BHIVA ‘Best of CROI’ Feedback Meetings

London | Edinburgh

Wakefield | Cardiff

Birmingham | Haydock

Newcastle
• Testing
• Prevention
• MTCT
• Cure
- Testing
- Prevention
- MTCT
- Cure
RCT of rapid HIV screening in US EDs

- Enhanced targeted screening (Denver risk score) vs traditional risk screening vs non targeted
- 25,000 each arm however only 4000 per arm tested
- 10+ves in non targeted, 7 in each of others
- All 3 strategies worked and were cost effective
- Risk screening probably not worth doing in ED
Pharmacy based HIV testing

- One minute insti test
- No risk assessment or counseling
- 3000+ tests, 25 +ve
- Good coverage of hard to reach groups (men, black africans)
- Most +ves linked to care, only 2 (lost to FU)
Africa’s Youth will Age into Young Adulthood
Age Structure Differs—Southern Africa ahead in demographic shift
Projected Growth: Absolute Increase in Africa’s Young Adult Population

Figure 1. Youth aged 15-24 years, by region, 1950-2060

Need to “Bend the Curve” for Adolescents


- Girls (aged 15-19) Continued progress
- Girls (aged 15-19) Stalled progress
- Boys (aged 15-19) Continued progress
- Boys (aged 15-19) Stalled progress
- All Adolescents (aged 15-19) Continued progress
- All Adolescents (aged 15-19) Stalled progress

AIDS-related deaths have tripled since 2000 in adolescents, while decreasing by 50% in all other age groups.

- Testing
- Prevention
- MTCT
- Cure
On Demand Post-Exposure Prophylaxis with Doxycycline for MSM Enrolled in a PrEP Trial


Hospital Saint-Louis and University of Paris 7, Inserm SC10-US19 Villejuif, Hospital Croix-Rousse, Lyon, Hospital Tenon, Paris, CHU de Nice, AIDES, Pantin, Paris Sud University, France
Study Flow-Chart

Eligible n=299

Randomized n=232

PEP Doxy n=116
- D/C participation n=10
  - Withdrew consent n=5
  - Lost to follow-up n=1
  - Other n=4
- Completed FU n=106 (91%)

No PEP n=116
- D/C participation n=10
  - Withdrew consent n=3
  - Lost to follow-up n=3
  - Other n=4
- Completed FU n=106 (91%)

Not randomized n=67 (22%)
- Not meeting eligibility n=10
- Withdrew consent n=2
- Lost to follow-up n=1
- Patients declined n=54 (19%)
KM Estimates of Time to a First Syphilis (ITT Population)

Log-rank test p=0.04

Median follow-up of 8.7 months (IQR: 7.8-9.7): 13 subjects infected

10 in no PEP arm (incidence: 12.9 / 100 PY), 3 in PEP arm (incidence: 3.7 / 100 PY)

Hazard Ratio: 0.27 (95% CI: 0.07-0.98, p<0.05)
KM Estimates of Time to a First Chlamydia (ITT Population)

Log-rank test $p=0.003$

Median follow-up of 8.7 months (IQR: 7.8-9.7): 28 subjects infected

21 in no PEP arm (incidence: 28.6/100 PY), 7 in PEP arm (incidence: 8.7/100 PY)

Hazard Ratio: 0.30 (95% CI: 0.13-0.70, $p=0.006$)
Conclusions

- PEP with doxycycline reduced the overall incidence of bacterial STIs by 47% in MSM on PrEP (8.7 months of FU)
- No effect on Gonorrhea but strong reduction (70-73%) in Chlamydia and Syphilis incidence
- Acceptable safety profile with mild/moderate GI AEs leading to D/C in only 7% of participants
- No evidence of risk compensation
- Analysis of antibiotic resistance pending
- Long-term benefit of PEP yet unknown
- Antibiotic prophylaxis for STIs still NOT recommended
- More research needed in the field of STIs
Truvada PrEP failure P953

- MSM 20+ sex partners per month
- Good TDP levels at 0 and month 6
- Flu type illness, HIV Ab +, Ag neg, RNA neg
  - Told to stop PrEP
- 2 weeks later RNA detected, wild type virus
- ? Was this PrEP failure or did he get infected after stopping PrEP
- ?hx ivdu- chem sex likely
Pharmacy PrEP P961

- Single arm n=245 (84% MSM ~34 yrs)
- Only 25% had a care provider
- At 1 yr: 75% retention, 1 new HIV
- HIV testing and PrEP in pharmacy highly acceptable
- BUT dedicated PrEP pharmacist
PrEP and microbiome

- IAS 2016 CAPRISA 1% tenofovir gel
  - HIV acquisition associated with absence of lacto bacilli
  - Mechanism proposed: gardnerella degrades TNF
  - Controversial

- Partners PrEP n=1785 oral TDF
  - X sectional study of vaginal swabs
  - BV (nugent score 7-10) was not associated with HIV
  - 73% efficacy v 77% efficacy
Impact of vaginal microbiota on tenofovir

- 1% TNF gel for 1 week.
- Samples taken day 0 & 7
- BV associated with low TNF levels in vaginal fluid and plasma
- Effect present within 2 hours of dosing
Male Circumcision O87

- VMMC highly effective. mechanism unknown
- VMMC Controls from Rakai cohort
- 16S qPCR of foreskin swabs
- HIV neg (n=136) v HIV seroconverted (n=46)
- HIV acquisition was associated with prevotella, anaerobes and IL-8
  - Modifiable
  - Could they be passing BV to female partners?
• Testing
• Prevention
• MTCT
• Cure
PrEP and pregnancy

- Partners PrEP
  - N=30 pregnancies:
    - No pregnancy loss
    - No preterm delivery
    - No poor infant growth
Results (5) - Kaplan-Meier estimate of time from sample collection to initiation of antiretroviral therapy

POC (median = 0 days)

SOC (median = 127 days)

(p<0.001)
Figure 1. Breast milk HIV RNA levels

 DETECTION OF HIV IN BREAST MILK AMONG PREGNANT/POSTPARTUM WOMEN WITH RECENT HIV

Alison L. Drake1, John Kinuthia2, Daniel Matemo2, Barbra A. Richardson1, Sandy Emery2, Vrasha Chohan3, Julie Overbaugh3, Grace John-Stewart1

1Univ of Washington, Seattle, WA, USA, 2Kenyatta Natl Hosp, Nairobi, Kenya, 3Fred Hutchinson Cancer Rsr Cntr, Seattle, WA, USA
MTCTM: birth outcomes 025
Update from PROMISE on pregnancy outcomes

The use of LPV/r-containing antiretroviral regimens (TDF+FTC+LPV/r, ZDV+3TC+LPV/r) was associated with an elevated risk for PTD and LBW, when compared to antenatal ZDV alone.

ZDV+3TC+LPV/r had a somewhat higher risk for severe outcomes, relative to the ZDV alone arm, but this was not statistically significant. However, the TDF+FTC+LPV/r arm had a significantly higher risk than either of the other arms.
Do HIV+ women on PIs deliver pre-term (UK & Ireland cohort)

**Fig 1** Adjusted OR for PTD stratified by ART at conception and CD4 count (≤350 and >350 cells/mm³)
It’s not the TDF (data from US cohorts)

Table 2. Risk of outcomes by initial regimen

<table>
<thead>
<tr>
<th>Initial antiretroviral regimen during pregnancy</th>
<th>TDF/FTC/LPV/r</th>
<th>TDF/FTC/ATV/r</th>
<th>ZDV/3TC/LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Risk (%)</td>
<td>n Risk (%)</td>
<td>n Risk (%)</td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td>27 (21.4)</td>
<td>86 (16.1)</td>
<td>184 (19.5)</td>
</tr>
<tr>
<td>Very preterm birth</td>
<td>5 (4.0)</td>
<td>26 (4.9)</td>
<td>44 (4.7)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>30 (23.8)</td>
<td>86 (16.2)</td>
<td>175 (18.8)</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>1 (0.8)</td>
<td>10 (1.9)</td>
<td>18 (1.9)</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>36 (28.1)</td>
<td>127 (23.7)</td>
<td>256 (27.2)</td>
</tr>
<tr>
<td>Severe adverse outcome</td>
<td>7 (5.5)</td>
<td>28 (5.2)</td>
<td>51 (5.4)</td>
</tr>
</tbody>
</table>

Table 3. Risk ratios and 95% confidence intervals for infant outcomes based on comparisons of initial antiretroviral regimen used during pregnancy

<table>
<thead>
<tr>
<th></th>
<th>TDF/FTC/LPV/r vs ZDV/3TC/LPV/r</th>
<th>TDF/FTC/ATV/r vs ZDV/3TC/LPV/r</th>
<th>TDF/FTC/LPV/r vs TDF/FTC/ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude 95% CI</td>
<td>Adjusted 95% CI</td>
<td>Crude 95% CI</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.10 (0.77, 1.58)</td>
<td>0.95 (0.66, 1.39)</td>
<td>0.83 (0.65, 1.04)</td>
</tr>
<tr>
<td>Very preterm birth</td>
<td>0.85 (0.19, 2.11)</td>
<td>1.04 (0.65, 1.68)</td>
<td>0.82 (0.32, 2.08)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1.27 (0.90, 1.78)</td>
<td>1.08 (0.76, 1.54)</td>
<td>0.86 (0.68, 1.09)</td>
</tr>
<tr>
<td>Very low birth weight</td>
<td>0.41 (0.06, 3.06)</td>
<td>0.97 (0.45, 2.10)</td>
<td>0.42 (0.05, 3.27)</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>1.03 (0.77, 1.39)</td>
<td>0.90 (0.66, 1.23)</td>
<td>0.87 (0.72, 1.05)</td>
</tr>
<tr>
<td>Severe adverse outcome</td>
<td>1.01 (0.47, 2.17)</td>
<td>0.96 (0.61, 1.51)</td>
<td>1.04 (0.47, 2.34)</td>
</tr>
</tbody>
</table>
What happens after pregnancy

**FIGURE 1. PROMISE 1077HS study design**

- 1917 Screened
- 1653 Enrolled
- 1 withdrew

**TABLE 2. Pregnancy outcomes recorded for the initial subsequent pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>HS Randomization Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuation of HAART (N=140)</td>
</tr>
<tr>
<td>Live Birth</td>
<td>100 (71%)</td>
</tr>
<tr>
<td>Spontaneous Abortion (&lt;20 weeks)</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>Stillbirth (IUFD ≥ 20 weeks)</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Spontaneous Abortion or Stillbirth</td>
<td>33 (24%)</td>
</tr>
</tbody>
</table>
And just to add to the bad news

### Weight for Age Z-score (WAZ)

<table>
<thead>
<tr>
<th>Comparison of WAZ between the two arms</th>
<th>Real Data</th>
<th>Least Squares Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LPV/r</td>
<td>Lamivudine</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Data censored at the end of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>541</td>
<td>547</td>
</tr>
<tr>
<td>26 weeks</td>
<td>474</td>
<td>487</td>
</tr>
<tr>
<td>50 weeks</td>
<td>115</td>
<td>128</td>
</tr>
</tbody>
</table>

### Spline regression model for WAZ

- Overall, the Mixed Model showed a significant increase of the WAZ difference between arms over time (p<0.01)
- The Spline Model confirmed this result, and showed that the WAZ difference between arms occurred early (p=0.02, Knot=118 days).
And finally two PK studies showing significantly reduced concentrations in pregnancy.
Elvitegravir but not Cobi crosses the placenta

Figure 5. Infant Elvitegravir Concentrations

<table>
<thead>
<tr>
<th>EVG</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>358 (140 - 519)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>4.4 (3.1 – 7.5)</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>7.4 (5.9 – 8.8)</td>
</tr>
</tbody>
</table>
Substantially lower rilpivirine conc in pregnancy

Cord:maternal ratio 0.5

2/16 had sub-therapeutic rilpivirine in T3

**Figure 1: Mean (±%CV) concentration-time profile after administration of RPV 25mg QD during third trimester and postpartum**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Third Trimester (n=16)</th>
<th>Postpartum (n=15)</th>
<th>GM Ratio (%) [90% CI] Third trimester / postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24h}$ (h*mg/L)</td>
<td>1.71 (37)</td>
<td>3.04 (39)</td>
<td>55 (46-66)</td>
</tr>
<tr>
<td>C$_{max}$ (mg/L)</td>
<td>0.11 (36)</td>
<td>0.17 (34)</td>
<td>65 (55-76)</td>
</tr>
<tr>
<td>C$_{min}$ (mg/L)</td>
<td>0.05 (50)</td>
<td>0.10 (42)</td>
<td>51 (41-63)</td>
</tr>
</tbody>
</table>
Rilpivirine PK in pregnancy is highly variable

25mg daily with 500 Cal food 1 hour after medication

<table>
<thead>
<tr>
<th></th>
<th>T3 (n=30)</th>
<th>PP (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC ng*hr/mL (range)</td>
<td>1669 (556 – 4312)</td>
<td>2387 (188 – 6736)</td>
</tr>
<tr>
<td>C 24hr ng/ml</td>
<td>56 (&lt;10 – 181)</td>
<td>81 (&lt;10 – 299)</td>
</tr>
<tr>
<td>&lt;10th centile AUC 0-24</td>
<td>2/28 (7%)</td>
<td>3/28 (11%)</td>
</tr>
</tbody>
</table>

Cord /Maternal blood ratio 0.55

One subject had <LDL at C24 despite observed dosing – either poor absorption or increased clearance

Tran et al JAIDS 2016;72:289-296
• Testing
• Prevention
• MTCT
• Cure
HIV PERSISTENCE AND REACTIVATION

VIRAL CONTROL INDUCED BY HIVCONSV VACCINES & ROMIDEPSIN IN EARLY TREATED INDIVIDUALS

Beatriz Mothe

IrsiCaixa-HIVACAT, Hospital Germans Trias i Pujol, Badalona, Spain
Background

• Early_cART during PHI has shown benefits in immune recovery\(^1,2\) and in limiting latent reservoir size\(^3,4\).
• Conserved therapeutic vaccines may help to tackle HIV-1 viral diversity in the viral reservoir driven by immune escape\(^5,6,7\).
• BCN 01 trial (NCT01712425) refocused T cells towards highly conserved regions of HIV-1 in early treated individuals but did not impact the viral reservoir size\(^8\).
• Combination of vaccines with drugs that reactivate latent virus (Kick & Kill) may be required to clear the viral reservoir\(^9\).

\(^1\)Le, 2013; \(^2\)Fidler, 2013; \(^3\)Ananworanich, 2014; \(^4\)Hocqueloux, 2013
\(^5\)Rolland, 2007; \(^6\)Letourneau, 2007; \(^7\)Deng, 2015; \(^8\)Mothe, CROI 2016, PO 320;
Methods

pVL pre
Acute / recent HIV-1
24s ChAd MVA
Extension BCN 01-RO
4
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45

HIVconv CTL
Total HIV CTL

Proviral DNA

Effect on viral rebound

Mothe B. et al, BCN 02
CROI 2017 - 1191-P
Monitored Antiretroviral Pause (MAP)

- 13 participants have interrupted cART to date.

8/13

5/13

Plasma HIV-1 RNA copies/ml

pre cART 0 4

weeks OFF cART

Percent OFF cART

BCN 02 (n=13)
TIBET (n=93)
RV411 (n=8)

p=0.0027

Ruiz, 2007; Colby, #124; Leal, #336; Genevieve, 2017; Saez-Cirion, 2013; Rosenberg, 2010; Cockerhan, 2016
Conclusions

- This is the first therapeutic vaccine trial reporting a durable control of HIV-1 after cART cessation in a substantial proportion of patients (≈35-38%, so far >12-24wks).
- BCN 02 data suggest that viral control can be achieved by an effective redirection of CTL towards conserved regions in the context of a limited viral reservoir.

![Diagram]

Early & Prolonged cART

↑ Viremic control

↓ Levels proviral DNA
↓ Diversity / Escaped virus

BCN 02
MVA_{boost} + LRA

↑ Functional T-cells / ↓ Exhaustion
↑ Plasticity to Red Educate CTL by 1st CM vaccination

°Rosas, CROI 2017, PO 271
Mothe B. et al, BCN 02
BHIVA ‘Best of CROI’ Working Party 2017

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Dr Steve Taylor
Dr Hiten Thaker