IAS 2015 Towards an HIV Cure symposium
Vancouver

CHERUB: Collaborative HIV Eradication of reservoirs; UK BRC;

Predictors of Post treatment control and viral reactivation strategies

Sarah Fidler on behalf of CHERUB
Imperial College London UK
Predictors of viral rebound after stopping ART initiated in Primary HIV infection
Spartac Trial

Randomisation

Standard of care (SOC = No ART)

ART-12 (12 week ART)

ART-48 (48 week ART)

Primary endpoint: confirmed CD4 count <350 cells/mm³ (within 4 weeks, and not within first 3 months) or initiation of long-term treatment
Untreated individuals from PHI:

Cox Model:

Univariable predictors:
- Total HIV-1 DNA  HR 4.16 (CI 2.10-8.26); p <0.0001*
- Int HIV-1 DNA      HR 5.41 (CI 1.65-18.04); p = 0.006
- Plasma VL        HR 1.74 (CI 1.13-2.68); p = 0.011

Multivariable analyses
- Total HIV-1 DNA  HR=3.57 (1.58-8.08); p=0.002
- CD4 count        HR=0.67 (0.53-0.84); p<0.001
- Not plasma viral load or Integrated DNA

*HR = per log_{10} increase
HIV-1 DNA at Treatment interruption PREDICTS TIME TO VL REBOUND

\[ p = 0.0038 \]

- low total
- high total

Percent without viral rebound

Time to rebound to 400 copies per ml plasma (weeks)
Conclusion

- Measures of CD4+ T-cell total HIV DNA predict rate of disease progression in PHI
- Total HIV DNA in CD4+ T-cell at treatment interruption predict time to VL rebound on stopping therapy but...
- Other cases these measures were not predictive; Mississippi baby, Boston transplant patients,
- Increase sensitivity of predictive value by generating an “algorithm”
HIV DNA is associated with “good prognosis” HLA class I alleles

Patients with ‘good’ Class I HLAs (n=20) have lower HIV-1 DNA than ‘progressive’ HLA alleles (n=55); p<0.001. (3.46 vs 4.05 log_{10} copies/million CD4 T cells)
## Biomarker Panel

<table>
<thead>
<tr>
<th>Biomarker ‘Class’</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>CD4 Cell Count</td>
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<td>Plasma Viral Load</td>
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<td>CD4/CD8 Ratio</td>
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<td><strong>Viral nucleic acid</strong></td>
<td>HIV-1 DNA (Total)</td>
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<td></td>
<td>HIV-1 DNA (Integrated)</td>
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<td>Cell-Associated Unspliced HIV-1 RNA</td>
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<td><strong>HIV-1 T cell immunity</strong></td>
<td>CD8 ELISpot</td>
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<td>CD4 ELISpot</td>
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<td><strong>T cell activation</strong></td>
<td>HLA-DR</td>
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<td></td>
<td>CD38</td>
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<td>CD25</td>
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<td>CD69</td>
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<td><strong>T cell exhaustion/ ‘immune checkpoint’</strong></td>
<td>PD-1</td>
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<tr>
<td></td>
<td>LAG-3</td>
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<td>TIM-3</td>
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<td><strong>Soluble markers</strong></td>
<td>IL-6</td>
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<td>D-dimer</td>
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</tbody>
</table>
PD-1, Lag-3 and Tim-3 Predict Time to Rebound after TI

### Biomarker expression on T cells

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted HR(CI) p-value</th>
<th>Adjusted for baseline HIV-1 DNA HR(CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 CD4+</td>
<td>1.35 [1.072-1.71] p=0.011</td>
<td>1.46 [1.06-1.85] p=0.016</td>
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<tr>
<td>PD-1 CD8+</td>
<td>1.15 [1.015-1.319] p=0.0293</td>
<td>1.37 [0.956-1.352] p=0.145</td>
</tr>
<tr>
<td>Tim-3 CD4+</td>
<td>1.25 [1.12-1.4] p&lt;0.001</td>
<td>1.36 [1.16-1.597] p&lt;0.009</td>
</tr>
<tr>
<td>Tim-3 CD8+</td>
<td>1.11 [1.04-1.2] p=0.0036</td>
<td>1.15 [1.06-1.20] p=0.0011</td>
</tr>
<tr>
<td>Lag-3 CD4+</td>
<td>1.08 [1.027-1.146] p=0.0036</td>
<td>1.082 [1.022-1.146] p=0.0066</td>
</tr>
<tr>
<td>Lag-3 CD8+</td>
<td>1.104 [1.025-1.19] p=0.0093</td>
<td>1.129 [1.029-1.280] p=0.056</td>
</tr>
</tbody>
</table>
CD4:CD8 ratio at seroconversion predicts time to VL rebound on stopping therapy

Kaplan Meier - ART Initiation CD4/CD8 ratio ≥1.2 compared to <1.2 and time to endpoint (VL>400 copies/ml)

N=206 Spartac + UK register of HIV seroconverters

Thornhill et al. Poster LB
The importance of viral blips and duration of therapy initiated in primary infection in maintaining viral control after stopping cART

Sarah Fidler¹, Ashley D. Olson², Julie Fox¹, Andrew Phillips², Charles Morrison³, John Thornhill¹, Heiner C. Bucher⁴, Roberto Muga⁵, Kholoud Porter² on behalf of CASCADE Collaboration in EuroCoord

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Each blip >400 copies HIV RNA/ml was associated with a 2 fold increased hazard of viral rebound

PI regimens were associated with a 38% decreased hazard of viral rebound as was more recent year of cART initiation

There was no association with time to viral rebound and CD4 cell count, SC age, risk group and sex
Treatment interruption algorithm

- Baseline HIV VL, CD4 count CD4:8 ratio
- Absence of viral blips > 400 copies HIV RNA/ml
- Markers of immune exhaustion and activation at baseline and prior to TI
- Total HIV DNA at baseline and prior to TI
- Longer duration of ART started in PHI
- Shorter duration of infection pre-ART start
How will we test the algorithm?

- Prospective observational cohort
- n = 220 participants treated within maximum of 12 weeks of PHI defined as < 12 weeks from previous negative test, p24+ antibody negative, RITA incident
- PITCH using our ART TI algorithm and identifying low risk to stop with very frequent HIV VL testing and planned ART re-initiation at VL > 1000 copies
A two-arm (proof of concept) randomised phase II trial
Design Summary

- Two-arm prospective randomised controlled trial in PHI
- Interventions to be compared:
  - Arm A (control): 4-drug cART including raltegravir
  - Arm B (intervention): 4-drug cART including raltegravir
    + vaccines (prime / boost)
    + vorinostat
- Hypothesis:
  - cART plus vaccines and vorinostat will confer a significant reduction in measures of HIV reservoir compared with cART alone.
Why Primary infection?

- Reservoir size smallest
- Reservoirs respond rapidly to immediate ART and sustained reduction compared with ART-treated chronic infection
- Better immune response and enhanced probability to recover to normal CD4 counts and function if start ART immediately with the assumption that there will be better response to vaccination
1-2 weeks prior to enrolment

Baseline data collection

Week 0

Eligible participants screened/enrolled
4-drug ART including Raltegravir commences

Week 24

Eligible participants randomised

Week 32

Arm A
4-drug ART including Raltegravir continues

Arm B
4-drug ART including Raltegravir continues
plus Anti-HIV Vaccines from week 24
plus Vorinostat from week 32

 Eligibility review*
*Those not eligible to commence vorinostat at week 32 are excluded

Week 40 and 42

Primary outcome measure: Change in total HIV total DNA at W40 and 42 (average taken)
Vaccination in Arm B

- Week 24, prime:
  - \texttt{ChAdV63.HIVconsv} IM into the deltoid muscle

- Week 32, boost:
  - \texttt{MVA.HIVconsv} IM into the deltoid muscle

- Both vaccinations take place at the Royal Free Hospital
Design ChAd-MVA.HIVconsv BCN trial

**ARM A: TDF/FTC + RAL 0-24 week vaccination (individuals 0 to 12)**

- V0 Diagnosis
- Screening (4 weeks)
- V1 (0w)
- V2 (4w)
- V3 (12w)
- V4 (24w)
- V5 (+1)
- V6 (+4)
- V7 (+12)
- V8 (48w)
- V9 (+1)
- V10 (+4)
- V11 (+12)
- V12 (+24)

HAART initiation

Vaccine ChAd prime

Vaccine MVA boost

0-24 week Prime-Boost

**ARM B: TDF/FTC + RAL 0-8 week vaccination (individuals 13 to 24)**

- V0 Diagnosis
- Screening (4 weeks)
- V1 (0w)
- V2 (4w)
- V3 (12w)
- V4 (24w)
- V5 (+1)
- V6 (+4)
- V7 (33w)
- V8 (+1)
- V9 (+4)
- V10 (+12)
- V11 (+24)

HAART initiation

Vaccine ChAd prime

Vaccine MVA boost

0-8 week Prime-Boost

S & Imm Vir Res
Samples from the SPARTAC trial have been a valuable resource to inform the development of a future Treatment interruption algorithm ad study.

Key parameters are measures of CD4+ total HIV DNA ART and prior to TI, measures of immune activation and exhaustion, HLA type, HIV-specific T-cell responses.

The RIVER trial will test the hypothesis of kick and kill using a combination of agents with previous experience in HIV patients in acute infection.
THANKS

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