BHIVA ‘Best of CROI’ Feedback Meetings

London | Birmingham
Haydock | Newcastle
Cardiff | Wakefield
Edinburgh
HIV testing Prevention and Cure

Dr Sarah Fidler
Imperial College London
HIV testing Prevention and Cure

- Testing
  - Cascade of care / 90 90 90
- Prevention
  - Maraviroc prep
  - Dalpiverine ring
- Cure
- MTCT
By 2020...UNAIDS and Partners

- 90% of all people living with HIV will know their HIV status.
- 90% of all people diagnosed with HIV will receive sustained antiretroviral therapy.
- 90% of all people receiving antiretroviral therapy will have durable suppression.
Second 90 Target: ART uptake, among those consenting to intervention

- **Men, Zambia (4,139):**
  - Pre-CHiPs: 71%
  - Post-CHiPs: 47%

- **Men, SA (890):**
  - Pre-CHiPs: 58%
  - Post-CHiPs: 43%

- **Women, Zambia (8,701):**
  - Pre-CHiPs: 72%
  - Post-CHiPs: 49%

- **Women, SA (2,382):**
  - Pre-CHiPs: 69%
  - Post-CHiPs: 55%
Position within the cascade per exposure time, TasP ANRS 12249 KZN S Africa

steady increase from ~20% to ~50% in 30 months
### Getting to 90:90:90 Research studies and data from implementation science trials

<table>
<thead>
<tr>
<th>Research studies</th>
<th>design</th>
<th>Primary endpoint</th>
<th>Population size</th>
<th>First 90 testing</th>
<th>Second 90 ART</th>
<th>Third 90 UD VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN071(Pop ART) Abstract 145</td>
<td>Community RCT arm A: combination prevention + UTT, arm B CP + ART guidelines and Arm C SOC</td>
<td>HIV incidence</td>
<td>Urban and peri-urban HIV prevalence 10-35% Population 1-1.2 million</td>
<td>89%</td>
<td>71%</td>
<td>n/a</td>
</tr>
<tr>
<td>SEARCH</td>
<td>Community RCT Uganda &amp; Kenya 2 arms UTT vs SOC</td>
<td>HIV incidence</td>
<td>Rural Prevalence 10-25% Population 350 000</td>
<td>94%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>TasP (ANRS 14429) Abstract 169LB</td>
<td>CRT 24 clusters South Africa KZN</td>
<td>HIV incidence</td>
<td>Rural</td>
<td>90%</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Botswana BCPP Abstract 111</td>
<td>Community RCT Botswana UTT vs SOC</td>
<td>HIV incidence</td>
<td>Rural and urban</td>
<td>82%</td>
<td>86% BUT</td>
<td>95%</td>
</tr>
</tbody>
</table>
Challenges to achieve 90:90:90

- **Uptake of nearly 90% HIV testing** seems to be feasible and acceptable in a combination household based model with campaigns, HCF testing and opt out testing.

- **Linkage to care and ART initiation**, congested poorly functioning clinics, over burdened systems, lack of lab reagents and failure to deliver results. One study\(^1\) showed offering same-day ART initiation to adult patients in South Africa increased uptake of ART by 36% and viral suppression by 26%.

- **Retention in care and viral suppression**: very variable, VL testing not routinely available in many settings, where in care good follow up, poor retention after option B+ in Malawi for pregnant women. Offer of community ART showed better uptake.\(^2\)
  - Poor retention especially amongst young people and young women Malawi (stable patient community delivery of ART\(^3\))
  - Individualized care pathways, for different patient needs S Africa\(^4\)

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1. RapIT (S Rosen)
2. Abstract 118 (Mugglin)
3 Abstract 122 (Grimsrud)
4 Abstract 121E Geng)
HIV testing Prevention and Cure

• Testing
  • Cascade of care / 90 90 90

• Prevention
  • Maraviroc prep
  • Dalpiverine ring

• Cure

• MTCT
## HPTN 069/ACTG A5305: Maraviroc Based PrEP in MSM Safety

<table>
<thead>
<tr>
<th></th>
<th>MVC (n=101)</th>
<th>MVC+FTC (n=106)</th>
<th>MVC+TDF (n=99)</th>
<th>TDF+FTC (n=100)</th>
<th>Total (N=406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2%</td>
<td>8%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Unintentional Weight Loss</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0.25%</td>
</tr>
</tbody>
</table>

### HPTN 069/ACTG A5305: Five Incident Infections

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study Arm</th>
<th>Week Tested Positive</th>
<th>Tropism</th>
<th>Genotypic Resistance</th>
<th>Plasma Drug Conc. at Seroconversion Visit (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20, Black</td>
<td>MVC+TDF</td>
<td>4</td>
<td>R5</td>
<td>none</td>
<td>MVC=0† TFV=0</td>
</tr>
<tr>
<td>61, Asian</td>
<td>MVC</td>
<td>16</td>
<td>R5</td>
<td>none</td>
<td>MVC=145</td>
</tr>
<tr>
<td>21, Mixed</td>
<td>MVC</td>
<td>24</td>
<td>R5</td>
<td>none</td>
<td>MVC=0</td>
</tr>
<tr>
<td>35, White</td>
<td>MVC</td>
<td>32</td>
<td>R5</td>
<td>none</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>36, Black</td>
<td>MVC</td>
<td>48</td>
<td>R5</td>
<td>none</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

Maraviroc Less Effective at Inhibiting HIV Following Infection of Tissue Explants

Prophylactic efficacy of FTC/TAF against rectal SHIV infection
ASPIRE Study: Phase III Trial of Dapivirine Vaginal Ring

## ASPIRE Study: Primary HIV-1 effectiveness ITT (15 sites)

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV-1 infections</td>
<td>71</td>
<td>97</td>
</tr>
<tr>
<td>HIV-1 incidence (Per 100 person-years)</td>
<td>3.3</td>
<td>4.5</td>
</tr>
<tr>
<td>HIV-1 Protection Effectiveness (95% CI) [p-value]</td>
<td>27% (1.46) [0.046]</td>
<td></td>
</tr>
</tbody>
</table>
ASPIRE: Phase III Trial of Dapivirine Vaginal Ring Efficacy by Age

Efficacy

Age 18 – 21
-27% (-133, 31)
Placebo incidence – 5.4%/y

Age 22 – 26
+56% (19, 76)
Placebo incidence – 6.1%/y

Age 27 – 45
+51% (8, 74)
Placebo incidence – 3.0%/y

Adherence by Plasma Drug Concentration and Concentration in Returned Ring

Month since randomization

Percent of Subjects

### Variable

<table>
<thead>
<tr>
<th></th>
<th><strong>Dapivirine (N = 1300)</strong></th>
<th><strong>Placebo (N = 650)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of confirmed seroconversions</td>
<td>77 (5.9%)</td>
<td>56 (8.6%)</td>
</tr>
<tr>
<td>Total person years of follow-up (years)</td>
<td>1888</td>
<td>917</td>
</tr>
<tr>
<td>HIV-1 seroconversion rate (per 100 person-years)</td>
<td>4.1</td>
<td>6.1</td>
</tr>
<tr>
<td>% reduction in HIV-1 seroconversion (95% CI) [p-value]</td>
<td>31% [0.9%, 51.5%] [0.040]</td>
<td></td>
</tr>
</tbody>
</table>
IPM027 Study: Efficacy by Residual Drug Level

<table>
<thead>
<tr>
<th>Cut-off ring residual level (mg)</th>
<th>Adherent vs. Non-adherent</th>
<th>% Reduction in HIV-1 seroconversion</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>65%</td>
<td>21% to 84%</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>44%</td>
<td>7% to 67%</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>36%</td>
<td>-8% to 62%</td>
<td></td>
</tr>
<tr>
<td>23.5</td>
<td>22%</td>
<td>-40% to 56%</td>
<td></td>
</tr>
</tbody>
</table>
### Overview of efficacy results for ASPIRE and The Ring Study

<table>
<thead>
<tr>
<th></th>
<th>Aspire</th>
<th>The Ring Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>37%*</td>
<td>31%</td>
</tr>
<tr>
<td>18-21 years old</td>
<td>No protection</td>
<td>15%</td>
</tr>
<tr>
<td>&gt;21 years old</td>
<td>56%</td>
<td>38%</td>
</tr>
</tbody>
</table>

* Excluding two non-adherent sites

§ >25 years old: 61% efficacy
Prep failure due to infection with multi drug resistant virus

- ART regimen optimized, and viral load remains undetectable to date
Determine if a Single 50 mg/kg CAB LA Dose Provide Sustained CAB Plasma Levels for Protection against IV Challenge
The Perils of LA PrEP

- Safety
- Acceptability
- Adherence
- Pharmacokinetics
- Resistance
- Operational complexity
Female participant receiving a single 1200 mg dose of rilpivirine
Summary

**Maraviroc for HIV Prevention**
- The number of incident infections in HPTN 069/ACTG A5305 and the low tissue levels suggest that maraviroc will not be effective for PrEP if used as monotherapy.

**Vaginal Dapivirine Ring**
- Rate of protection was disappointing.
- Rate of sub-optimal adherence higher than expected.
- Are there any biological differences that explain the poorer rate of protection in the younger women?

**Long-acting injectables for prevention**
- Maybe effective and much better accepted but the PK tail could be a real challenge.
HIV testing Prevention and Cure

- **Testing**
  - Cascade of care / 90 90 90
  - Partner notification strategies
- **Prevention**
  - Maraviroc prep
  - Depo prep
  - Dalpiverine ring
- **Cure**
  - MCTC
Viral rebound in African SPARTAC versus UK SPARTAC

African (n=22) and UK SPARTAC (n=44) participants undertaking TI after 48 weeks of ART
## Treatment interruption studies and post-treatment control (PTC)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No</th>
<th>ART Length</th>
<th>Outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract 332 ULTRASTOP</td>
<td>Early chronic treated patients with ultra-low reservoirs ultralow HIV-DNA (&lt;66 cp/106 PBMC).</td>
<td>10</td>
<td>n/a</td>
<td>Viral rebound &gt;400 copies/ml after TI Or CD4 &lt; 400 after TI</td>
<td>10% PTC 1 individual VL &lt; 20 up to week 56 after TI 9/10 rebounded between weeks 2-12 Virus rebounds from transitional memory CD4 T-cell population</td>
</tr>
<tr>
<td>Abstract 346</td>
<td>Analysis of 6 ACTG TI studies</td>
<td>235</td>
<td></td>
<td>confirmed VL rebound ≥200 HIV RNA copies/mL and VL set point (mean log10 VL during ATI weeks 12-16)</td>
<td>Pre-ART VL and VL set point were correlated with time to VL rebound (CHI higher than PHI) PTC 10%</td>
</tr>
<tr>
<td>Spartac Abstract 87</td>
<td>Acute HIV infection RCT to ART48 vs no immediate ART</td>
<td>91</td>
<td>48 weeks or none</td>
<td>Time to VL rebound and total HIV DNA</td>
<td>PTC 5/22 (22.7%) Africans maintained VL&lt;400 copies/ml over a median 188 weeks follow-up (range 147-203) much longer than UK MSM cohort</td>
</tr>
<tr>
<td>Abstract 347</td>
<td>Review of 8 ACTG TI studies</td>
<td>497</td>
<td></td>
<td>VL &lt; 400 for &gt; 24 weeks</td>
<td>PTC 16/497 3.2% More common in early treated group vs chronic</td>
</tr>
</tbody>
</table>
Results: Viral rebound

- Majority of participants rebounded by week 5
  - 2 participants with delayed rebound at 8, 11 weeks
- Time to rebound not associated with VRC01 level, age, nadir or entry CD4 ct, time on ART
ACTG 5340: Time to Rebound in Viral Load After Infusions with VRC01

- 38% vs. 13% suppression at 4 weeks, p=0.04
- 8% vs. 3% suppression at 8 weeks, p=0.44
  - compared to historical controls on non-NNRTI regimens undergoing ATI in ACTG studies

Bar K, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 32LB.
Decrease in Latent Reservoir Following Therapeutic Vaccination and Romidepsin

Infectious units per million

Vacc-4x/rhuGM-CSF
Romidepsin
ATI

Day -21 Day 91 Day 161

Leth S, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 26LB.
Gene therapy approaches for HIV cure:

- Integrating gene transfer vectors: retroviral and lentiviral
- Adoptive T cell therapy
- Autologous HSC transplants in cancer patients
- Autologous HSC transplants in non-cancer patients (non-myeloablative conditioning)
- Targeted nucleases (Zinc Finger Nucleases, TALENs, CRISPR/Cas9) - more precise gene therapy

ZFN-treated T cells – SB-728-T: 5 trials, completed or ongoing

Endpoints:
- Safety
- CD4 counts
- HIV reservoir measures
- CCR5 editing
Virological control after ART interruption

- 6/9 individuals controlled HIV after TI (2 <1,000, 4 <10,000 copies/ml)*
- They look like elite controllers

*SB-728-1101, cohorts 3, 5, 3*
## Treatment interruption studies after intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention/study design</th>
<th>No participants</th>
<th>Years on ART</th>
<th>Outcome</th>
<th>Time to VL rebound</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG5340</td>
<td>VCR01 antibody 40mg/kg every 3 weeks for 3 infusions</td>
<td>14</td>
<td>4.7</td>
<td>All rebounded after TI</td>
<td>&gt;200 copies 8 weeks max</td>
</tr>
<tr>
<td>Abstract 32LB</td>
<td>Suppressed VL &gt; 3 years CD4 &gt; 450 Infusion of VRC01 (40mg/kg) 3 days prior to and 14 and 28 days following interruption of ART</td>
<td>10</td>
<td>Median 10.6 years</td>
<td>Viral rebound after TI</td>
<td>9/10 subjects experienced plasma viral rebound (&gt;40 copies/ml) between 11-54 days (median 39) Despite adequate levels of antibody in serum</td>
</tr>
<tr>
<td>Abstract 311LB</td>
<td>Suppressed VL &gt; 3 years CD4 &gt; 450 Infusion of VRC01 (40mg/kg) 3 days prior to and 14 and 28 days following interruption of ART</td>
<td>10</td>
<td>Median 10.6 years</td>
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</tr>
<tr>
<td>Abstract 26LB</td>
<td>Single arm 6 x Vacc 4x + GMCSF adjuvant then 3 x 5mg/m2 weekly Romidepsin infusion</td>
<td>20 17 completed</td>
<td>-</td>
<td>Data on 6/17 showed reduction in total DNA by 36% IUMP 40% All rebounded after TI</td>
<td>&gt;50 copies 14 days</td>
</tr>
<tr>
<td>Abstract 358LB</td>
<td>CD4 &gt; 500 preconditioned with 0.1-2.0 g/m2 of Cytoxan prior to infusion of SB-728-T then TI</td>
<td>18</td>
<td>-</td>
<td>VL &lt; 10,000 after TI</td>
<td>6/9 treated participants maintained VL control below threshold 10,000 up to 14-24 months</td>
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# Treatment interruption studies and post-treatment control (PTC)

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Summary of Cure research intervention studies

- ART alone is VERY unlikely to confer cure or even PTC (except if ART started in acute infection)
- Intervention studies with disappointing results: VRC01 antibody, Vax4, GMCSF Romidespin, Anti-PD-L1, all patients interrupting ART after intervention had VL rebound (rapidly within 4-8 weeks)
- Gene therapy looks promising…
- Where are the reservoirs, what cells, what sanctuary sites, how to measure reservoir with clinical meaning?

- Dr Jasmini Alagaratnam
- Prof Brian Angus
- Dr David Asboe
- Dr Sanjay Bhagani
- Dr Daniel Bradshaw
- Dr Kate Childs
- Dr Duncan Churchill
- Dr Amanda Clarke
- Dr Paul Collini
- Mr Simon Collins
- Prof Satyajit Das
- Dr Annemiek de Ruiter
- Prof David Dockrell
- Prof Lucy Dorrell
- Dr Ellen Dwyer
- Dr Sarah Fidler
- Dr Julie Fox
- Dr Andrew Freedman
- Dr David Hawkins
- Prof Saye Khoo
- Prof Clifford Leen
- Prof Derek Macallan
- Dr Achyuta Nori
- Dr Ed Ong
- Dr Chloe Orkin
- Dr Adrian Palfreeman
- Dr Brendan Payne
- Dr Frank Post
- Dr Iain Reeves
- Dr Jonathan Underwood
- Dr Ed Wilkins
- Dr Jaime Vera
**Study Design**

**Participants:**
- Chronically infected, on ART with VL < 50 copies/ml for > 6 months
- CD4 count > 400 cells/ml, nadir CD4 > 200 cells/ml
- INSTI or PI-based regimen

**Power:** 13 evaluable participants 90% power to detect 40% increase in suppression at week 8
**Study Design**

**Intervention:**
- 40 mg/kg IV VRC01 every 3 weeks
  - PK modeling suggested plasma levels >50 ug/ml x 10 wks
- ATI 1 week after VRC01 initiation
- Weekly monitoring for viral rebound, ART reinitiation upon confirmation
Results: Study Population

- 14 participants enrolled at 2 clinical sites
  - 13 evaluable. 1 participant stopped ART before the infusion.
- Demographics:
  - 100% male
  - Median age 38, range 27-52 years
  - 50% African American (n=7), 50% Caucasian (n=7)
    - 14% Latino (n=2)
- HIV clinical data:
  - Median CD4 count: 896 cells/µL (range 470-1,586)
  - Median 4.7 years on ART (range 2.7-14.5)
  - 71% INSTI, 29% PI-based regimens
Why did high concentrations of VRC01 fail to suppress rebound viremia?

- **Suboptimal antiviral effect?**
  - Evidence of selection
  - A5340 participant who stopped ART early had 2 log drop in plasma viremia (50,000→500 c/ml)
    - Similar to VRC601: 1.1-1.8 log drop in viremics

- **Neutralization resistance to VRC01?**
  - Pre-existent and/or rapidly acquired resistance likely relevant to VRC01 efficacy

- **Different activity of VRC01 in vivo?**
  - *In vitro* neutralization measures not predictive of full range of antiviral activity needed to inhibit virus *in vivo*