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

HIV prevention program – CAB LA for PrEP.

Highlighted work from research partners to be presented at CROI 2024.

- Implementation study.
  - Randomized trial of SEARCH dynamic choice HIV prevention including injectable cabotegravir (oral #172). Offered structured choice among CAB LAI and oral PrEP or PEP; participants allowed to transition to the therapy of their choice.
- Important insights from the HPTN 083 trial.
  - Site-based HIV testing assay performance for CAB and TDF/FTC PrEP failure (oral #128).
  - No increased HTN risk with CAB-LA vs TDF/FTC for HIV PrEP (poster # 789).
  - CAB maintains protective efficacy in setting of bacterial STIs (oral #131).

Progress in global access/LMIC roll out in collaboration with global partners (PEPFAR, Global Fund, LA PrEP Coalition) and community stakeholders (AWCAB, AfroCAB, KP WG, and HPTN CWGs).

- Voluntary licensing agreement executed with MPP to enable access to CAB LA for PrEP in 90 countries (7 months after FDA approval).
- Open-label extensions started in all HPTN 084 countries.
- >75% regulatory submissions (n=13) and approvals (n=14 + EU) in LMICs.
- WHO pre-qualification.
- Non-profit price decrease from 2023 to 2024.
- Planning coordination efforts, supply chain, and service delivery efforts.
- Executing supply agreements with PEPFAR, Global Fund, and MSF.
- Programmatic research underway in sub-Saharan Africa as well as implementation science studies.
- Working with the selected generic manufacturers on technology transfer for the CAB LA product.

HIV treatment program – combination LAI CAB regimens and pipeline of novel CAB formulations.

CAB LAI + RPV LAI.

- CARES study – Week 48 results (CROI 2024 late breaker #122).
  - Ongoing P3b randomized (1:1) OL, active-controlled, multicenter, parallel group noninferiority study of Q8W CAB LAI + RPV LAI vs QD oral ART (SOC) among VS PWH in Kenya, South Africa, and Uganda.
  - Informs treatment and use of the regimen in sub-Saharan Africa.
- ACTG 5352 Latitude (CROI 2024 late breaker #212).
  - CAB LAI + RPV LAI vs oral SoC ART among PWH in US with suboptimal adherence (persistent HIV-1 RNA >200c/mL or loss to follow up).
  - Multiyear effort: first enrollment in 2019, but significantly impacted by COVID pandemic, then restarted.
  - DSMB review Feb 2024: Q4W CAB LAI + RPV LAI had superior efficacy vs QD oral ART; all participants offered the choice to receive open-label therapy to ensure best possible health outcomes.

CAB LAI + bNAb IV (VRC07-523LS or N6LS).

- ACTG 5357 trial (CROI 2024 oral abstract #119).
  - P2 three-step study assessing safety and efficacy (maintenance of virologic suppression) of VRC07-523LS (bNAb targeting HIV-1 CD4 binding site) + CAB LAI in VS PWH.
  - Step 1 (proof of concept): QD oral CAB + 2NRTIs x 4 weeks; Step 2: Q4W CAB LAI + Q8W bNAb (20mg/kg) IV x 48 weeks; Step 3: SOC ART x 48 weeks.
- Embrace trial (NCT05996471).
  - P2 study of CAB LAI + N6LS IV or SC with rHuPH20.
  - Initial dosing is Q4W CAB LAI with potential to introduce CAB ULA dosing by amendment.

Novel CAB formulations for extended dosing intervals.

- Approach 1: Use recombinant human hyaluronidase PH20 (rHuPH20) to administer higher doses and volumes of the current approved CAB200 formulation as a SC injection.
  - CAB200+rHuPH20 (800mg in 4mL, 1600mg in 8mL, 3200mg in 16mL).

- Approach 2: Administer ultra-long-acting CAB (CAB-ULA) formulation as a SC or IM injection.
  - CAB-ULA (800mg in 2mL, 1200mg in 3mL, 1600mg in 3mL).
- Ongoing P1 OL single-dose dose-escalation study (NCT05418868; CROI 2024 oral abstract #130).
  - Safety, tolerability, and PK of CAB200 (800-3200mg) + rHuPH20 SC and CAB-ULA (800-1600mg) SC or IM.
  - Approach 1 discontinued due to unacceptable safety and tolerability with higher doses, particularly the ISR profile.
    *rHuPH20 allowed SC administration of CAB200 at higher doses.
    *PK similar to dose-normalized CAB200 IM.
  - Approach 2 is moving forward.
    *PK profiles of SC and IM administration support dosing intervals ≥ Q4M.
    *Safety and tolerability are encouraging at CAB-ULA doses 2.7-fold (1600mg) higher than the approved CAB200 dose.
    *Q4M CAB-ULA IM formulation selected for upcoming HIV treatment and prevention studies.

Summary.

- CAB LA for PrEP – new insights from HPTN 083 (HIV testing performance, efficacy in setting of bacterial STIs, and no increased HTN risk) and good progress in LMIC access.
- HIV treatment datasets are expanding – new data on use in the sub-Saharan Africa setting, adherence-challenged PWH, and in combination with bNAbs (VRC07-523LS and N6LS).
- Novel CAB-ULA formulation demonstrates Q4M PK profile – IM dosing selected for further development in clinical trials of HIV PrEP and treatment.