UPDATES ON INDIVIDUAL AND UNIVERSAL HIV TREATMENT STRATEGIES

EECA INTERACT, NOVEMBER 19, 2019

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Disclosures

- None
Outline

- Individual and Public Health Outcomes of Universal ART Coverage
- Novel Treatment Approaches from 2019
- Key Themes
HIV Treatment in Serodiscordant Couples

• PARTNER Phase 1
  • 888 heterosexual couples in 14 European countries
    • Positive partner with UVL, couple with condomless sex
    • 0 linked transmissions after 36,000 condomless sex acts

• Opposites Attract
  • 343 gay couples contributed 591 couple years of follow up
  • 0 linked transmissions after 16,800 condomless sex acts

• PARTNER Phase 2
  • 783 gay couples contributed 1596 couple years of follow up
  • 0 linked transmissions after 77,000 condomless sex acts

*No documented cases of transmission from a person with UVL*

Evidence Supporting Universal Coverage of ART

- **HPTN052:** Cohen, NEJM, 2016
- **TEMPRANO:** TEMPRANO study group, NEJM 2015; 373:808-22
- **START:** INSIGHT START study group, NEJM 2015; 373:795-807

**Research Objectives:**
- To compare the efficacy of immediate vs deferred ART in reducing HIV incidence (052/TEMPRANO) or HIV-morbidity/mortality (START) in adults

**Hazard Ratio for the primary endpoints:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPRANO</td>
<td>0.56</td>
<td>(0.41-0.76)</td>
</tr>
<tr>
<td>START</td>
<td>0.43</td>
<td>(0.30-0.62)</td>
</tr>
<tr>
<td>HPTN052 (Initial)</td>
<td>0.04</td>
<td>(0.01-0.27)</td>
</tr>
</tbody>
</table>
Objective: To evaluate the effect of early ART, initiated irrespective of CD4 count criteria, on HIV incidence in the general population in the same setting


6-monthly rounds of home-based HIV-testing

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat all HIV+ individuals regardless of CD4 count and clinical stage</td>
<td>Treat all HIV+ individuals according to South African guidelines (≤350 CD4, WHO stage 3 or 4 until Dec 2014, ≤500 since Jan 2015)</td>
</tr>
</tbody>
</table>

Phase 1: 2012 - 2014
Phase 2: 2016

# ANRS 12249: Universal Treatment Trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART initiation within 3 months in TasP clinics among patients not on ART at first TasP clinic visit</td>
<td>91%</td>
<td>52%</td>
</tr>
</tbody>
</table>

**Viral load** <400 copies/ml among patients not on ART at first TasP clinic visit

- At month 6: Intervention: 93%, Control: 92%
- At month 12: Intervention: 95%, Control: 95%

**Estimated ART coverage** *(as of 1st January 2016)*

- Intervention: 45%
- Control: 43%

**ART coverage improvement since baseline**

- Intervention: +14
- Control: +7

*Estimated from TasP + Department of Health data

## ANRS 12249: HIV incidence comparison

<table>
<thead>
<tr>
<th></th>
<th>Number of HIV-positive DBS tests</th>
<th>Person-years</th>
<th>Incidence for 100 person-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>268</td>
<td>11,787</td>
<td>2.27</td>
<td>2.00-2.55</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>227</td>
<td>10,646</td>
<td>2.13</td>
<td>1.85-2.41</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>495</td>
<td>22,434</td>
<td>2.21</td>
<td>2.01-2.40</td>
</tr>
</tbody>
</table>

### Adjusted risk ratio*

<table>
<thead>
<tr>
<th></th>
<th>aRR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention vs control</td>
<td>0.95</td>
<td>0.79-1.14</td>
<td>0.5821</td>
</tr>
</tbody>
</table>

*Estimated with Poisson regression, adjusted on sex, age, change in national ART guidelines, baseline cluster HIV prevalence and ART coverage.

Project SEARCH (Sustainable East Africa Research In Community Health)

- Universal ART with a multi-disease “patient-centered” care model
  - Hypertension, Diabetes, TB, and HIV
- N=320,000
  - 32 Communities with ~10,000 Persons each in Uganda, and Kenya
  - Aged 15+

Project SEARCH Outcomes

Annual TB incidence rate among baseline HIV+ (N=13,066)

- TB incidence rate per 100,000 PY
- Study Time: Year 1, Year 2, Year 3
- Intervention vs Control

Among baseline HIV+

- Probability of death by Year 3
  - All: RR: 0.79, 95% CI: 0.65, 0.96, p=0.02
  - CD4<350: 6% vs 8%
  - CD4≥350: 2% vs 2%

- Proportion with HTN control at year 3
  - Prevalent HTN*: 47% vs 37%
  - Prevalent HTN* & HIV+: 55% vs 48%
  - Measured HTN & HIV+ (dual control): 52% vs 42%

Project SEARCH Viral Suppression

2020 UNAIDS population viral suppression 73% target

Project SEARCH HIV Incidence Outcomes

No difference in 3 year cumulative HIV incidence between arms

HPTN 071/PopART

Location of the 21 PopART clusters in Zambia and Western Cape (SA), 2012

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929317/
HPTN PopART Design

21 Community Clusters
12 in Zambia / 9 in South Africa
Average of approx. 55,000 individuals in each cluster
Approximately 500,000 total adults across all communities

Randomization

Arm A
Clusters: 4 Zambia / 3 South Africa

Intervention
Combination prevention including:
- Universal household-based testing
- Active linkage to care
- Immediate ART eligibility

Evaluation
Population Cohort A
One adult from each of 2,500 randomly selected households in each cluster
Health Centre Data A
 Routinely collected data from Health Centres in the community
CHIPs Data A
Data collected from community members during household visits

Arm B
Clusters: 4 Zambia / 3 South Africa

Intervention
Combination prevention including:
- Universal household-based testing
- Active linkage to care
- ART eligibility according to national guidelines

Evaluation
Population Cohort B
One adult from each of 2,500 randomly selected households in each cluster
Health Centre Data B
 Routinely collected data from Health Centres in the community
CHIPs Data B
Data collected from community members during household visits

Arm C
Clusters: 4 Zambia / 3 South Africa

Standard of Care
Control Arm:
- Existing prevention & testing services and referral for care
- ART eligibility according to national guidelines

Evaluation
Population Cohort C
One adult from each of 2,500 randomly selected households in each cluster
Health Centre Data C
 Routinely collected data from Health Centres in the community

Primary Outcome Measure
* HIV incidence measured over 3 years in Population Cohort (from Arms A, B and C)

Secondary Outcome Measures
- Population Cohort: HIV incidence measured over 1st, 2nd, and 3rd years, HSV-2 incidence, sexual risk behaviour, community VL*, viral suppression (ART patients)*, drug resistance (ART patients with detectable VL)*
- Population Cohort and Health Centre Data: ART Adherence, HIV disease progression and death, ART toxicity, HIV stigma
- Health Centre Data: TB notification and TB mortality rates
- Population Cohort, Health Centre Data, CHIPs Data: uptake of PMTCT, uptake of male circumcision, ART screening and uptake, uptake of HIV testing and retesting, time between diagnosis and initiation of care

* Subject to funding for these assays.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929317/
HPTN 071 HIV Incidence Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Incidence</strong></td>
<td>198/12,990 (1.45%)</td>
<td>157/14,149 (1.06%)</td>
<td>198/12,563 (1.55%)</td>
</tr>
<tr>
<td>(geometric mean of community incidence rates)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted Rate Ratio (95% CI)</strong></td>
<td>0.93 (0.74, 1.18)</td>
<td>0.70 (0.55, 0.88)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Incidence compared to Arm C</strong></td>
<td>7% reduction</td>
<td>30% reduction</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.51</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age category, sex and baseline community HIV prevalence. Reported numbers include imputation for PC12 and PC24 missed visits.
U=U and UTT Trials
HIV Treatment and Incidence Data

Source: UNAIDS, 2018
Viral suppression increased slightly from 2012–2015 in the 38 US jurisdictions and across all 5 FTC/TDF PrEP use quintiles.

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Mean % Virally Suppressed</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>60.5</td>
<td>7</td>
</tr>
<tr>
<td>Low</td>
<td>52.6</td>
<td>7</td>
</tr>
<tr>
<td>Medium</td>
<td>52.4</td>
<td>9</td>
</tr>
<tr>
<td>Medium</td>
<td>52.4</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>60.1</td>
<td>10</td>
</tr>
</tbody>
</table>

PrEP Use and HIV Diagnoses in US

Low PrEP Uptake States in US

High PrEP Uptake States in US

Challenges Ahead

- Lower PrEP uptake among younger gay men which may further concentrate remaining HIV infections in youth
New HIV diagnosis among Gay & Bisexual Men in the United Kingdom
NTD Risk and Pregnancy
Tsepamo: Neural Tube Defects and DTG Exposure

- Birth outcomes surveillance study among Botswanan women ± HIV infection
  - Initial findings in May 2018 found apparent increase in NTD incidence among women who conceived while receiving DTG[1]
  - Warnings issued from WHO, EMA, FDA regarding use of DTG at time of conception[2-4] and some countries halted plans to use DTG-based ART as preferred first-line therapy

- Current analysis reports updated birth outcomes as of March 2019[5,6]
  - From July to September 2018, surveillance area expanded to capture ~ 72% of all births in Botswana; data abstracted from obstetric cards of all in-hospital deliveries
  - Government midwives trained to assess congenital abnormalities performed infant surface exams; abnormalities photographed with maternal consent and reviewed by external medical geneticist (blinded to drug exposure history)

Tsepmo: NTD Prevalence by ARV Exposure

- As of March 2019, rate of NTDs with DTG at conception lower than initially signaled \(^{[1,2]}\)
- No significant difference in major external structural malformations with DTG vs non-DTG ART \(^{[1,2]}\)
- WHO released updated recommendations reconfirming use of DTG-based ART as preferred first-line and second-line therapy \(^{[3]}\)

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>At Conception</th>
<th>DTG in Pregnancy</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTDs per exposures, n/N</td>
<td>5/1683</td>
<td>15/14792</td>
<td>70/89372</td>
</tr>
<tr>
<td>Prevalence difference, % (95% CI)</td>
<td>Reference</td>
<td>0.20 (0.01-0.59)</td>
<td>0.22 (0.05-0.62)</td>
</tr>
<tr>
<td>NTDs per exposures since May 2018, n/N</td>
<td>1/1275</td>
<td>1/3492</td>
<td>9/23,315</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Tsepamo: Additional Adverse Birth Outcomes

- No difference between DTG and EFV for any single adverse birth outcome, including preterm/very preterm birth (< 37/< 32 wks), small gestational age, stillbirth, in-hospital neonatal death

- Analysis included single births since October 2016

<table>
<thead>
<tr>
<th>Birth Outcome, n (%)</th>
<th>DTG at Conception (n = 1271)</th>
<th>EFV at Conception (n = 4430)</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse</td>
<td>422 (33.2)</td>
<td>1550 (35.0)</td>
<td>0.94 (0.86-1.02)</td>
</tr>
<tr>
<td>Any severe (SB, NND, vPTB, vSGA)</td>
<td>151 (11.9)</td>
<td>568 (12.8)</td>
<td>0.89 (0.74-1.05)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, education, gravida.
Addtional NTD Data From Botswana and Brazil

- Prospective birth outcomes surveillance study among Botswanan women commissioned by Botswana Ministry of Health and Wellness in response to May 2018 Tsepamo findings[1]
  - Surveillance area included 22 facilities not covered by Tsepamo (October 2018 to March 2019); potential NTDs evaluated by trained midwives prior to discharge with suspected NTDs reviewed by blinded geneticist

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HIV Positive</th>
<th>HIV Negative (n = 2328)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG (n = 152)</td>
<td>Any Non-DTG ART (n = 381)</td>
</tr>
<tr>
<td>NTDs, n (%) [95% CI]</td>
<td>1 (0.66) [0.02 to 3.69]</td>
<td>0 (0) [0 to 0.79]</td>
</tr>
<tr>
<td>Prevalence difference, % [95% CI]</td>
<td>Reference</td>
<td>0.66 [-0.73 to 4.16]</td>
</tr>
</tbody>
</table>

- Retrospective cohort of Brazilian women with HIV found no NTDs among births to women with possible exposure to DTG at conception from 2017-2018 (n = 384)[2]
New Directions in ART: What’s on the Horizon and How Will it Help Expand Treatment Coverage?

- Current options are excellent, what more could be needed?
  - More options that offer different strategies allows for greater individualization to better accommodate broader range of patient needs
  - Requirements for new options: robust and durable efficacy and safety must be comparable or better than current options

- 2 prominent trends in development
  - Fewer drugs: dual therapy options emerging and in development that reduce the burden of drug classes
  - Long-acting formulations: injectables, implants; much less frequent dosing to simplify disease management
## Reducing Dose Frequency and Number of Drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA</th>
<th>Phase</th>
<th>Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elsulfavirine(^1)</td>
<td>NNRTI</td>
<td>I</td>
<td>Long acting</td>
</tr>
<tr>
<td>GS-6207(^2)</td>
<td>Capsid inhibitor</td>
<td>I</td>
<td>Long acting, fewer than 3 drugs</td>
</tr>
<tr>
<td>Islatravir (MK-8591)(^3)</td>
<td>NRTTI</td>
<td>II</td>
<td>Long acting, fewer than 3 drugs</td>
</tr>
<tr>
<td>Leronlimab (PRO140)(^4)</td>
<td>Anti-CCR5 mAb</td>
<td>IIb/III</td>
<td>Long acting, fewer than 3 drugs</td>
</tr>
<tr>
<td>CAB + RPV(^5,6)</td>
<td>INSTI + NRTI</td>
<td>III</td>
<td>Long acting, fewer than 3 drugs</td>
</tr>
<tr>
<td>DTG/3TC(^7,8)</td>
<td>INSTI/NRTI</td>
<td></td>
<td>FDA approved (initial therapy), III (maintenance) Fewer than 3 drugs</td>
</tr>
<tr>
<td>DTG/RPV(^9)</td>
<td>INSTI/NRTI</td>
<td>FDA approved (maintenance)</td>
<td>Fewer than 3 drugs</td>
</tr>
<tr>
<td>Ibalizumab(^10)</td>
<td>mAb CD4-directed post-attachment HIV-1 inhibitor</td>
<td>FDA approved (multidrug resistant HIV-1)</td>
<td>Long acting</td>
</tr>
</tbody>
</table>

**GEMINI-1,-2 and TANGO: Virologic Outcomes With DTG + 3TC as Initial or Switch Therapy**

- **GEMINI-1,-2:** Initial therapy with DTG + 3TC noninferior to DTG + TDF/FTC for primary endpoint of HIV-1 RNA < 50 c/mL\(^1\)
  - Adjusted Δ: -1.7% (95% CI: -4.4% to 1.1%)

- **TANGO:** Switch to DTG/3TC noninferior to continued TAF-based ART for primary endpoint of HIV-1 RNA ≥ 50 c/mL\(^3\)
  - Adjusted Δ: -0.3% (95% CI: -1.2% to 0.7%)

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US Guideline Recommendations: First-line Dual-Therapy Regimens

**DHHS**[1]

“when ABC, TAF, or TDF cannot be used or are not optimal”

**IAS-USA**[2]

“when individuals cannot take ABC, TAF, or TDF”

*Neither guideline has been updated since 96-Wk GEMINI and 48-Wk TANGO data have been reported.*

Phase III Studies of Injectable Long-Acting Therapy

- **FLAIR**[1]
  - **ART-naive patients** started **20-wk induction phase with oral DTG/ABC/3TC**, patients achieving suppression continued to maintenance phase of **monthly CAB IM + RPV IM** after oral lead-in

- **ATLAS**[2]
  - **Virologically suppressed patients** switched to **monthly CAB IM + RPV IM** after oral lead-in


Slide credit: clinicaloptions.com
ATLAS and FLAIR Pooled Analysis: Efficacy at Wk 48 in ITT-E Population

Participants (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>LA CAB + RPV (n = 591)</th>
<th>Continue oral ART (n = 591)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Nonresponse (≥ 50 c/mL)</td>
<td>1.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Virologic Success (&lt; 50 c/mL)</td>
<td>93.1</td>
<td>94.1</td>
</tr>
<tr>
<td>No Virologic Data</td>
<td>5.1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Key Secondary Endpoint (HIV-1 RNA < 50 copies/mL)
LA CAB + RPV noninferior to continued BL ART

Primary Endpoint (HIV-1 RNA ≥ 50 copies/mL)
LA CAB + RPV noninferior to continued BL ART

*Adjusted for sex and BL third agent class.


Slide credit: clinicaloptions.com
HIV Pandemic Control Goal (2020)

It is 42 days, 17 hours, 9 minutes, 55 seconds
until Wednesday, 1 January 2020 (Almaty time)
Key Themes

- Universal treatment for HIV
  - Efficacious and Effective
    - Improving the quality and quantity of life for those living with HIV
    - In reducing HIV incidence **only** we treat those people living with HIV who have onward transmission risks

- Emerging Treatment Strategies including longer acting drugs (q8 weeks) and 2-drug regimens (lower cost, less A/E)

- Decreasing HIV incidence necessitates
  - Recognizing that depending on who is in 10:19:27, even HIV epidemics can be sustained or grow
  - Leveraging implementation research to study optimal strategies for delivering ART to marginalized communities