The impact of vorinostat & therapeutic vaccine on gut HIV DNA
The RIVER gut study

Presented by Dr John Thornhill
on behalf of the RIVER study team and investigators
Barriers to HIV cure: viral latency and reservoirs

HIV infects CD4+ cells

Some become resting memory cells; ‘reservoir’

Gut associated lymphoid tissue is the largest collection of CD4+ cells in the body

1. Finzi D et al. Science 1997; 278: 1295-300

Figure adapted from Coiras M, et al. Nat Med 2009;7:798–812
On ART – Gut-associated lymphoid tissue (GALT) is a key site of HIV persistence

Graphical representation of the proportion of vRNA$^+$ cells in each organ system before and during suppressive ART.

Estes et al. Nature Medicine 2017
The RIVER study investigated the HIV Cure approach “Kick and Kill”

**RIVER study design**

- **Cohort - Treated Primary HIV infection:**
  - lowest reservoirs, preserved immune responses
- **The Kick:**
  - HDAC inhibitor Vorinostat
- **The Kill:**
  - ChAdV63.HIVconsv and MVA.HIVconsv*
- **Design:**
  - Randomised control comparison with ART alone
- **Primary endpoint:**
  - Total HIV DNA in peripheral blood CD4+ T-cells at weeks 16 & 18 post randomisation

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*Letourneau S Plos One 2007*
The RIVER RCT – Main Study Results

**Primary endpoint:** Difference (ART+V+V minus ART only) in mean log_{10} HIV DNA copies/million CD4+T cells averaged across PR weeks 16 and 18: 0.04 (95% CI: -0.03 to 0.11); p=0.26

Fidler et al. 22nd IAC, 23-27th July 2018, the Netherlands
Methods
Individual with Primary HIV infection

Commenced on Immediate ART & achieved an undetectable HIV viral load

Randomisation

ART-only ARM
Stay on ART alone

ART plus intervention arm (ART+V+V) Stay on ART plus
T-cell prime-boost vaccination
Vorinostat

Completion of RIVER Study main protocol – primary outcome: HIV DNA in PBMCs

Enrolled in RIVER gut sub study – secondary outcome: GALT HIV DNA
### RIVER Gut study - methods

RIVER study participants who completed the main study protocol enrolled at 2 London sites.

#### 1. Gut Biopsies
- Rectum
- Terminal Ileum

#### 2. Blood Samples
- PBMCs
- Plasma

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<table>
<thead>
<tr>
<th>Laboratory assays</th>
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<tbody>
<tr>
<td><strong>HV Reservoir</strong></td>
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<tr>
<td>Total HIV DNA qPCR assay</td>
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<tr>
<td><strong>Tissue p24 levels</strong></td>
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<tr>
<td>p24 measured in activated tissue supernatants</td>
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<tr>
<td><strong>Immune Activation &amp; Immune exhaustion in gut</strong></td>
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<tr>
<td>HLA-DR, CD38 &amp; PD-1 expression measured on CD4+ cells by flow cytometry</td>
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<tr>
<td><strong>Marker of bacterial translocation</strong></td>
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<tr>
<td>sCD163 &amp; sCD14 was measured in plasma</td>
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Results
### RIVER Gut study – participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>ART-plus-intervention Arm (n=6)</th>
<th>ART-only Arm (n=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>37 (27-46)</td>
<td>33 (27-35)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Results at Enrolment</strong>:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HIV viral load, Log_{10} CPM</td>
<td>4.1 (3.9-5.3)</td>
<td>4.9 (4.6-5.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>CD4 count cells/mm³</td>
<td>492 (435-561)</td>
<td>543 (449-548)</td>
<td></td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>0.55 (0.35-0.90)</td>
<td>0.54 (0.49-0.58)</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Median (IQR) time from</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDI to ART start, days</td>
<td>75 (31-86)</td>
<td>65 (25-97)</td>
<td>0.93</td>
</tr>
<tr>
<td>Completed RIVER protocol to biopsy, months</td>
<td>9 (3-14)</td>
<td>6 (6-14)</td>
<td>0.69</td>
</tr>
<tr>
<td>ART start to biopsy</td>
<td>22 (21-24)</td>
<td>17 (16-22)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Results at time of Biopsy</strong>:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count cells/mm³</td>
<td>669 (618-920)</td>
<td>1058 (809-1186)</td>
<td>0.06</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.40 (1.18-1.5)</td>
<td>1.60 (1.28-2.13)</td>
<td>0.51</td>
</tr>
<tr>
<td>HIV viral load</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td></td>
</tr>
</tbody>
</table>

Values given represent n (%) categorical variables and median (interquartile range) for continuous variables. * refers to measure closest to serconversion. Abbreviations: EDI, estimated date of infection; RITA, recent infection testing algorithm. EDI, estimated date of HIV infection.
Gut HIV DNA levels, all participants

P value calculated using Friedman’s test & corrected for multiple comparisons
**HIV DNA level in Gut-Associated Lymphoid Tissue (GALT), by study arm**

**Terminal ileum**

- **Log$_{10}$ CPM CD4 T cells**
  - ART Only ARM: 3.0, 3.5, 4.0
  - ART plus intervention ARM: 3.0, 3.5, 4.0

- **Total HIV DNA**
  - ART Only ARM: 3.0, 3.5, 4.0
  - ART plus intervention ARM: 3.0, 3.5, 4.0

- **P-value**: 0.43

**Rectum**

- **Log$_{10}$ CPM CD4 T cells**
  - ART Only ARM: 3.0, 3.5, 4.0
  - ART plus intervention ARM: 3.0, 3.5, 4.0

- **Total HIV DNA**
  - ART Only ARM: 3.0, 3.5, 4.0
  - ART plus intervention ARM: 3.0, 3.5, 4.0

- **P-value**: 0.31

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**No Difference in measures of HIV reservoir in GALT between study arms**

P-values calculated using a Mann-Whitney test
No Difference in immune activation or exhaustion in GALT between study arms

P values calculated using a Mann-Whitney test
p24 measured in tissue cultures, by study arm

No Difference in p24 production at day 7 or day 21 post activation, between study arms

P values calculated using a Mann-Whitney test
Bacterial Translocation, by study arm

No Difference in sCD14 but higher levels of sCD163 were observed in the ART plus intervention arm

P values calculated using a Mann-Whitney test
Limitations

• Unlike the main RIVER study which examined HIV DNA in PBMCs, this sub study had a small sample size and the findings should be interpreted with caution.

• However, tissue data is lacking from most studies of HIV cure and this data adds important insights into the impact of cure interventions on HIV tissue reservoir.
Conclusions

• These data suggest that vorinostat in combination with a T-cell prime-boost-vaccine during PHI did not impact the GALT HIV reservoir

• Similarly measures of immune exhaustion & activation on GALT CD4+ T-cells were not impacted by the intervention

• Measures of bacterial translocation appear to be increased in ART plus intervention compared to ART-only arm warranting further investigation in a larger cohort
Thank you to BHIVA and the MRC for their funding of the RIVER gut study

• BHIVA research award
• MRC clinical research training fellowship
All the RIVER gut study participants
RIVER Chief Investigator: Sarah Fidler
RIVER co-investigator and laboratory lead: John Frater
RIVER Gut Study Collaborators: Jonathan Hoare, Heather Lewis & Simon Peake
RIVER statisticians: Abdel Babiker, Wolfgang Stöhr

RIVER laboratory investigators: Lucy Dorrell, Tom Hanke, Andrew Lever, Myra McClure, Steve Kaye, Matt Pace, Axel Fun, Mikaila Bandara, Maryam Khan, Andrew Lovell, HongBing Yang, Jakub Kopycinski, Natalia Olejniczak, Helen Brown, Nicola Robinson, Otto Erlwein, Alison Crook

RIVER trial management team: Rachel Bennett, Michelle Gabriel, Fleur Hudson, Aminata Sy, Adam Gregory, Mary Rauchenerberger, Yinka Sowunmi, Shaadi Shidfar, Dominic Hague, Hanna Box, Cherry Kingsley, Katie Topping, Gemma Wood, Charlotte Russell, Sarah Pett

RIVER clinical investigators: Sarah Fidler, Sabine Kinloch, Sarah Pett, Julie Fox, Amanda Clarke, Mark Nelson, Margaret Johnson

RIVER Trial Steering Committee (TSC): Independent Members: Eric Sandström, Janet Darbyshire, Frank Post, Chris Conlon, Jane Anderson, Mala Maini
RIVER Clinical Site Teams: Sarah Fidler, Sarah Pett, Mark Nelson, Sabine Kinloch, Amanda Clarke, Julie Fox, Nneka Nwokolo, John Thornhill, Heather Lewis, Kristin Kuldanek, Maddalena Cerrone, Nadia Castrillo Martinez, Tristan Barber, Alexandra Schoolmeesters, Christine Weaver, Orla Thunder, Jane Rowlands, Christopher Higgs, Serge Fedele, Margherita Bracchi, Lervina Thomas, Peter Bourke, Gaynor Lawrenson, Marzia Fiorino, Hinal Lukha, Margaret Johnson, Alice Nightingale, Nnenna Ngwu, Patrick Byrne, Zoe Cuthbertson, Martin Jones, Thomas Fernandez, Martin Fisher – in memoriam, Rebecca Gleig, Vittorio Trevitt, Colin Fitzpatrick, Alyson Knott, Tanya Adams, Fionnuala Finnerty, Julianne Lwanga, Hiromi Uzu, Ming Lee, Simon Merle, Patrick O'Rourke, Isabelle Jendrulek, Taras Zarko-Flynn, Mark Taylor, Juan Manuel Tiraboschi, Tammy Murray

RIVER Independent Data and Monitoring Committee (IDMC): Tim Peto, Peter Sasieni, Veronica Miller, Ian Weller

Community of people living with HIV: Simon Collins, Damian Kelly

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