HIV Infected Newborns: Functional Cure, Induced Remission

2014 HIV Breakfast Club Meeting
Hilton Garden Inn, Albany, NY

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DISCLOSURE
No conflict of interest

INTRODUCTION
- March 3, 2013 (NIH News) – “an HIV-infected child who appears to have been functionally cured of HIV infection.”
- March 3 – 6, 2014 (Abstract 75LB, CROI) – Very early cART in Perinatal HIV infection: Two case studies
  - Mississippi child, Long Beach baby
- July 10, 2014 (NIH News) – the Mississippi child… “now has detectable levels of HIV.”

http://www.natap.org/2014/CROI/croi_38.htm

TERMINOLOGY
- Functional cure – HIV infected, VL too low, seroreversion
- Residual viremia – <20 copies of plasma HIV RNA/mL
- Induced remission, prolonged remission, sustained remission, viral remission
- Durable HIV VL suppression – undetectable VL conferred by cART (<40 copies/mL)


GOALS
- Describe the clinic courses of the functionally cured infants.
- Review key recommendations in the care of HIV-exposed & HIV-infected infants.
- Provide various insights on the significance of functional cure or induced remission towards HIV cure.

HIV CURE
- the Berlin Patient, the only documented HIV cure for >5 years
- s/p treatment for AML, total ablative chemotherapy, radiation therapy, stem-cell transplantation (donor, homozygous CCR5 delta32), GVHD
- Off cART without subsequent viral rebound
- This case suggested that HIV reservoir may be viable therapeutic target
MISSISSIPPI BABY

- Mother delivered at 35 weeks gestation via spontaneous vaginal delivery
- No prenatal care, (+) rapid HIV at delivery
- No cART during pregnancy, No IV ZDV at delivery


MISSISSIPPI BABY

- Diagnostic criteria for HIV (+): 30 hrs of life, HIV DNA (+); 31 hrs of life, HIV VL 19,812 copies/mL
- cART was started a 30 hrs of age
  - ZDV 2 mg/kg every 6 hrs, 3TC 4 mg/kg BID; NVP 2 mg/kg BID (prophylaxis for high risk MTCT)
- 1 week of age: ↓ risk of HIV resistance with low adherence
  - changed NVP to LPV/r


MISSISSIPPI BABY

- The decline in the viral load is biphasic similar to other HIV-infected infants.
  - Initial rapid, exponential decline (~90% viral clearance) → slower, exponential 2nd-phase decline.


MISSISSIPPI BABY

- Sustained control of the HIV-1 RNA levels during the cART (30 hrs-18 mos.) & after discontinuation of cART (18-30 mos.).

MISSISSIPPI BABY

- The CD4+ T cell % were within or greater than the normal range for age at all time points tested.
- The shaded area indicates the normal range for age (10th – 90th percentile).
- Growth & development have been normal.


BABY STEPS ON HIV CURE

- Best characterized cellular reservoir for HIV, resting memory CD4+ T cell
  - Intermittent release of infectious virus
- Implications of persistence of HIV in reservoirs
  - Ongoing immune activation despite virologic suppression
  - Biggest challenge to achieving complete eradication of replication-competent HIV


MISSISSIPPI BABY

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Antiretroviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid HIV antibody at delivery</td>
<td>Positive</td>
<td>None</td>
</tr>
<tr>
<td>HIV ELISA and confirmatory Western blot, at birth</td>
<td>Positive</td>
<td>None</td>
</tr>
<tr>
<td>Viral load, at 24 hr</td>
<td>2423 copies/mL</td>
<td>None</td>
</tr>
<tr>
<td>CD4+ T cell count, at 14 days</td>
<td>646 cells/µL</td>
<td>None</td>
</tr>
<tr>
<td>HIV-1 genotypic subtype, at 14 days</td>
<td>Wild type, subtype B</td>
<td>None</td>
</tr>
<tr>
<td>qPCR coefficient at 24 months</td>
<td>511 copies/µL</td>
<td>None</td>
</tr>
<tr>
<td>qPCR coefficient at 8 months</td>
<td>14,600 copies/mL</td>
<td>None</td>
</tr>
<tr>
<td>HIV-1 env (at 24 months)</td>
<td>A1, A2, Fab, 1A, C2, C3, Env, and C1</td>
<td>None</td>
</tr>
<tr>
<td>Mutant status at C250 Hif224L, at 24 months</td>
<td>Unmutated</td>
<td>None</td>
</tr>
<tr>
<td>Frequency of infected cells, at 24 months</td>
<td>157 SUM</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1. Laboratory Testing and Antiretroviral Therapy Received by Mother and Child


BABY STEPS ON HIV CURE

- Challenging questions on the Mississippi baby
  - Was infection established in the infant?
    - Yes, met the criteria for neonatal HIV infection: (+) HIV DNA PCR (30 hrs of life); HIV RNA VL 19,812 copies/mL (31 hrs of life)
  - Are the early virologic findings a result of maternal-fetal circulatory exchange?
    - No, HIV RNA VL in the baby is 8x the mother of 2423 copies/mL (at 24 hrs)


BABY STEPS ON HIV CURE

- The million dollar question, “is the child cured of HIV infection?”
  - Definitive maybe... no
  - The need for long term follow-up while off cART and the imprecision in measuring viral reservoir
    - “we have to exercise caution before inferring general principles from this case report.”
  - Case report: proof of principle, stimulate hypotheses, lead us down the road to HIV cure
    - “A journey of a thousand miles begins with a single step.” (Lao-tzu)

LETTER TO THE EDITOR

- The mother being a long-term nonprogressor (LTN) which controls replication
  - The underlying mechanism is unknown
- An inherent protective characteristic of NK cells in long-term nonprogressor
  - Which may protect patients from innocent-bystander killing of CD4+ cells induced by HIV Ag gp41 peptide S3.
- The mother could have transmitted this protective immunogenetic trait to the infant

AUTHORS REPLY

- Viral or host factors may have contributed to the sustained remission
- No evidence of known host factors associated with elite controller, no CCR5 deletions (CCR5 Δ32), & no protective alleles (HLA-B27, B*57)
- Investigation of other host factors will continue as available blood volumes allow
- The phenotype for LTN & elite controllers is uncommon

LONG BEACH BABY

<table>
<thead>
<tr>
<th>HIV DNA Test</th>
<th>MSISSISSI BABY</th>
<th>LONG BEACH BABY</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) 24 mos.</td>
<td>(-) 6-47, 67 days of life</td>
<td></td>
</tr>
<tr>
<td>Replication-competent HIV</td>
<td>(-) 24 mos.</td>
<td>(-) 1-, 3 mos. of age but HIV DNA (+) at 1 mos.</td>
</tr>
<tr>
<td>HIV ab (gp 160)</td>
<td>(-) 24 mos.</td>
<td>Indeterminate, 3 mos.</td>
</tr>
<tr>
<td>CD4+ T cell percentages</td>
<td>Normal for age</td>
<td>Normal for age</td>
</tr>
<tr>
<td>cART Restarted</td>
<td>~4 years</td>
<td>Continued</td>
</tr>
</tbody>
</table>

LESSONS LEARNED

- N = 2, findings support “restriction of HIV spread with very early cART”
- Need for standardized approaches & the use of sensitive laboratory markers to guide the very early cART towards viral remission
- The challenges in HIV cure research is to determine the best way to measure virus reduction in the reservoir.
GOALS
- Describe the clinic courses of the functionally cured infants.
- Review key recommendations in the care of HIV-exposed & HIV-infected infants.
- Provide various insights on the significance of functional cure or induced remission towards HIV cure.

KEY RECOMMENDATIONS
- January 2014 – NYS-DOH, Care of the HIV-Exposed Infant with Indeterminate Status
- NVP was given at higher therapeutic doses rather than standard prophylactic doses.
- LVP/r was substituted for NVP at 7 days of life that preceded warnings from the FDA against the use of LPV/r in infants <14 days.

KEY RECOMMENDATIONS
- Further investigation is on-going, & clinical trials are planned to address whether early cART is safe & effective in infants.
- This Committee continues to recommend that regimens other than those in Table 1 should only be used in consultation with a pediatrician with experience in HIV treatment & management.

CASE SCENARIO #1
- July 2014: 25 yo HIV (+) pregnant ♀ at 30 wks gestation with resistant HIV, HIV VL 910 copies/mL; what regimen to use once the baby is born?
CASE SCENARIO #1

- Table 2 – mother has known drug-resistant HIV, consider a 2- or 3-drug regimen in consultation with HIV specialist/experts
- Plans: improve adherence while on ATV/r TDF-FTC; obtain another HIV VL, if detectable obtain HIV resistance assay; if undetectable continue cART
- 3-drug regimen in the previous pregnancy (ZDV, 3TC, NFV); compounded NFV 625 mg/tab to suspension.

CASE SCENARIO #1

- PACTG 1043, 1 drug (ZDV); 2-drug regimen (ZDV, NVP); 3-drug regimen (ZDV, 3TC, NFV)
- MTCT – 4.9%; 2.2%; 2.4%
- Neutropenia was significantly more common in the 3-drug regimen than with the 2-drug or zidovudine alone i.e. 27.5% vs. 15%
- NFV is no longer available in pediatric formulation in the US

CASE SCENARIO #2

- 6 mo. infant, HIV-exposed from birth, lost to follow up after obtaining HIV RNA viral load & starting ZDV
- For diagnosis – 2 negative NAT results, one obtained at ≥ 4 weeks of age & at ≥ 4 months, definitively exclude HIV infection (no ab test <18 months)
- Loss of efficacy when ZDV prophylaxis was delayed beyond 48 hours after birth

GOALS

- Describe the clinic courses of the functionally cured infants.
- Review key recommendations in the care of HIV-exposed & HIV-infected infants.
- Provide various insights on the significance of functional cure or induced remission towards HIV cure.
March 3 – 6, 2014 (Abstract 53, CROI) – Luzuriaga, K. presented “the impact of early ART on HIV persistence in children”
- ART initiated within 3 months of birth is needed to preserve the immune function
- ↓ HIV DNA within cells, ↓ replication-competent reservoirs on the 1st year of treatment
- Followed children for >10 yrs.: ↓ proviral DNA, no recoverable replication-competent HIV-1, no detectable HIV-specific immune responses

PACTG 356 – 15 children treated within 2 weeks to 3 months after birth (mean, 1.9 mos.)
- Virologic suppression by 16 wks (Md, 8 wks)
- Maintained suppression have seroreversion by 15 mos.
- These children have now been treated for 18 years, ↓ HIV PBMC (<10 copies/million)
- No virus evolution in those with recoverable replication-competent virus compared to neonatal sample

Cure Symposium
- Mississippi child thought to have been cured of HIV after very early ART was still infected.
- Now age 4, currently on cART & asymptomatic
- Provided insights into HIV pathogenesis, viral persistence, & immune control in infected newborns
- NIH is committed to invest in HIV cure research

IMPAACT P115
- International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)
  - Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission
  - A Phase II/II Proof of Concept Study
  - Open label, non-randomized, safety/ efficacy study
  - This study is currently recruiting participants (6/14)
  - Infants infected with HIV in utero
  - AIM: explore the effects of early intensive ART on achieving HIV remission among infected infants.
ETHICAL ISSUES

- The strategy used to the Mississippi baby is important to establish if it can be replicated
- Ethical issues in the pursuit of functional cure should be addressed
- Difficult trade-offs associated with choosing the study population & broader social implications

ON POPULATION & DESIGN

- The strategy of very early cART
  - To conduct observational research similar to longitudinal studies i.e. identify & study these infants
- It is not clear if there is enough scientific reason to conduct a randomized controlled trial
  - A design most likely to answer the question, maximizing benefit & minimizing harm
  - One-arm interventional trial or an observational study

ON POPULATION & DESIGN

- Careful testing should rule out potential confounders
  - Infants identified are HIV infected, elite controllers
- Subjects from low & middle income countries (LMIC) vs. high income countries (HIC)
  - Might exploit subjects in LMIC if interventions will benefit those in HIC
  - Functional cure is relevant in the health priorities in LMIC with high burden of AIDS
  - Drugs that are available in LMIC

ON POPULATION & DESIGN

- Study enroll subjects from high risk of MTCT or low risk?
  - Ethical trade-offs: women at high risk for MTCT may belong to the vulnerable group (less educated, less integrated in the health-care, lower socioeconomic)
  - Automatic exclusion of the vulnerable group is misguided since it is not intended to target them
  - Inclusion of women at high risk for MTCT is to increase chance of benefit to the vulnerable infant

ON POPULATION & DESIGN

- The risk of MTCT is ~8.5% if the mother is not taking ART & presenting to the hospital in labor
- The risk of MTCT is 1-2% if the mother is taking ART
  - Enroll & expose many newborns to the risk of early cART in which most of whom would not be infected (requiring large sample size)
  - All things considered: proof-of-concept research should enroll infants at high risk of infection

RISKS & BENEFITS

- Children are vulnerable subjects since they cannot consent for themselves
- The risks justified by potential benefits or that any risks not justified by benefits are low & justified by social value
- To ↓ the risk of ART exposure to uninfected infants, mothers at ↑ risk for MTCT should be included & uninfected infants taken off ART
  - high risk MTCT, 8.5% HIV infected vs. 91.5% unnecessarily exposed to ART for ~2 weeks
RISKS & BENEFITS

- The study should have safety procedures to minimize risks (short term ART)
  - Monitoring for anemia & changes in liver functions
  - Mitochondrial toxic effects, transient growth & hematological abnormalities
  - Exclusion of premature infants
  - Counselling & other strategies to maintain adherence to ART


RISKS & BENEFITS

- All things considered: early cART in high risk MTCT offers potentially large benefits & a moderate risk which is a reasonable alternative to lifelong cART


INDUCED REMISSION

- "even if such cases are irrelevant for the cure of infected adults, they are critical wake-up calls for efforts to define safe and effective methods for the immediate treatment of HIV-exposed newborns with fully effective ART" (Luzuriaga, K)

http://www.natap.org/2014/CROI/croi_38.htm

TAKE HOME MESSAGE

- Clinic courses of the “Mississippi-” & the “Long Beach-” babies after very early cART.
- 2 drug regimen (ZDV, 6 wks & NVP, 3 doses in 1 wk) as supplemental postnatal prophylaxis
- Functional cures or induced remissions are major steps toward an HIV cure

THANK YOU