develop DcNP formulations of existing HIV drugs?

- Enabled "All-in-one cART" via a single SC injection vs combining separate single-agent IM injections (LAI CAB + LAI RPV).
  - ◊ Drug ratio is not as flexible, but DcNP could enhance patient acceptability and achieve higher HIV clearance in cells.
- DcNP extends the plasma $t_{1/2}$ of short-acting oral ARVs (hundreds of hours in NHPs vs hours to days in humans).
- DcNP targets all drugs in the formulation to HIV host cells and tissues (data from LPV/RTV/TFV DcNP).
  - ◊ Enables LA and higher multi-drug levels in lymph nodes and PBMCs vs plasma (lymph nodes > PBMCs > plasma).





*70% of DcNP dose is quickly localized to lymph nodes and retained for enhanced exposure (first pass/slow clearance), and excess DcNP (30% of dose) enters the blood (PBMC>plasma/ intermediate clearance.

- ◊ Enables higher PBMC:plasma ratio than possible with oral cART.
  - * DcNP in NHPs vs oral in humans: LPV (4.02, 0.27); RTV (7.40, 0.52); and TFV (3.01, 0.65).

Progress in the DcNP cART platform.

- Five LA cART candidates validated in NHPs.
  - ◊ LA PK; cell:plasma ratio >1 for all drugs in combination; and basic safety. LPV/RTV/TFV DcNP is entering first-in-human studies.
- DcNP technology licensed for global use through MPP.
- TLD DcNP formulation is stable and scalable
  - ◊ single and 2-drug combinations (TD/TL) may be feasible; several 3-drug formulations are being evaluated for LA PK in NHPs.
- Manufacturing process has been simplified to scale.
  - ◊ Eliminated removal of unbound drug to reduce cost (based on MBPK and PBPK modeling).
- Conducted modeling simulations of LPV/RTV/TFV DcNP formulation.
  - ◊ MBPK modeling indicates that water-insoluble (LPV, RTV) and water-soluble ARVs (TFV) remain associated with DcNP *in vivo*.
  - ◊ PBPK modeling of the free-drug mixture vs DcNP formulation.
    - * DcNP-bound drugs are retained in cells in lymph nodes, leading to the targeting and LA PK outcomes.
    - * The model can validate and project the PK time course for tissues and nodes of interest.

Potential global impact of oral TLD to LAI-TLD transition – CEPA outcome projections.

- 2.3% gain in viral suppression among PLWH on ART by 2030 (assuming 100% transition starting in 2025).
- 75% reduction in HIV non-suppression due to treatment disruption.
- Potential to gain fast-track targets (with improved clinical outcomes, well-tolerated among PLWH, and cost parity with oral formulation).

Summary and Next Steps.

- LAI-TLD is at the proof-of-product concept stage and moving towards market (Preparing to improve patient acceptance and adherence and implementation science).
- DcNP platform has the flexibility to adapt if the field moves to more potent product compositions.
- We continue to seek supporting partners to improve outcomes and impact of the project.

David Ripin Executive Vice President of Infectious Diseases and Chief Science Officer at CHAI

"CADO 4/PADO 5: Approach to delivery of LA ARVs for HIV treatment and Prevention in LMICs – Cabotegravir as a precedent-setting case study"

Summarized conference highlights and how LA ARVs can be affordably delivered in LMICs.

CADO 4 overwhelmingly prioritized investment in developing LA products for HIV treatment and prevention (JHU, CHAI, WHO).

- Priority List – impact within 5 years.
  - ◊ LA CAB (HIV prevention).
  - ◊ LA LEN (HIV prevention and treatment).
- Watch List – impact in 5-10 years.
  - ◊ Once 6-monthly SC injectable 2-drug regimen, or
  - ◊ 1-2 year acting implantable 2-drug regimen.
- Reasons for prioritizing LA products
  - ◊ Ease of adherence and discretion (particular benefit for key populations).
  - ◊ Assumed affordable, easy to deliver and cost-competitive with products on the market.
  - ◊ Assumed the generic supply model could be reproduced for LA products
- CHAI independent analysis to illustrate the affordability of CAB-LA deployment for HIV prevention.

Background for CAB-LA case study – HIV prevention remains an unmet need despite the efficacy and availability of oral PrEP.

- Global burden of new HIV infections was 3-fold higher than the UNAIDS fast-track target in 2020 (1.5 million vs 500,000).
- Key populations represent 65% of new infections and can be targeted for HIV prevention (young women in sub-Saharan Africa are at particularly high risk – 6 of 7 new infections among adolescents).
- Oral PrEP poses challenges
  - ◊ Daily pills not preferred, adherence, stigma, fragmented roll out.
  - ◊ Uptake is insufficient to meet the UNAIDS target (1,000,000 users in LMICs, yet > 13 million adolescents in SSA (15-24y) experienced STI symptoms in past year).
- Uptake of LA CAB would need to grow by many orders of magnitude, but delivery to scale may be possible to drive a step-change.
  - ◊ Product preference research.
    - * Women 18-30y in South Africa indicate a preference for infrequent injections (every 2-3 months) over daily pills (93% probability).
  - ◊ Scale up of LA product comparators provides a precedent for feasibility – scale up of this magnitude has been accomplished in the family planning space with LARC.
  - ◊ The user base for LARC or injectable contraception in SSA informs the target for scale used to estimate CAB LA cost (~36 million women aged 15-49y).

CAB-LA COGs calculation – a conservative estimate for a generic manufacturer in a low-cost location.

- Cost of API is based on DTG pricing (similar molecular structure) and assumes a decrease over time as volume increases from launch to scale.
  - ◊ 20kg DTG imported from China to India @$3232/kg in 2016 vs 3MT DTG imported @$774/kg in 2019.
  - ◊ CAB API at launch ($3000/kg) – $1.80 for 600mg of CAB – $10.80 PPPY (6 vials).
  - ◊ CAB API at scale ($1000/kg) – $0.60 for 600mg of CAB – $3.60 PPPY (6 vials).
- Cost to formulate FDF
  - ◊ $2.00 per vial x 6 vials – $12.00 PPPY (formulation cost for injectables made at very large scale is ~$0.50 per vial).
  - ◊ Generics will likely need to invest in high-volume sterile fill/finish lines, but the upgrade cost would be relevant to a variety of HIV and non-HIV related products
- Cost of gamma irradiation to sterilize CAB API and FDF.
  - ◊ $0.70/kg – $0.04 PPPY (can be done at industrial scale).
- Capital expansion and development considerations.
  - ◊ Specialized Nanomill (API to nanoparticulate) – $2,000,000 (2-fold above market cost).
  - ◊ Bioequivalence studies – $1,000,000 (5-fold higher than an oral daily product due to study duration and enrolment required).
  - ◊ Other development costs – $5,000,000 (5-fold higher than typical development costs).
- CAB COGs estimate (API + formulation + irradiation).
  - ◊ $22.84 PPPY at launch to $15.64 PPPY at scale.
  - ◊ Cost per infection averted highlights CAB-LA cost-effectiveness, which is comparable to voluntary male medical circumcision (CAB $722-$962 vs VMMC $555-$4.4K).

Timing and delivery considerations.

- Earlier licensing is critical to meet market expectations.
- Operational research and design of delivery systems should be done in parallel with product development to ensure market uptake when generic available.
- Financial risk sharing mechanisms will be critical to investment – new product class with a new delivery system.

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

Focus groups were 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. Each group engaged in a crucial dialogue intended to inform how to collaboratively and strategically advance the LA field amidst a continually evolving landscape.

Focus Group 1
LA formulations for HBV/HDV treatment and prevention

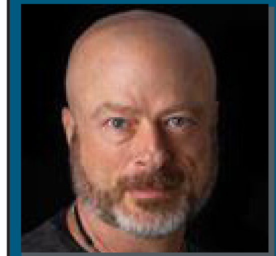
Focus Group 2
LA oral formulations vs other routes of delivery

Focus Group 3
Converting approved ARVs to LA: to prodrug or not to prodrug?

Focus Group 4
Developing combination LA products and regimens

Advancing the agenda for LA hepatitis therapies

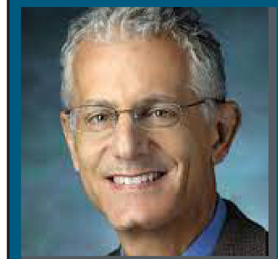
Rapporteur



Andy Kaytes
Co-chair, Community Advisory Board at UCSD Antiviral Research Center

Moderators

Jennifer Kiser
Associate Professor of Pharmacology at University of Colorado



David Thomas
Professor of Medicine at Johns Hopkins University

"Developing LA formulations for treatment and prevention of HBV and HDV"

1. Public health and clinical needs?
2. Review of existing LA efforts.
   HBV -
   ◊ Tenofovir prodrugs/TAF (Arnab Chatterjee and Benson Edagwa)
   ◊ TAF and/or TFV (Marc Baum)
   ◊ Entecavir and others
   ◊ Peginterferon
   ◊ RNAi
   HDV - Bulevirtide/Hepcludex
3. Challenges and solutions - are there any agents in the industry pipeline?

Clinical and Public Health Needs

LA therapy is convenient and could prevent HBV reactivation stemming from poor adherence.

- Current HBV therapies are effective, but adherence drops off with daily long-term therapies.

Jordan Feld from University Health Network reviewed clinical scenarios for LA HBV treatment.

- During pregnancy for PMTCT.
  - ◊ Oral medications can be challenging during pregnancy; a one-time LA dose would be beneficial.
- In the setting of immunosuppression.
  - ◊ HBV reactivation is a life-threatening complication of immunomodulatory therapies (i.e., cancer chemotherapy and biologics).
  - ◊ ***Avoiding daily HBV therapy where missed doses could have severe consequences would be helpful.***
- Rural/remote areas.
  - ◊ LAIs are particularly suited to high burden areas where care is intermittent or unavailable (i.e., SSA and many parts of Asia).
  - ◊ ***LAIs, even with current therapies, would be a significant benefit.***
- HBV cure.
  - ◊ Delivering a stable backbone without interruption is important to achieve cure with a purely antiviral approach (backbone of current NRTIs is likely).
  - ◊ If immunomodulatory therapies are added, need to ensure the safety of no interruptions.
- Pediatrics.
  - ◊ Children are not always willing or able to take pills.
- HIV-HBV co-infection.
  - ◊ Including HBV-active drugs in a LA HIV approach could control both conditions at the same time.
- Other potential areas exist.

Public health considerations.

- An estimated 257 million people are living with chronic HBV worldwide – large market from a pharmaceutical perspective.
- Most new cases occur in infants at birth (MTCT).
  - ◊ Birth dose HBV vaccination is a practical and effective PMTCT approach, but ***only 39% of infants born to HBV+ mothers received a birth dose vaccine in 2015***.
  - ◊ This number may be hard to raise due to the number of children born in non-traditional settings.
- Giving a LA agent during pregnancy could prevent some of these MTCT events – global health level.

Discussion Highlights

Chari Cohen from Hep B Foundation (represents patient/community voice).

- Daily pills can be stigmatizing or empowering - depends on the individual.
- Systemic access and discrimination are a concern for any non-curative treatment in RLS.
- Any treatment needs to lead to surface antigen negative status to be widely accepted – cannot get employment without seronegativity.
- It will be a challenge to deliver LA medications during pregnancy (due to access to care)

U=U campaign for HBV could be powerful in addressing discrimination/stigma.

LA HBV in pregnancy: in RLS, home deliveries are really the issue limiting the current PMTCT strategy.

- Many pregnant women attend at least one ANC visit (even if they deliver at home).
- Could implement a system – confirm HBV viremia via POC test and administer a LAI in the same ANC visit (would need to establish safety and same benefit as birth dose vaccination).
- As an add on, there is a need to train and license midwives to administer HBV birth dose vaccination at home deliveries.

Review of Existing LA HBV Efforts

TAF implants - Marc Baum (Oak Crest Institute)

- TAF is one of few drugs potent enough to theoretically enable drug delivery up to 6mo from an implant.
- Overview of technologies being studied.

Research Group	Implant	Toxicity
Alessandro Grattoni (Methodist Hospital)	Refillable titanium capsule with a nano-fluidic membrane	No significant toxicity in macaques at 3mo
Pat Kiser and Tom Hope (Northwestern Univ)	Polyurethane-based reservoir device with solid TAF microtablets at the core	Severe toxicity in rabbits (3mo) and macaques (30/90d)
Oak Crest Institute	Silicone device with microchannels covered in polyvinyl alcohol (a sustained release polymer)	No significant toxicity Clinical trial with CAPRISA is ongoing (data blinded) –passed 3 DSMB reviews.

- Toxicity of Northwestern implant is possibly due to a combination of factors – mechanical, polyurethane material, fumaric acid plus TAF and wound healing.

TFV ProTides - Benson Edagwa (UNMC)

- Single IM injection of a novel TFV prodrug formulation (NM1TFV) suppresses HBV replication for up to 4mo in HBV-infected, humanized mice.
  - ◊ NM1TFV gets distribution in lymph nodes and hepatocytes without specific organ targeting.
  - ◊ Prodrug formulations are well-tolerated (preliminary toxicology and injection site examination).
- Nanoformulated TAF (control) administered at the equivalent IM dose had a minimal effect on HBV replication.
  - ◊ Changing from oral to parenteral route of administration affects TAF biodistribution and delivery into the liver.

TFV prodrug bolus approach - Arnab Chatterjee (Calibr)

- Finding the right form of TAF and the right way to deliver it is key.
- Observed different release rates and differences in conversion to TFV-DP among oil-based vs aqueous suspensions of TAF – better results seen with free-base form compared to heavy fumarate.
- IM bolus of TAF (aqueous suspension) in dogs sustained good drug levels in PBMCs (TFV and metaboltes) over 80 days.
  - ◊ Good shelf stability for LMICs (potentially up to 6 months).
  - ◊ Bolus approach allows ISR to resolve vs continual release strategies – still have work to do with histopathology.

Discussion Highlights

Are treatment and prevention targets for intracellular TFV-DP the same for HIV and HBV?

- PK targets for HBV treatment may be higher than HIV.
  - ◊ Small study of patients with HIV-HBV coinfection: TFV levels were consistent with four doses/week and suppressed HIV, but not HBV.
  - ◊ HBV is replicated exclusively in the liver. ***Without oral delivery, the advantage of first pass metabolism is eliminated –need to target the tissue.***
- There are no strategies for targeting the liver with parenteral therapy.
  - ◊ TFV ProTides have high drug levels in lymphocytes and liver tissue – enough to suppress HBV in mice, but do not specifically target the liver. Therapeutic concentration may have to do with the lipophilicity of the formulation.
  - ◊ Rodney Ho also has evidence that TFV is taken up in lymphocytes and liver.
- Combining HIV prevention with a TFV product and HBV prevention in pregnancy would be useful.
  - ◊ Meg Doherty (WHO): There is great public health use for this work. There are many places where birth dosing is not happening – LA TFV for HBV and LA PrEP would be a nice correlate. How long from this stage to human to reality?

Need to engage industry to accelerate development.

- 257 million people represents a huge potential market for a LA formulation – large enough to offset small profits on an indivual basis.
- This group can engage in consciousness raising with the pharmaceutical and biotech industry.

This is an ongoing dialogue ....

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"LA oral drugs and formulations: How do they stack up compared to other routes of drug delivery?"

1. How do oral options compare with injectables, patches, implants?
2. How long is long enough to make the oral option preferable?
3. How do we monitor adherence for LA orals?
4. Who are the optimal patient populations for LA oral options?
5. What are the considerations around development of oral options?

Oral Formulations vs Injectables, Patches and Implants

Current use indications for oral LA agents.

- Osteoporosis (Qday and Qweek); malaria; and TB prevention (Qweek).
- ISL and LEN are in development for HIV.

Possible demise of ISL as a LA oral agent for HIV treatment (once weekly in combination) and PrEP (once monthly).

- All studies are on hold as of 18 Nov 2021.
- The only AE is a selective reduction in TLC – mean 30% reduction in CD4 count and TLC was observed across treatment and prevention trials; the effect appears to be dose related.
- Many questions remain:
  - ◊ Mechanism?
  - ◊ Could the effect be mitigated by a different delivery method?
  - ◊ Is there less concern with HIV prevention? CD4 counts are not typically monitored in HIV-neg people, and a drop may not be as serious as it is in a person with a low CD4 count to begin with.
  - ◊ Can ISL be salvaged using different doses?

Overall enthusiasm for LA oral options compared to other routes of delivery.

- Familiarity/status quo – most feel comfortable with oral.
- Self-administration is a huge advantage.
  - ◊ LAIs (CAB IM) need to be administered in a clinic setting.
  - ◊ Greater burden on the client and stretching the health system.
- No extra high tech support needed (refrigeration, syringes, etc).
- No extra visits – in LMICs, systems are now using multi-month prescribing and 3 to 6 month visits. No extra health care workers and less HCW training.

Tia Morton (DAIDS) - integration of behavioral social science research and development of LA agents.

- A portfolio of researchers are looking at discrete choice experiments where consumers weigh various pros and cons (e.g., oral vs injectable).
- Unveils interesting trade-offs and informs what attributes patients are willing to give up.
- Looking for ways to work with LEAP – pairing biomedical and biobehavioral researchers to address issues early in development to foster uptake and use.

How Long is Long Enough?

Need a range of options suitable for different preferences - choice is important, but logistics need to be simple.

- Any one approach does not have to be the solution for everyone, but if it works for a sizable proportion of population, then it should be pursued.
- The simpler the better for patients and facilities – need to be mindful of patient support issues during development (counseling, reminder process, linkage to care, peer HCWs).
- Dosing schedule needs to be equally simple to remember as daily (the status quo) – should be a regular interval that can be linked to other regular events (e.g., the first of the month or every week after church, etc).
- There is not one solution – learn from the family planning space –***there needs to be choice to allow for personal preference, especially for prevention***.

General enthusiasm for once weekly or once monthly - anything more complicated was considered a disadvantage.

- Qweek vs Qday – some improved adherence data with weekly administration (higher adherence and longer persistence).
- Every other anything (week or month) becomes difficult to consistently remember and other logistical issues arise, such as insurance company coverage of refills (only allowed a certain # of refills per month).
- Qmonth may be the upper limit for oral formulations – there are pharmacological barriers to dosing intervals.

How to Monitor Adherence?

Most people would prefer traditional HIV support methods over newer digital strategies - there are scenarios where higher tech options may be preferred.

- Higher tech monitoring options.
  - ◊ Digital pills with sensors that track whether a patient has taken the medication – first implemented in psychiatry (Abilify) without huge uptake.
  - ◊ Digital monitoring platforms (digital adherence).
- Pediatric monitoring.
  - ◊ Parents and caregivers might be more open to additional support when there are multiple caregivers, multiple households, or parents are juggling their own treatment with administering to their child.
  - ◊ Digital tablets could help ensure that the child receives their medication.
- People taking PrEP may not consider themselves patients in need of monitoring.

Optimal Patient Populations for LA Orals?

"Everyone" – anyone struggling with adherence, but certain populations are particularly vulnerable.

- Newborn prophylaxis, infants, children and adolescents.
- The postpartum period is characterized by many changes and transitions – women could link LA oral HIV agent to contraception (e.g., vaginal ring once-monthly).
- Patients already receiving directly observed therapy (e.g., methadone maintenance, syringe exchange etc) could link LA oral to this – DOT program is burdensome and would welcome less frequent dosing (i.e., TB).
- Any life circumstance with a sudden increase in burden or decreased access to care.
- Choice – ability to go back and forth between strategies.

Considerations for Development

How to roll out LA oral to pregnant women and children.

- A one-time "squirt" would be useful for neonatal prophylaxis.
- Breastfeeding infants (3TC/NVP).
- Mother fully suppressed (pregnant women)

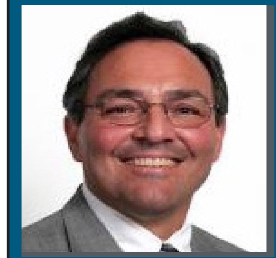
Regulatory barriers unique to LA oral.

- There are no extra regulatory or manufacturing issues for tablets.
- Fewer concerns about price and supply issues with fewer meds to take or deliver.
- HIV treatment regimen needs to be one cadence – need to settle on one cadence for multiple active agents.
  - ◊ Weekly ART could have potential for everyone, preferably in a combined tablet.

The issue is how people will engage with the health system.

Need to maintain regular conversations with generic manufacturers - LEAP can help with this.

Rapporteur



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"Best practices for conversion of immediate-release, approved ARVs: To prodrug or not to prodrug?"

1. Are there particular drugs or drug classes that may be more amenable to prodrug derivatization?
2. What are the relative merits of systemic prodrug delivery relative to prodrugs that fully hydrolyze prior to absorption?
3. What is the impact on the nonclinical safety package? Considerations for treatment versus prevention?
4. Are there any differences between children and adults?

What Drugs or Drug Classes are Amenable to Prodrug Derivatization?

Creating LA prodrug formulations depends on water-insoluble drugs, yet many current drugs are water-soluble (e.g., nucleoside analogs).

- Nucleoside analogs are the backbone of HIV care – need to explore how to prodrug this class of drugs to improve the quality of care given their drug resistance profile.
- Creating a combination product is difficult – UNMC began with HIV prevention.

Five topics in prodrug development.

- Optimize drug hydrophobicity: nucleosides are challenging – INSTIs are easiest (CAB, BIC and DTG prodrugs created with $t_{1/2}$ of one year); PIs are most difficult.
- Fine-tune drug hydrophobicity and pair with excipients and surfactants to be water-soluble.
- Optimize the prodrug moiety structure and stability
  - ◊ Change linker and linker position, length of the carbon chain, and the use of active agent dimers and trimers.
- Optimize chemical and enzymatic hydrolysis rates of the prodrug to the active agent.
- Aim to create stable nanocrystals in depot cells and predominantly mononuclear phagocytes at the injection site or lymphatic system.

Prodrug development considerations.

- Various reasons for using prodrugs:
  - ◊ Improve bioavailability; target specific cell or tissue uptake and improve uptake; improve compatibility with dosage formulation; and extend duration of effectiveness via non-oral dosing.
- Critical to understand the duration of drug presence and effectiveness, safety, and methods for depot removal.
- Goals must drive research: Are we trying to improve absorption, clearance, safety, liver metabolism, targeting the drugs to a specific site, duration of effectiveness, etc.?

Why aren't protease inhibitors a LA target?

- Half-life is relatively short and may still require ritonavir, even if dosed non-orally.
- Potency requires a large dose.
- Local inflammation observed in various models.
- Active agent is associated with a substantial number of complex DDIs – raises concerns about long-term management as a LA product.
- The field appears to be moving away from PIs, so interest is waning.

Merits of Systemic Prodrug Delivery vs Prodrugs that Fully Hydrolyze Before Absorption

A goal for a prodrug should be to improve the therapeutic distribution to the site of action and reduce adverse events.

- Concerns about LA drug clearance and mechanisms for eliminating the drug quickly in cases of toxicity or appearance of drug resistance.
  - ◊ OLI is not practical given the clinical characteristics of patients that would benefit from LA regimens.
- All derivatives of the product need to be followed.
- Optimization of size and shape and selection of surfactants may be the most critical components in developing prodrugs that are effective and safe.
  - ◊ Drug-linker-tail model – excipients and size and shape of the 100nm and 200nm nanocrystal impact how crystal and drug dissociate and hydrolyze from the depot.

Importance of the prodrug tail in HIV, TB and HCV and how we think about LA duration and effectiveness.

- Challenge of targeting to the lung (TB) or liver (hepatitis) while developing a drug with a duration appropriate to the need.
- Importance of the tail depends on the duration of treatment – HCV cure (8 weeks) vs drug-susceptible TB (4-6 mo) vs HIV (lifelong).
- Need to be diligent about monitoring drugs during the tail to ensure no unintended consequences, such as sub-therapeutic doses that could lead to drug resistance.

Impact on Non-Clinical Safety Package?

FDA advice and preclinical work depends on the parent product and is case-specific

- Variables include: what is known about safety, how much of that data can be leveraged, what are you doing to that product, and how it will be delivered
- The lifetime of the product in circulation matters.
  - ◊ Suitable nonclinical safety and PK exposure models must be identified to measure the prodrug, metabolites, and the active agent.
  - ◊ If the product breaks down quickly, and the prodrug is mostly undetectable or undetectable, then could potentially leverage existing oral data.
  - ◊ The nature of the metabolites is critical. If the prodrug is radically different from the API, you will need to do more. If the PK and the metabolite are not that different from the original product, an abridged preclinical program might be possible.
  - ◊ Anticipate performing some bridging studies.
- Novel excipients and involvement of a device will change the course of action.
  - ◊ If the product is combined with a device, biocompatibility of those materials must be studied.
  - ◊ ISRs and safety of excipients will need to be studied.

Given that PK is a surrogate, could it be misleading to use oral PK to guide a non-oral program?

- ADME of oral vs non-oral delivery – absorption could be dominant for oral drugs, and clearance could be dominant for non-oral formulations.
- Focused on the safety aspect – you would assess organ distribution and organ toxicity. It would be a good sign if non-oral PK safety and toxicity profiles are comparable to the oral drug profiles.

Does the nonclinical safety package depend on targeting treatment versus prevention?

- FDA would not be that flexible for a prevention product given that the target audience is people at high risk but otherwise healthy. There is a different risk-benefit ratio for treatment versus prevention.
- Even if a product is specifically targeted for prevention, treatment studies may still be required – you may need to include a small preclinical treatment package.

Children vs Adults?

Began with the assertion that we typically try to extrapolate from adult studies.

- Children require smaller doses – the ideal scenario would be a two-month drug dose at birth, followed by six-month incremental dosing.
- Need to address variability and absorption, metabolism differences, and metabolism changes as the child ages.
- Need to address differences in absorption and distribution of a drug or prodrug and the impact of the nanomaterial following IM or SQ administration in a baby.

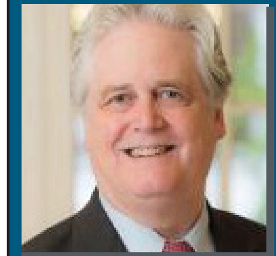
Examples of changes in prodrug conversion rates as a function of age or weight of a baby.

- Various esterases mature with the baby, but unsure if this translates into any clinically relevant changes in PK.
- Transport systems mature in babies and could affect PK.
- Gut pH in babies (4.5) is higher than an adult and can affect the release of an encapsulated drug.
  - ◊ Taste-masking LPV – no drug was released when administered in the first 2 weeks of life.
- Carboxylesterases increase by 2-3 fold from <3 weeks to ≥6 years old (https://pubmed.ncbi.nlm.nih.gov/26825642/).

Using in-vivo and in-silico models to help with infant studies.

- FDA will look at safety in NHP models, but does not use PK data as a surrogate for infants – the developmental profiles of NHPs and human infants are different.
- In-silico models must account for size, volume and function and include a continuous growth mode – be mindful about children's growth and maturation; Model validation is important.

Rapporteur



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"Challenges in developing combination LA products and regimens"

1. How well-matched do products need to be?
   Specific considerations
   Differences for treatment vs prevention

2. Do platforms need to be matched in treatment regimens?

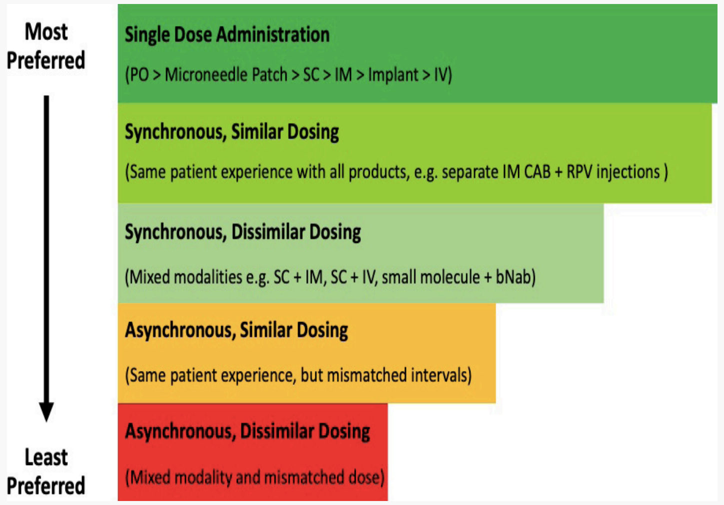
3. Two drugs or three? Two-drug regimens are becoming the standard for oral regimens -
   Is it the best option for all ARVs/products?
   Is it the best option for all populations?

How Well-Matched Should Products Be?

Primary considerations for any combination formulation.

- Same as for any single LA formulation.
- Safety, efficacy and tolerability.
- Target Product Profile (TPP): design and develop with the end goal in mind.

Rank order of Matching options - "simpler is better."



Additional Considerations.

- Longer dosing intervals are appealing, but may introduce trade-offs and less optimal profiles.
  - ◊ Require higher drug volumes; low utility for infants and children with rapid changes in drug disposition.
- Different populations have different TPPs.
  - ◊ Infants and children <2y: rapid metabolic and weight changes; injections are difficult.
  - ◊ Pregnancy – PK changes during pregnancy and postpartum.
  - ◊ MSM in Brazil prefer injectable PrEP, whereas other populations prefer pills.
- Self-administration (pills or patch) is a big advantage vs HCP administration.
- Ready-to-use vs reconstitution and other dose administration issues.

Should the inherent characteristics of the API drive development of LA formulations?

- Not all APIs are amenable to combinations.
- Not all APIs will be amenable to all LA formulations.
- To match API to delivery system, either manipulate the drug or manipulate the system.
- Potential for including "boosters" to modify hepatic metabolism of one of the drugs to better align the match between dissimilar APIs and the delivery system.

Combining LA formulations could potentially address multiple use cases.

- HIV PrEP + hormonal contraceptives.
- HIV PrEP + opioid use disorder treatment (e.g., buprenorphine).
- HIV treatment + HBV treatment.

Special considerations for LA combination therapy for HIV in Latin America, Asia and SSA.

- DDIs, particularly TB treatment (rifamycins)
- HBV coinfection.
- Policy, regulatory, and implementation issues can block or delay access to effective treatments.

Mothers and children.

- Infants will require frequent dose adjustments – short dosing intervals and flexible dosing formulations are needed.
- MAP advantages:
  - ◊ Avoids injections (challenging in the very young).
  - ◊ Potential for dose adjustments for age, weight and gestational age.
  - ◊ Self (or caregiver) administration.
  - ◊ Can be removed.
- bNAb advantages:
  - ◊ Multiple delivery options (IM, SC, IV).
  - ◊ Maybe easier/safer than small molecules.
- Therapeutic drug monitoring could inform dose adjustments, but will be challenging in terms of access and implementation.

Consensus is that there are differences for prevention vs treatment - examples:

- LA mono-entity efficacy enables better product profiles for PrEP than for treatment.
- LA PrEP has potential for longer dosing intervals.
- Efficacy for PrEP may be achieved with lower drug levels than for treatment.
- Side effect vs efficacy balance is different for PrEP and treatment – PrEP for "healthy" people requires a higher safety profile.

Two vs Three Drugs?

Safety and efficacy are the priority, not the number of agents.

- May not even need 2-3 agents for some case indications.
- Enhanced potency and higher barrier to resistance of current ARTs and pipeline, as well as favorable PK of some LA/ER formulations.

Summary of Considerations for Combinations of LA/ER Formulations

Safety and efficacy are the first priorities - after that "simple" is better.

Achieving "Simplicity" depends on:

- The ability to match APIs when possible.
- The ability to match delivery systems and dosing interval when possible.
- Addressing the needs of different populations that might require different formulations and have different use cases.
- Recognizing that different formulations will have different market forces and different regulatory, implementation and scalability issues.
- PrEP and treatment use cases will likely require different formulations.
- The Islatravir story is a "wake up call" – plans for combination therapy may have been derailed "late in the game" by unexpected side effects.

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Long-Acting/Extended Release
Antiretroviral Research Resource Program