SCIENCE AND COMMUNITY IN THE RESPONSE TO HIV IN WESTERN AFRICA

AIDS 2018 POST-CONFERENCE WORKSHOP

Ghana, 12-13 May 2019
Key Messages from AIDS 2018
Day 1

Key Messages from AIDS 2018
Elzette Rousseau-Jemwa, Desmond Tutu HIV Foundation
Linda-Gail Bekker, International AIDS Society
AIDS 2018: Track A

Cure
Viral reservoir
Viral persistence
Remission
Vaccine

22nd International AIDS Conference (AIDS 2018)
Amsterdam, Netherlands.
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Cure Research

• Strategies to modulate HIV expression in ART-treated people to either reactivate it in “Kick and Kill” strategies or to stop transcription in “Block and Lock” strategies

• Anti-α4β7 administration could induce virological control after ART in non-human primates, the same results were not seen when the study was repeated or in an open-label human trial of vedolizumab.

• New molecules able to enhance HIV transcription:
  – a histone deacetylase inhibitor Chidamide,
  – the CCR5-inhibitor MVC
  – a modified proteinase K agonist GSK445A, that showed promising activity in reactivating HIV when tested in vivo in human or non-human primates with no toxicity.
How can we prevent HIV transmission?

Jo-Ann Passmore, TUSY09

Jonathan Carlson, TUSY09; Zabrina Brumme, TUSY09

Vaccine-induced antibodies

TUAA0102, TUAA0103, TUSY09, TUPDA0106LB, THAA0101, THAA0102, THAA0103
New Tools to Prevent HIV Infection

Increased protection against SHIV challenge of immunized monkeys in the presence of a CD4-mimetic compound

Navid Madani, TUAA01
Better Antibodies to Block HIV

Native envelope spike

SOSIP gp140

Native like env immunogen

Rogier Sanders, THSY04

Sanders et al. 2002. J.Virol. 76: 8875

AUTOGOUS neutralization titers

P < 0.0001

TUAA0101, WEAA0204, THSY04, THAA0104, THAA0105
How Can We Induce HIV Remission?

Drain the HIV reservoir
= Eliminate HIV-infected cells

Reinforce the dam
= Boost the immune response to HIV

Brad Jones,
WEPL01

TUAA0203, TUAA0204, TUAA0205
Two Strategies to Target HIV on ART

**Shock**
- Latency reversing agent
- Kill

**Block**
- Latency enhancing agent
- Lock

**Shock and Kill**
- TUPDA0102, WEAA0104, WEAA0105, WESY09
Vaccine approaches to prevent HIV

• Novel concepts, based on advanced technology such as nanoparticles able to elicit higher neutralizing antibody titers and B cell activation

• Novel vaccine mucosal delivery and out-of-the-box concepts such as small molecules blocking CD4 binding of gp120

• Combination of broadly neutralizing antibodies: provide protection up to 6 months in SHIV model

• APPROACH trial in human (Phase 2a): immune responses elicited by the Ad26/Ad26mosaic and gp140 regimen remained durable 48 weeks after the final boost. Even better antibody titer persistence compared to antibodies in monkeys receiving the same regimen and showing protection after SIV challenge
Ad26/Ad26 HD gp140 vaccine-induced immune responses from APPROACH compare favorably to non-human primates

Frank L Tomaka, TUAA0104
Lancet, July 6, 2018

HIV vaccine tested in APPROACH

Ad26/Ad26 HD gp140 vaccine-induced immune responses from APPROACH compare favorably to non-human primates

TUAA0104, TUAA0105
Summary

• Broadly neutralizing antibodies show promising data in HIV prevention and remission

• APPROACH vaccine trial data are encouraging and data from the main trial available in 2021

• Many new molecules are in development to prevent infection, reactivate or silence the latent HIV reservoir

• So far, remission trials with/without ART interruption do not induce sufficient sustained viral control
AIDS 2018: Track B

Dolutegravir in triple, dual, mono therapy
Dolutegravir and Pregnancy
Dolutegravir & TB
Switch studies
Community trials
Drive Forward
Diamond - Test n Treat

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## Baseline characteristics

<table>
<thead>
<tr>
<th>Regimen</th>
<th>%</th>
<th>VS (%)</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC+TDF+DTG</td>
<td>7.2</td>
<td>85.2</td>
<td>1.42</td>
<td>(1.32-1.52)</td>
</tr>
<tr>
<td>3TC+TDF+EFV</td>
<td>74.0</td>
<td>78.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3TC+AZT+LPV/r</td>
<td>4.9</td>
<td>67.2</td>
<td>0.59</td>
<td>(0.55-0.63)</td>
</tr>
<tr>
<td>3TC+TDF+ATV/r</td>
<td>4.6</td>
<td>71.3</td>
<td>0.67</td>
<td>(0.63-0.72)</td>
</tr>
<tr>
<td>3TC+AZT+EFV</td>
<td>3.5</td>
<td>72.9</td>
<td>0.94</td>
<td>(0.87-1.02)</td>
</tr>
<tr>
<td>3TC+TDF+LPV/r</td>
<td>2.0</td>
<td>63.7</td>
<td>0.54</td>
<td>(0.49-0.60)</td>
</tr>
<tr>
<td>Others</td>
<td>3.7</td>
<td>67.9</td>
<td>0.67</td>
<td>(0.62-0.73)</td>
</tr>
</tbody>
</table>

3TC+TDF+DTG introduced as first line in 2017

VS = Virologic suppression (< 50 copies/ml at 6 months)

**42% higher odds and 7% absolute difference in virologic suppression vs efavirenz**

Veloso Meireles et al, TUAB0101
GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies

- ART-naive adults
- VL 1000-500,000 c/mL
- No evidence of pre-existing viral resistance
- No HBV infection or need for HCV therapy

Double-blind phase

DTG + 3TC (N=716)

Open-label phase

DTG + TDF/FTC (N=717)

Continuation phase

DTG + 3TC

Day 1

Week 24

Week 48

Week 96

Week 144

Baseline stratification factors:
- HIV-1 RNA (vs >100,000 c/mL)
- CD4 (≤200 vs >200 cells/mm³).

Primary endpoint
HIV-1 RNA <50 c/mL (ITT-E snapshot)

• −10% noninferiority margin for individual studies.

Cahn et al. AIDS 2018, TUAB0106LB.
**GEMINI**

**Confirmed Virologic Withdrawals Through W48: ITT-E Population**

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>DTG + 3TC (N=716)</th>
<th>DTG + TDF/FTC (N=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVW</td>
<td>6 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Treatment-emergent resistance</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Overall safety and tolerability at W48: comparable between the 2 regimens
- Fewer drug-related AEs with DTG + 3TC
- Change in renal and bone biomarkers significantly favors DTG + 3TC

**Snapshot Analysis W48, Stratified by baseline HIV RNA and CD4**

- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
- Cahn et al. AIDS 2018, TUAB0106LB.

### Baseline HIV-1 RNA, c/mL
- DTG + 3TC: 91, 94
- DTG + TDF/FTC: 92, 90

### Baseline CD4+ cell count, cell/mm³
- DTG + 3TC: 93, 93
- DTG + TDF/FTC: 79, 93

### Overall safety and tolerability at W48:
- Comparable between the 2 regimens
- Fewer drug-related AEs with DTG + 3TC
- Change in renal and bone biomarkers significantly favors DTG + 3TC

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Monotherapy

- France: MONCAY Study (non-inferiority study)
  - Open-label, randomized, controlled trial in 9 sites

- Virological results at week 24: DTG was non-inferior to DTG/ABC/3TC but significantly more participants in the monotherapy arm developed virological failure before week 48
- Monotherapy arm has stopped early according to safety monitoring board
- Emphasized that dolutegravir is not recommended as monotherapy
DTG and Pregnancy

→ When started during pregnancy, EFV and DTG appear equivalent in terms of pregnancy outcomes (including birth defects)

→ But adverse outcomes with EFV or DTG ART are still higher than in HIV-uninfected women
Dolutegravir in late pregnancy
DolPHIN-1 pilot trial

Results – Viral load at Post-partum Visit

Greater proportion of mothers initiating ART late in pregnancy achieved HIV-1 RNA <50 copies/mL with DTG- compared to EFV- based regimens

Khoo et al, THAB0307LB
Tsepamo Study (May 1, 2018 with update to July 15, 2018)

NTD Prevalence Difference by Exposure

May 1, 2018

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>DTG-CONCEPTION</th>
<th>ANY NON-DTG ART-CONCEPTION</th>
<th>EFV-CONCEPTION</th>
<th>DTG STARTED DURING PREGNANCY</th>
<th>HIV-NEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTDs/Exposures</td>
<td>4/426</td>
<td>14/11,300</td>
<td>3/5,787</td>
<td>0/2.812</td>
<td>61/66,057</td>
</tr>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.94% (0.37%, 2.4%)</td>
<td>0.12% (0.07%, 0.21%)</td>
<td>0.05% (0.02%, 0.15%)</td>
<td>0.00% (0.00%, 0.13%)</td>
<td>0.09% (0.07%, 0.12%)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>-0.82% (-0.24%, -2.3%)</td>
<td>-0.89% (-0.31%, -2.3%)</td>
<td>-0.94% (-0.35%, -2.4%)</td>
<td>-0.85% (-0.27%, -2.3%)</td>
</tr>
</tbody>
</table>

July 15, 2018: Updated prevalence of DTG exposure at conception is 4/596 (0.67%, 95% CI of 0.26%, 1.7%)
-- 95% CI still does not overlap with any other exposure group
Tsepamo Updated Analysis Plan

• **Next formal analysis will occur after 31 March 2019**
  – Will include women already exposed to DTG from conception prior to recent guideline change
  – Plans in place to expand from 8 to 18 sites, increasing from 45% to 72% of births in the country

• **Final analysis in 2019 to include:**
  – NTDs
  – All major malformations
  – Other adverse birth outcomes (stillbirth, preterm, SGA, NND)
### WHO 2018 recommendations for first-line

<table>
<thead>
<tr>
<th>Population</th>
<th>Preferred</th>
<th>Alternatives</th>
<th>Special situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult men and adolescent boys</td>
<td></td>
<td>TLD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AZT+3TC+ EFV600&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnant (from eight weeks after conception) and breastfeeding women and adolescent girls</td>
<td>TLD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TLE600, TLE400</td>
<td>TDF+3TC (or FTC)+PI/r&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women and adolescent girls with effective contraception or not of childbearing potential</td>
<td>TLE600</td>
<td>TLE400</td>
<td>AZT+3TC+ EFV600&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women and adolescent girls of childbearing potential who want to become pregnant and have no effective contraception</td>
<td>TLE600</td>
<td>TLE400</td>
<td>TDF+3TC (or FTC)+PI/r&lt;sup&gt;c&lt;/sup&gt;, RAL</td>
</tr>
</tbody>
</table>

- **TLD** = TDF + 3TC + DTG  
- **TLE** = TDF + 3TC (or FTC) + EFV

a) In PLHIV with TB using rifampicin, the dose of DTG needs to be increased to 50 mg twice daily.
b) NVP may be used in special circumstances where alternative options are not available.
c) If national prevalence of EFV pretreatment drug resistance exceeds 10% or if no other alternatives are available.

A woman-centered approach: promoting human rights + promoting gender equality – enable women to make informed choices
These international phase 3 studies randomised 1024 participants on stable ART (>6 months) to either switch to open-label oral dolutegravir + rilpivirine (DTG/RPV) or continue on their current ART.

After week-48, all participants were able to switch to dual-ART with DTG/RPV.
Results

- Viral response rates <50 copies/mL at week 48:

- Non-inferiority was met
- Safety was generally good and consistent with known side-effect profiles of individual drugs
- One person with virological failure included drug resistance to RPV, but also had NNRTI resistance at baseline
- No cases of DTG resistance were reported
TB Co-infection

INSPIRING

HIV/TB co-infected ART-naive adults

TB therapy

Screening −28 to −14 days

HRZE (2 months)  HR (4 months)a

Day 1

Interim analysis:
% <50 copies/mL (modified Snapshot)

52 weeks
End of randomized phase

Primary endpoint at Week 48: % <50 copies/mL (modified Snapshot)

Continuation Phase (ART)

2 confirmed virologic failure on DTG with no treatment-emergent resistance mutations

DTG C\textsubscript{\text{tau}} with DTG 50 mg bid +RIF was similar to that of DTG 50 mg qd without RIF

DTG was well tolerated;
- no AEs leading to withdrawal
- Low rates of TB- and non–TB-associated IRIS in both groups;
- No AEs meeting the stopping criteria for drug-induced liver injury in either group

Dooley TUAB0206
Treatment Cascade

Strengthening the treatment cascade

• Five trials of universal test and treat reported impressive progress
  – PopART: home-based testing and support to linkage and retention delivered by lay health workers
  – SEARCH: “health fairs” delivered services and improved all aspects of the cascade
  – MaXART: early ART appeared to improve retention
  – BCPP: community based interventions to drive testing plus immediate ART
  – TasP: Home-based HIV testing and immediate ART
Cascades- Europe
Incidence - Europe
Mortality trends
Biomedical interventions
- TasP U=U
- PrEP
- Rapid and same day ART
Addressing syndemics
Key Population-led
Transgender issues
Does U=U?

PARTNER2 (WEAX0104LB)

Estimate of transmission risk in serodifferent gay couples when the HIV-positive partner is virally suppressed

783 gay couples (median 1.6 years of follow-up)

The ability to phylogenetically link transmissions during eligible CYFU

Among serodifferent gay couples who had sex ~77,000 times without condoms with undetectable viral load (<200 copies), there were zero phylogenetically-linked transmissions during ~1600 CYFU

Results indicate that the risk of HIV transmission when HIV viral load is suppressed is effectively zero

Undetectable = Untransmissible!
PrEP

ANRS Prévenir

- Ongoing prospective cohort study in Paris region enrolling high-risk individuals to take daily or on-demand prep
  - All tested for HIV at baseline, 1 month and every 3 months after
  - Daily sexual behaviour recorded and everyone counselled on adherence
  - 45.4% chose daily prep and 54.6% chose on demand
  - Both methods of taking prep are effective

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Daily)</td>
<td>443</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td>TDF/FTC (On Demand)</td>
<td>506</td>
<td>0 (0-0.7)</td>
</tr>
</tbody>
</table>

n = 3,000

May 3rd 2017

TDF/FTC
Daily

TDF/FTC
On Demand

May 31st 2020

Show 15% reduction in new HIV diagnoses among MSM in the Paris Region

Molina WEA0406LB

www.iasociety.org
Oral PrEP Global Roll-out in 2018

Est. numbers on PrEP:
- <100
- 100 - 1,000
- 1,000 - 10,000
- 10,000 - 100,000
- >100,000

The Politics of PrEP THSY02: Jean-Michel Molina

Data from AVAC.org 2018 - https://www.prepwatch.org/country-updates/
PrEP in the real world (TUPDX01)

• Increased scale-up for PEPFAR funded programs FSW, MSM, TG
• Less condom use with casual partners among MSM in Melbourne
• PrEP as harm reduction “MTV”
• Elevated HCV and re-HCV Netherlands
• Feminizing hormones and PrEP – results from 2 studies
  – lower plasma TFV exposure (13%) in the presence of FHT
  – Altered TDF/FTC pharmacology in rectum
PrEP Delivery

- Zimbabwe: higher uptake of PrEP in rural compared to urban clinics
  - village chiefs who mobilized stakeholders were involved in demand increase
- Brazil: encouraging data using three measures of adherence: pill count (returned bottles), self-report and medication possession ratio
  - All three measures were highly correlated and had good positive predictive value although rates of false negatives were relatively high

- Sub-Saharan Africa: integration with family planning clinics
  - Kenya and Zimbabwe show successful delivery alongside birth control and FP clinics could be key access points for women to obtain PrEP
Emerging issues in PrEP

- Risk compensation and higher STI rates,
- Elevated risk of new HVC infections among MSM
- Feminizing hormones have no meaningful impact on TFV exposure in transgender women
- Vulnerabilities of marginalised populations (overcome stigma and inequality toward MSM, TG women, homeless, PWID (including MSM-PWID) adolescents and younger age (25-29), migrants and indigenous populations). Programming must take account of these vulnerabilities.
- Prevention programmes: importance of comprehensive sexuality education + address the psychosocial conditions
- Risk perception may be low. Offer PrEP through health system friendliness

- We are still short of the UNAIDS goals of linking 3 million persons to PrEP by 2020.
Universal test and treat

Testing

• Malawi: facility-based HIV self-testing increased uptake of HIV testing among outpatients compared to provider-initiated HIV testing
• Strategies for uptake of HIV testing
  – performance-based incentives in health facilities
  – point-of-care early infant diagnosis
  – community-based index HIV-testing
  – health facility-based HIV self-testing

Testing uptake by sex and age across arms (n=5,885+)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Youth (15-24 yrs)</th>
<th>Men (25+ yrs)</th>
<th>Women (25+ yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard PITC</td>
<td>AOR:1.19</td>
<td>ref</td>
<td>AOR:1.24</td>
<td>ref</td>
</tr>
<tr>
<td>Optimized PITC</td>
<td>AOR:1.52*</td>
<td>ref</td>
<td>AOR:0.89</td>
<td>ref</td>
</tr>
<tr>
<td>Facility-based HIVST</td>
<td>AOR:7.39**</td>
<td>ref</td>
<td>AOR:5.73**</td>
<td>ref</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AOR:7.83**</td>
<td></td>
</tr>
</tbody>
</table>

Dovel TUAE0105

www.iasociety.org
Rapid and same-day initiation of ART is achievable in LMIC settings, when services are delivered in accessible community settings.

- The CommLink program in eSwatini (including community-based testing, mobile care, and peer-based linkage) achieved 96% ART initiation, and 73% rapid initiation (Williams, THAC0201)

- Implementing fast-track ART initiation in Botswana improved median time from linkage to first viral suppression from 210 to 104 days (Lebelonyane, THAC0204)

- At a Bangkok sexual health clinic, 79% of diagnosed patients received same-day ART and were 2.2 times as likely to be virally suppressed vs. standard of care (Seekaew, THAC0203)
Prevention interventions

Innovations

- **USA**: smart phone app to help with prep adherence among young MSM and young trans women who have sex with men
  - Testing increased more than 60% after campaign
- **Philippines**: online campaign, offline and gay-networking apps to promote testing
  - Testing increased more than 60% after campaign
- **China**: internet-based self-testing model
  - Reached MSM never previously screened
- **Vietnam**: Facebook community that promoted HIV testing using influencers and offline lay testers
- **Challenges remain in scale up of ART for treatment and PrEP worldwide to achieve elimination targets**

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**Online to offline HIV testing cascade March 2016 – March 2018 Vietnam**

- #client counselled: 3626
- #client got HIV tested: 2808
- #client having confirmed HIV+: 331
- #client enrolled into ARV: 331
Prevention interventions

Innovations

• Technology-based interventions prove to be acceptable to ‘hard to reach’ populations including young MSM and trans women

• Thailand: online time-based videos to deliver HIV/STI prevention sessions (vialogues)
  – Showed reductions in high risk behaviours and higher rates of condom usage

• Thailand: methods to provide counselling and testing to MSM and TGW
  – Result: those who access online had lower rates of linkage to ART compared to offline or mixed
Key population-led services

Services led by peers and KP CBOs increase access to HIV prevention and treatment

- More than half of people tested by KP CBOs in Vietnam were first-time testers, and 90% of those diagnosed enrolled in treatment (Ngo, THAC0202)
- In Malawi, HCP training and differentiated service delivery increased case finding and linkage among FSW and MSM (Kamanga, THAC0201)
- At a Bangkok sexual health clinic employing KP staff, 79% of diagnosed patients received same-day ART and 90% were successfully referred to long-term ART care (Seekaew, THAC0203).

Differentiated services to address unique needs of KPs

- At Bangkok’s Tangerine Clinic, TGW accessing hormone therapy were more likely to repeatedly test for HIV and to access PrEP (Janamnuaysook, THAC0204)
Men

- The biggest gap in the treatment cascade is diagnosing men, particularly men aged 25-34
- Men are less likely to know their HIV-positive status than women in a number of sub-Saharan African countries
- How to reach men:
  - HIV self-testing and community-based HIV testing services
  - Geomapping to provide holistic package of services in appropriate locations
  - Reaching men where they gather
Syndemics

- Co-occurring psychosocial conditions that interact synergistically to exacerbate the risk for HIV transmission
- Multi-component interventions often fail to address social forces beyond the individual level and are often limited to one disease/condition
- Recognize social and political forces that drive structural vulnerabilities
- Requires systems thinking for which there may be limited experience and/or political will
- When fully applied, can promote interventions at the policy as well as clinical and individual levels
Syndemic Interventions

- India Integrated Bio-Behavioural Surveillance (men)
  - Alcohol use, drug use and violence victimisation (physical and/or sexual violence in the past year) predicted condom use
- Women’s Health Coop (WHC+)
  - Intervention impacted drinking, IPV, condom use, ARV adherence
- Project IMPACT (USA)
  - CM using MSM enrolled in RCT using behavioral activation
  - Intervention participants reported fewer CAS acts with men who were HIV-infected or status unknown
  - Fewer CAS acts under the influence of CM with men who were HIV-infected or status unknown
  - More continuous days abstaining from crystal methamphetamine
Thank You