Very Early Intensive Treatment: Update on P1115

Cure Scientific Committee Update
IMPAACT Members and Collaborators Meeting
18 June 2015
Outline

• Updates to P1115
  – Modifications in past year
  – Upcoming amendment

• 2007 Protocol in development
  – Phase I Maraviroc in neonates
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study

Primary Objective:
- To assess *HIV remission* among HIV-infected neonates who initiate ART within 48 hours of birth

*Remission* = having no confirmed plasma HIV RNA at or above the limit of detection (LOD) of the assay for 48 weeks following ART cessation
P1115 Opened to Accrual
July 2014

Mississippi Baby: Clinically Asymptomatic Rebound Viremia Following 27 months of Virologic Remission

Persaud, IAS,,2014
Protocol Response to Reports of Virologic Rebound

- Accrual temporarily halted
- Limitation of viral reservoirs remained an important goal
- Letter of Amendment (LoA)
  - Consent form updated
  - Appoint expert panel to review current state of cure research and biomarker criteria to stop ART
    - First review ~1 year before first enrolled infant eligible to stop ART; periodically thereafter
  - Family meeting to review current data prior to stopping ART; re-consent to stop ART
  - Follow up extended to 5 years for all children who achieve remission
- Accrual resumed after LoA approved
Progress Since P1115 Re-opened

- 12 US sites activated: Baltimore, Boston, Chicago, Denver, Fort Lauderdale, Memphis, Jacksonville, Miami, New York, San Juan
  - 4 subjects enrolled
    - 3 Cohort 1 → all uninfected and now off study
    - 1 Cohort 2 → remains on study
- Additional US sites, South Africa and Uganda expected to activate shortly (e.g. June or July)
- Sites in other countries undergoing IRB/EC and drug regulatory approvals
  - ~40 total sites expected
IMPAACT P1115 Study Sites

Breastfeeding sites in:
- Haiti
- India
- Kenya
- Malawi
- South Africa
- Tanzania
- Uganda
- Zambia
- Zimbabwe

Formula feeding sites in:
- Argentina
- Brazil
- Thailand
- USA
Building on P1115

• With virologic rebound in the MS baby, other approaches are warranted
• Timing of in utero infection is uncertain
  – If weeks prior to birth → less likely that ART will enable a prolonged remission
• Intrapartum and early breast milk transmission
  – early ART may be more effective in restricting establishment of viral reservoirs to enable HIV remission
• Amendment to P1115: exploring early intensive ART to achieve remission in newborns infected perinatally or through early breast feeding
P1115 Amendment Study Design

• Cohort 1 infants enrolled in P1115 who have a negative birth HIV PCR
  – Switch to local ART prophylaxis at 2 weeks
  – HIV PCR performed at 4, 6, 8, 10 and 12 weeks
    • Expect 6-10 infants to be infected at/after birth
    • Enter Step 2 and start 4-drug cART
  – Negative PCR at 12 weeks = uninfected; exit study
Newer Drugs Needed for Very Early Treatment

- Higher potency +/- tolerability
- Transmitted NVP resistance
- Integrase inhibitors
  - P1110: neonatal PK of raltegravir
    - 13 infants enrolled to date
    - Daily dosing cohort to open soon
- CCR5 inhibitors
  - Maraviroc has been studied in children >2 years
  - Approved for protocol development for neonates
- When PK/safety of newer drugs established, hope to substitute for/add to NVP and LPVr in P1115
IMPAACT 2007: “Phase I Safety and Pharmacokinetics of Maraviroc in HIV-1-Exposed Neonates at Risk of Acquiring HIV-1 Infection“

Co-sponsored by IMPAACT and ViiV

- **Design:** Phase I safety and PK study with 2 sequential dosing cohorts
- **Study Population:** Full-term neonates <72 hours old born to HIV infected mothers at risk of HIV-1 transmission. In addition to Maraviroc, infants will receive standard of care ARV prophylaxis that does not include a potent cytochrome P450 CYP3A4 inhibitor or inducer.
- **Sample Size:** A minimum of 6 and 12 infants in Cohorts 1 and 2, respectively, treated at the final dose recommended for each cohort.
- **Study Treatment:**
  - Cohort 1: Infants receive a single 8 mg/kg dose of maraviroc solution between 0 and 72 hours and on day 7-14 of life with intensive PK sampling
  - Cohort 2: Infants receive daily dosing starting within 72 hours of birth and continuing through 6 weeks of life with maraviroc solution at dose determined from Cohort 1 data.
- **Study Duration:** Safety monitoring x 6 months. Accrual is expected to require approximately 24 months.
Barriers to Enrollment into P1115

• High-income countries
  - Few women untreated during pregnancy (Cohort 1)
    • Most live far distance from IMPAACT sites
  - Mothers at highest risk for transmission may be least amenable to research +/- intensive neonatal ART (Cohorts 1 and 2)

• Low-middle income countries
  - Birth PCR testing not routinely available
  - Some sites must purchase ART (not supplied by study)
    • Must be HIV-diagnosed before 3-drug Rx available through country sources
    • Liquid NRTI’s not available in-country: fixed dose dispersible tablets used for ages >=6 weeks
Remaining Issues

• Decisions about treatment cessation
  – Sensitive biomarkers are needed to predict potential for prolonged remission
  – Exploring other non-blood reservoirs (gut, CNS)

• Newer potent ARVs

• bNAbs as adjunctive therapy
Q4 2014: US sites open to enrollment

Q3-4 2015: International sites open for enrollment

Q2-3 2016: Maraviroc PK Protocol opens

Q2 2017: P1115B Raltegravir protocol

Q4 2018: P1115D VRC01 protocol