Sero and virologic Reversions in Successfully Treated Children: Role of latent pro-viral DNA reservoirs on remission and reversion

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Do we have kids on ART who turned HIV negative while on treatment?

• Yes

• No
NS: A Story of The Saved Child

• Tested positive for HIV with DNA PCR at the age of 2.3 months in 2009 in clinic Xx.

• Started on ART at age of 4 months as an infant vertically infected with HIV-1
  • Baseline CD4 = 2079 (40%)

• Transferred out to another hospital after five months on ART

• VL done at 7, and 19, months of ART came out 83 and 35.29 RNA copies/ml respectively.
NS: A Story of The Saved Child

- Viral load at 26 and 35 months of ART: TND
  - This VL report prompted HCWs to do rapid test
    - Non-reactive at 3.2 years of age.

- Subsequently the child was tested with HIV DNA PCR which was also negative.
What’s the interpretation?

• Cured

• Not initially positive

• False negative now

• We don’t know

• Other?
Case Reports

We had four different cases of children between 2011 and 2012 with the following characteristics:

- Diagnosed with HIV during infancy using single HIV DNA PCR
- Started ART during infancy and one around 21 months of age
- All displayed good adherence and adequate virologic suppression
- Sustained undetectable VL, prompted HCWs to do RT and subsequent DNA PCR tests
  - When the rapid tests turned negative care givers were informed that the children were HIV un-infected
• What would you have done in these cases? [VL-TND, serologic and virologic tests negative, care givers were informed that the kids were HIV-negative]
  • Stop ART and discharge the children from care

• Declare HIV negative status

• Stop ART and closely monitor the children for VL while ensuring OI screening and early detection of signs of HIV progression, prophylaxis, counsel and support family etc.
Case 1: HIV Diagnosis and Course of Treatment

- **Born**: April 09
- **5 mos**: DNA PCR: Pos
- **6 mos**: ART started
- **20 mo VL**: 2x Rapid Test: -ve
- **26 mo VL**: 2x DNA PCR: -ve
- **30 mo VL**: 1x Western Blot: IDT
- **36 mo VL**: Viral Load (Log 10)
- **6,89**: VL: 7mo
- **2,34**: 19 months
- **1,85**: 33 months
- **25 months**: VL: 13mo
Case 2: HIV Diagnosis and Course of Treatment

- Born: June 09
- DNA PCR: Pos
- ART started: 4 mos
- VL: 1,92 (18 mo-VL)
- Rapid Test: -ve
- Elisa: -ve
- DNA PCR: -ve
- VL: 6, 12, 28 months
- VL: 29, 35, 37 mo
- STI
- VL: 6, 12, 28 months
- 2 mos DNA PCR: Pos
- 7 mo-VL
- STI
Case 3: HIV Diagnosis and Course of Treatment

- Born Feb 06
- 10 mo DNA PCR +ve
- 21 mo: ART started
- VL: 29-54 months
- STI
- VL: 3 6 11 18 21 24
- 2 Rapid Test: -ve
- First negative at 50
Why is Very Early Treatment so Important for latent reservoirs?
Immune function becomes dysfunctional after Peak Viral Load

Window of opportunity

Dysfunctional cellular immune responses

[Graph showing plasma virus RNA levels over days following HIV-1 transmission with phases I, II, and III highlighted.]
Impact of early /late treatment on Total HIV-DNA

Hocqueloux et al. JAC 2013

- Immunological benefit significantly better in PHI patients

- 372 Chronic Patients
- 25 PHI patients
- HIV-RNA<50copies/ml
- >1200 samples HIV-DNA

Chronic Phase

Primary Infection

Modèle exponentiel à effets mixtes
(effet fixe et variables aléatoires)

Hocquelou et al. JAC 2013
CD8 T Cells in AHI Impact Viral Set Point
The Earlier the ART Started, the Smaller the Latent Reservoir

**Timing Of ART Initiation**

- **Very Early** (within 2 days)
  - Minimal HIV Exposure
  - Minimal Proviral Replication

- **Early** (3 days to 3 months)
  - Limited HIV Exposure
  - Limited Proviral Replication

- **Late** (>3 months)
  - Longer HIV Exposure
  - Arrested Proviral Replication

- **No Treatment**
  - Extensive HIV Exposure
  - Proviral Replication

Rainwater-Lovett et al 2015 Curr Opin HIV AIDS
Early and Very Early Therapy Restrict the Size and Modify the Persistence of HIV-1 Reservoirs

Luzuriaga, CROI, 2014; Persaud, CROI, 2015; Luzuriaga, JID, 2014; Persaud, JAMA Peds, 2014; Ananworanich, AIDS, 2014; van Zyl, JID, 2015; Bitnun, CID, 2014
Cases of Remission from elsewhere in the world
The Mississippi Child: Timeline of Events

- **BIRTH**
- **30 hours**
  - HIV detected in blood
- **18 months**
  - Began ART
- **23 months**
  - Stopped ART
  - No HIV detected in blood plasma (for 23 months)
- **46 months**
  - HIV detected in blood at 2 separate time points

Persaud et al 2013 NEJM; Luzuriaga et al 2015 NEJM
...but everything has not been rosy for every little kid....

Days to viral rebound after treatment cessation

- **Dublin Child**
  - (8 days; VL=11,230 c/ml)

- **Canadian Child**
  - (14 days; VL=7797 c/ml)

- **Milan Child**
  - (14 days; VL 36,840 c/ml)

- **Mississippi Child**
  - (828 days; VL=16 copies/ml)

So what was the difference?

- Stage of *in-utero* infection
- Viral load of mother
- HIV exposure duration and VL
- Genetic differences in immune response
- ART adherence
- Co-infections
- Latent reservoir size
- Viral strain

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial VL (c/mL)</th>
<th>ART Initiation</th>
<th>ART Duration</th>
<th>Remission Duration</th>
<th>Rebound VL</th>
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<tbody>
<tr>
<td>Mississippi Child</td>
<td>19,812</td>
<td>30 hours</td>
<td>18 months</td>
<td>27 months</td>
<td>16</td>
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<tr>
<td>Dublin Child</td>
<td>&lt;24 hours</td>
<td>&lt;24 hours</td>
<td>4 years 8 days</td>
<td>11,230</td>
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<tr>
<td>Canadian Child</td>
<td>808</td>
<td>&lt;24 hours</td>
<td>3 years 14 days</td>
<td>7,797</td>
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<tr>
<td>Milan Child</td>
<td>152,560</td>
<td>4 days</td>
<td>3 years 14 days</td>
<td>36,840</td>
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</tr>
</tbody>
</table>

...in any case treatment interruption is not desirable...prevent potential circumstances that would lead you to that decision?
Summary of Issues Related to Our Cases

• Reversions:
  • Proviral DNA
  • “Sero”

  *Such phenomena may lead to potential misclassification of their HIV status*

• Caregivers trauma

• Ultra-short lived remission-off treatment

• Significant immune destruction- off treatment
Summary

• Early ART (ET) initiation can result in excellent suppression of viral replication such that specific antibodies may not have initially been produced. ⁵

• VET can lead to prolonged viral remission even after treatment interruption⁶

• ART started shortly after birth may lead to reversion of HIV plasma viremia, pro-viral DNA in PBMC, viral culture, and serum HIV antibodies to negative.⁶

• In our cases, reversion of virologic and serologic tests to negativity was observed in infants who started ART at variable times.

• Structured treatment interruptions led to rapid rebound viremia. This epitomizes the fact that unless infants get VET, the likelihood of massive seeding of replication competent proviral DNA is huge.

Discussion (2)

• Significant decline in CD4 counts were observed with in the first several weeks of treatment interruptions

• The reversion of serological and nucleic acid tests to negative may lead HCWs to erroneously stop ART in such children and declare that they are actually cured or are HIV negative.7

• Reversion can be maintained through out suppressive ART and into adulthood,
  • Such patients may wrongly be accepted as blood donors if their HIV status is not disclosed7

• HIV sero-reversion is extremely rare in adults and reported to occur only in those adults who started HAART immediately after acute-HIV infection.8-9

7AIDS 2010, Vol 24 No 17  
Next Steps/Recommendations

• All healthcare workers should be made familiar on the phenomenon of reversion.

• Initial HIV diagnosis shall be confirmed by a repeat qualitative DNA or baseline quantitative RNA PCR test
  • Any detectable viral load while on treatment may also be taken as confirmatory for HIV Infection

• Children with HIV infection should receive timely disclosure of HIV statuses
Next Steps/Recommendations

- Guidelines that recommend repeat Rapid Test at 24 months in infants who were tested positive and on ART would lead to confusions.

- Structured treatment interruptions in children should ‘not be’ attempted.
Early ART is good in young infants also...

• Should ART be started earlier than 6 weeks of age in vertically infected infants in Namibia?

• Can we diagnose HIV earlier than 6 weeks?

• How simple would treatment regimens be?
1. Namibian ART Guidelines 2nd Edition
3. Malawi Integrated Guidelines for providing HIV Services, 2014
References (2)

7. Alessandra v et al, failure to eradicate hiv despite fully successful haart initiated in the first days of life. *J pediatr* 2006;148:389-91


Thank You!