Analytical Treatment Interruptions in HIV Clinical Trials: A Systematic Review

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Background

• Treatment interruption (TI) has been studied in clinical trials since triple therapy ART has been available
  – Minimise toxicity
• SMART study: RCT continuous vs CD4 guided ART
  – Sig ↑ risk of death, OI, and non-AIDS events

1SMART study Group, NEJM, 2006
Analytical Treatment Interruptions

• HIV cure clinical trials assess strategies and interventions aimed at achieving HIV remission or virological control off ART

• Analytical treatment interruption (ATI) is a structured, closely monitored, and temporary cessation of ART

Analytical Treatment Interruptions

• Immunological and virological dynamics during ATI are a critical outcome in cure trials

• Common feature of modern HIV cure trials
  – Poses potential risks
  – No standardised study protocols
Aim

Perform a systematic review of the literature around TI methodology in HIV clinical trials

– cure focused trials
– non-cure focused trials

Methods:

• Systematic review (PRISMA) of clinical studies where ART was interrupted by a clinician or investigator.

• Studies from 2000-2017

• Excluded case reports, TI shorter than 2 weeks

• Extracted data

• Descriptive analysis
Results

- 161 TI studies (Jan 2000-July 2017)
- 101 non-cure focused
- 60 cure focused
Number of studies without an intervention have declined

Cure interventions

• Therapeutic vaccines (31)
• IL-2 (4)
• Interferon (3)
• Antibodies (4)
• Gene editing (2)
• Hydroxyurea (2)
• Early ART (3)
• Combination (5)
• Other (6)
TI studies

<table>
<thead>
<tr>
<th></th>
<th>Non-cure focused (n=101)</th>
<th>Cure focused (n=60)</th>
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<tbody>
<tr>
<td>Study design</td>
<td>39 (39%) RCT</td>
<td>37 (62%) RCT</td>
</tr>
<tr>
<td>Median n (IQR)</td>
<td>27 (13-27)</td>
<td>29 (25-74)</td>
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<tr>
<td>Median age (IQR) yrs</td>
<td>39 (35-42)</td>
<td>40 (38-44)</td>
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<tr>
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<td>7 paeds studies</td>
<td>1 paeds studies</td>
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<tr>
<td>Majority male</td>
<td>64/72 (89%)</td>
<td>44/45 (98%)</td>
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<td>4 studies - all male participants</td>
<td>12 studies - all male participants</td>
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Lower VL threshold to restart ART in cure focused trials
Cure focused studies monitor VL more frequently

Variation in reported duration of TI

- Set duration (38)
- Opened ended (5)
- Multiple sequential (9)
- Minimum (5)
- Maximum (17)
- Mean (5)
- Median (30)
Cure focused studies did not have shorter TI

Set point vs time to viral rebound

• BNAb studies (3)
  – Time to viral rebound
  – 200-1000c/mL

• Therapeutic vaccine studies (31)
  – Set point
  – 3000c/mL-300,000 c/mL
Adverse Events

- 31/101 (31%) non-cure focused studies reported AEs
- 15/60 (25%) cure focused studies reported AEs
- 1 death in cure focused studies
  - out of 2148 participants
  - Myocardial infarction 15 weeks into ATI

Prevention of HIV transmission

- 9/101 (9%) non-cure focused studies, 1/60 (2%) cure focused studies reported counselling participants about possible transmission risk and advised safe sexual practices.
- No studies reported offering PrEP to partners of participants
• Cure studies: more frequent monitoring, restart ART based on VL, lower VL threshold → less adverse events reported
• Set point vs time to viral rebound T
• PrEP not offered to seronegative partners of participants

Limitations
• Heterogeneity of studies
• Missing data
• Unpublished conference abstracts
Conclusions

• ATI increasingly being used
• Heterogeneity in TI methodology, evolved over time
• Different aims to achieve HIV cure/remission reflect different TI methods
• PrEP and counseling re: transmission risk reduction should be included in study protocols for ATI trials

Poster #67
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