A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals

Brief Description:
This 4 step study compares Long-Acting (LA) Injectable Antiretroviral Therapy (ART) to standard of care (SOC) oral ART in previously non-adherent individuals. Step 1 is the induction phase and all participants receive study provided SOC oral ART. Participants receive financial incentives for meeting study specified goals. Step 2 is the randomization phase and participants are randomized 1:1 to receive LA ART or continue on SOC for 52 weeks. Step 3 is the crossover/continuation phase. Participants randomized to LA ART will continue that therapy and eligible SOC participants will crossover to receive LA ART for 52 weeks. Step 4 is the observational phase that switches participants who received at least one LA ART injection and are no longer eligible for injections back to locally-sourced oral SOC ART for 52 weeks.

Objectives:
To compare regimen success of LA ART (using RPV-LA and CAB-LA) to Standard of Care (SOC) in previously non-adherent, HIV-infected individuals by 48 weeks of follow-up after an incentivized oral induction period.

Key Inclusion Criteria:
- HIV-1 infected individuals who are 18 years of age or older.
- Prescribed ART for at least 6 months.
- Screening HIV RNA is greater than 200 copies/mL.
- Women must not be pregnant, planning to become pregnant, or breastfeeding. Women who can become pregnant must agree to use 1 form of effective birth control.
- There is evidence of non-adherence to their HIV medications. Non-adherence to HIV medications will be defined as having one of the two criteria below:
  1. Poor virologic response within the last 18 months (defined as $<1 \log_{10}$ decrease in HIV-1 RNA from the participant's historical baseline value or HIV-1 RNA $>200$ copies/mL at two time points at least 4 weeks apart) in individuals who have been prescribed ART for at least 6 consecutive months.
  2. Lost to clinical follow-up within the last 18 months with ART non-adherence for $\geq 6$ consecutive months. Lost to clinical follow-up is defined as either no contact with provider or missed 2 or more appointments in a 6-month period. ART non-adherence is defined as a lapse in ART $\geq 7$ days (consecutive or non-consecutive), in the 6-month period where they were lost to clinical follow-up per participant report.

Key Exclusion Criteria:
- Previous use of rilpivirine or cabotegravir.
- Uncontrolled seizures.
- Advanced liver disease.
- Unwilling to receive injections in the buttocks.
- Chronic Hepatitis C with anticipated use of anti-HCV therapy prior to the completion of step 2.
- Active Hepatitis B infection.

Study staff will be able to provide a complete list of inclusion/exclusion criteria.

Treatment:
Step 1: The first 24 weeks of treatment will consist of at least 3 HIV medications. One of those drugs must be a protease inhibitor or an integrase inhibitor.

Step 2: LA ART Arm:
  - Weeks 0-4: Oral cabotegravir 30 mg and rilpivirine 25mg daily
  - Weeks 4-52: LA Injectable cabotegravir and rilpivirine every 4 or weeks.
SOC arm:
Participants will continue their oral ART regimen from Step 1 for 52 weeks.

**Step 3:** LA ART Arm:
Participants continue LA Injectable cabotegravir and rilpivirine every 4 weeks for 52 weeks.

Crossover arm:
Participants with an HIV RNA <50 copies cross-over to the LA regimen.
Weeks 0-4: Oral cabotegravir 30 mg and rilpivirine 25mg daily
Weeks 4-52: LA Injectable cabotegravir and rilpivirine every 4 weeks.

**Step 4:** Participants who received at least one injection and transitioned off LA injectable before the end of Step 3 will enter step 4. Participants will take oral ART locally sourced.

**Duration of Study:**
Steps 1-3 combined are a total of 128 weeks. Step 4 lasts 52 weeks. The study provides ART in steps 1-3 and participants will transition to locally sourced ART for step 4.

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