OVERCOMING CHALLENGES IN HIV WITH SCIENCE, INNOVATION AND COLLABORATIONS IN SOUTHEAST ASIA

IAS 2019 POST-CONFERENCE WORKSHOP

THE HILTON HOTEL, KUALA LUMPUR, MALAYSIA | 4-5 OCTOBER 2019
IAS TOOLKITS

TRACK A:
BASIC SCIENCE

IAS 2019 HIGHLIGHTS

PRODUCED BY THE INTERNATIONAL AIDS SOCIETY
OCTOBER 2019
Contents

- Cellular and tissue reservoirs
- Latency-reversing agents
- Remission
- Hormonal influences on HIV
- Primary infection
• Recognition of primary infection and early initiation of ART may offer later opportunities for new therapeutics
• Very early ART initiation (< 14-16 days after infection) limits reservoir size, preserves HIV-specific immunity, reduces immune activation and exhaustion
Basic science and translational research: highlights

- **Promising developments**: range of new latency-reversing agents and immunotherapeutics to promote remission

- **Challenges**: the breadth of cell types and tissues forming the HIV reservoir requires fresh thinking about `shock and kill` and latency-reversal strategies for HIV cure
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TRACK B: CLINICAL SCIENCE

IAS 2019 HIGHLIGHTS

PRODUCED BY THE INTERNATIONAL AIDS SOCIETY
OCTOBER 2019
Overview

- Dolutegravir
  - Neural tube defects
  - WHO guidelines
  - Paediatric dosing
  - ADVANCE study
  - Weight gain

- Treatment simplification
  - First-line 2-drug regimen
  - Maintenance 2-drug regimen
  - Injectable ART

- TB/HIV
  - TB diagnosis, prevention and treatment
  - First-line ART

- Investigational agents
  - Ilatravir (MK-8591)
  - Fostemsavir
  - GS-6207 (capsid inhibitor)
Dolutegravir

Neural tube defects

May 2018: Tsepmo birth outcomes surveillance study, Botswana, reported elevated risk of neural tube defects (NTDs) with dolutegravir (DTG) exposure at conception – 0.94% [95% CI 0.37%-2.4%] prevalence

- Warnings issued by EMA, FDA on DTG use by women of childbearing age, some countries paused plans to implement DTG-based therapy as preferred first-line
- 19 countries introduced restrictions on DTG use in women of child-bearing potential; strongly opposed by community
- Updated analysis to March 31 2019:
  - Surveillance expanded to capture 72% of all births in Botswana 2014-2019
  - Published in NEJM to coincide with IAS2019
## Neural tube defects: Tsepamo results

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>DTG-CONCEPTION</th>
<th>ANY NON-DTG ART CONCEPTION</th>
<th>EFV CONCEPTION</th>
<th>DTG PREGNANCY</th>
<th>HIV-NEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTDS/Exposures</td>
<td>5/1683</td>
<td>15/14792</td>
<td>3/7959</td>
<td>1/3840</td>
<td>70/89372</td>
</tr>
<tr>
<td>% with NTD (95% CI)</td>
<td><strong>0.30%</strong> (0.13, 0.69)</td>
<td><strong>0.10%</strong> (0.06, 0.17)</td>
<td><strong>0.04%</strong> (0.01, 0.11)</td>
<td><strong>0.03%</strong> (0.0, 0.15)</td>
<td><strong>0.08%</strong> (0.06, 0.10)</td>
</tr>
<tr>
<td>Prevalence difference (95% CI)</td>
<td><strong>Ref</strong></td>
<td><strong>0.20%</strong> (0.01, 0.59)</td>
<td><strong>0.26%</strong> (0.07, 0.66)</td>
<td><strong>0.27%</strong> (0.06, 0.67)</td>
<td><strong>0.22%</strong> (0.05, 0.62)</td>
</tr>
</tbody>
</table>

**Zash, MOAX0105LB**
Dolutegavir

Neural tube defects: additional surveillance

- Botswana: supplementary surveillance from 22 facilities not covered by Tsepamo – prevalence of neural tube defects 0.66% in DTG-exposed (N=152)
- Brazil: women possibly exposed to DTG at conception 2017-2018 (n=382) – no NTDs
- Antiretroviral Pregnancy Registry: 1 NTD in 248 DTG exposures (0.4% prevalence) to 31 January 2019
- **Overall prevalence of NTDs in Antiretroviral Pregnancy Registry:** 0.03%, consistent with background rate in countries with food folic acid supplementation (0.01% - 0.08%)
- To rule-out a 3-fold increase in a rare event like NTD (prevalence 0.1%), APR would need to accumulate reporting on ~2,000 preconception exposures

[References: Raesima, MOAX0106LB; Pereira, MOAX0104LB; Mofenson, TUAB0101]
Dolutegravir with an NRTI backbone is recommended as the preferred first-line regimen for:

- Adults and adolescents initiating ART *(strong recommendation, moderate-certainty evidence)*
- Infants and children with approved DTG dosing *(conditional recommendation, low-certainty evidence)*

Efavirenz at low dose 400mg plus an NRTI backbone is recommended as the alternative first-line regimen *(strong recommendation, moderate-certainty evidence)*
Dolutegravir
ADVANCE study: first-line regimens

• Alternative first-line to efavirenz needed in South Africa – 15% baseline NNRTI resistance
• ADVANCE study population: 60% female, ≈100% Black
• Drawn from a group representing a quarter of the global epidemic
Dolutegravir

ADVANCE study, primary outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Difference in response (98.3% CI)</th>
<th>P value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC+DTG vs TDF/FTC+DTG</td>
<td>-1.1% (-7.7%, +5.4%)</td>
<td>0.68</td>
</tr>
<tr>
<td>TDF/FTC+DTG vs TDF/FTC/EFV</td>
<td>+6.3% (-0.7%, +13.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>TAF/FTC+DTG vs TDF/FTC/EFV</td>
<td>+5.1% (-1.9%, +12.2%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

- 48-week HIV-1 RNA outcomes:
  - TDF/emtricitabine/dolutegravir 85%
  - TAF/emtricitabine/dolutegravir 84%
  - TDF/emtricitabine/efavirenz 79%

- Higher frequency of emergent NRTI & NNRTI resistance in EFV arm;
- Higher rate of grade 3 & 4 adverse events in EFV arm
- Renal and bone toxicity in line with established safety profiles
- Greater weight gain in the DTG study arms

Venter, WEAB0405LB
Treatment simplification

First-line, 2-drug regimen: GEMINI 1 & 2

- A 2-drug first-line regimen has the potential to reduce long-term toxicities and cost of therapy
- **Dolutegravir/lamivudine (DTG/3TC)** non-inferior to DTG/TDF/FTC in 48-week primary analysis of GEMINI 1 & 2
- 96-week secondary analysis shows non-inferiority of DTG/3TC
- Very low virological failure rate, no treatment-emergent resistance

Cahn, WEAB0404LB
2-drug maintenance regimen: TANGO

- A 2-drug maintenance regimen has the potential to reduce long-term toxicities and cost of therapy
- TANGO is an ongoing phase III, non-inferiority trial evaluating efficacy and safety of a switch from a 3 or 4-drug TAF-based regimen to DTG/3TC
- 48-week primary analysis showed non-inferiority of DTG/3TC
- 1 virologic failure in TAF arm, no treatment-emergent resistance
- No viral rebound in 7 study participants with proviral M184V/I at baseline

Virologic outcomes

<table>
<thead>
<tr>
<th></th>
<th>Proportion of participants, %</th>
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<tbody>
<tr>
<td>HIV-1 RNA...</td>
<td>0.3% 0.5%</td>
</tr>
<tr>
<td>HIV-1 RNA...</td>
<td>93.2 93.0</td>
</tr>
<tr>
<td>No virologic...</td>
<td>6.5  6.5</td>
</tr>
</tbody>
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Van Wyk, WEAB0403LB
Treatment simplification

Acceptability of long-acting injectable ART: ATLAS

Acceptability of long-acting injectable

ATLAS study
- Phase III study of long-acting injectable ART (cabotegravir & rilpivirine) vs oral 3-drug ART
- Tolerability, frequency and acceptance of injection site reactions improved significantly from baseline to week 48
- CAB + RPV LA participants demonstrated significantly greater improvement from baseline in treatment satisfaction vs CAR at Weeks 24 and 44
- 97% preferred injectable treatment (CAB & RPV) to oral treatment at week 48

Murray, MOAB0103
Improving TB prevention, care and treatment in people living with HIV

• TB remains under-diagnosed in PLWH; 464,633 TB cases in PLWH and 300,000 TB deaths in 2017

• Late HIV diagnosis and treatment initiation contributes to high TB incidence; 4-country study across high, middle and lower-income settings showed:
  – Late presentation (CD4 < 350 at HIV diagnosis) associated with a 6-fold increase in risk of incident TB
  – Avoiding late presentation (LP) will have the highest impact on preventing TB; 91% of TB among LP and 86% of cases in the complete study population could be averted in the first year if LP were prevented

• Optimum interval between TB treatment initiation and ART initiation established for adults but has been unclear for children and adolescents:
  – 6-country retrospective study showed ART initiation within 8 weeks of TB treatment initiation reduced the risk of unfavourable TB outcome by 65% in children and adolescents with HIV
  – Risk of unfavourable TB outcomes higher in younger ART-naïve children

Severe, TUSY0803; Caro-Vega, TUPEB154; Mandalakas TUPEB158
First-line ART in TB coinfection

- Alternatives to efavirenz (EFV)-based first-line ART regimens are needed for patients co-infected with HIV and tuberculosis (HIV/TB) to address CNS tolerance and drug resistance to NNRTIs.
- ANRS 12300 REFLATE: phase 3 non-inferiority comparison of RAL 400mg bid vs EFV 800mg qd, plus TDF/3TC qd, 460 participants in Brazil, Côte d’Ivoire, France, Mozambique, Vietnam.
- Non-inferiority criteria not met; EFV 800mg qd should still be considered as the preferred first-line therapy for HIV/TB co-infected patients.
TB/HIV

Improving TB prevention

• UN High Level Meeting on TB, 2018 commitment – provide TB preventive therapy to 6 million PLHIV by 2022
• Key messages from TB/HIV 2019 pre-meeting on TB prevention in PLHIV:
  • Newer, short-course regimens have the potential to greatly increase use of preventive therapy in high-risk populations
    – 3HP is easy, safe, and effective, and can be used with EFV or DTG
    – 1HP is easy, safe, and effective and can be used with EFV
    – Research is underway or planned to evaluate current regimens in important populations such as pregnant women and children

Newer drugs and routes of administration may further improve TPT for PLHIV

  – Long-acting TB preventive regimen could be a game changer BUT current TB drugs are not ideal candidates
  – Vaccines: 3 vaccine candidates in phase 3, 8 candidates in phase 2 studies
Clinical Science highlights

Promising developments

• Dolutegravir – neural tube defects associated with dolutegravir occur at a lower frequency than first reported.
• First-line treatment with dolutegravir & 2 NRTRIs receives strong recommendation from WHO: low-cost, robust, well tolerated regimen will support global treatment goals.
• Simplification: more evidence that 2-drug regimens are robust, potentially reducing lifetime drug exposure & treatment costs.
• New long-lasting agents show the potential for injectable treatment regimens.

Challenges

• Weight gain associated with dolutegravir is greater in women – who form the majority of people living with HIV in sub-Saharan Africa. More research needed on mechanisms, risk factors.
• Continued need for better-tolerated first-line regimens suitable for use in TB/HIV coinfection.
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TRACK C:
PREVENTION SCIENCE

IAS 2019 HIGHLIGHTS

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Overview

Key populations: emerging issues
- Transgender populations
- Syndemics
- Young men who have sex with men
- SRH integration

PrEP
- Impact
- STIs
- Same-day initiation
- New products
- Testing and resistance

New interventions
- New prevention products in the pipeline
- Vaccine
- Multi-level interventions

Self-testing
- Engaging men
- Peer distribution

New prevention products in the pipeline

SRH integration

Testing and resistance

Vaccine

Multi-level interventions

Engaging men

Peer distribution

Same-day initiation

New products

STIs

Impact
Syndemics: the synergistic interaction of two or more diseases / epidemics

HIV / mental health / substance use / STIs – syndemics may affect prevention and treatment outcomes but screening often lacking

People affected by syndemics may be challenging to reach – the 10/10/10 left behind

Latin American MSM Internet Survey (2018): 13.6% reported use of drugs to enhance sexual experience, 72% reported unprotected anal intercourse, 53% an STI diagnosis BUT only 2.6% using PrEP

Screening for depression and substance use in Zimbabwean & South African adolescents w/HIV revealed < 5% prevalence of substance use – and fourfold higher risk of virological failure in substance users

High rate of depression among Peruvian MSM: >40% of MSM screened at community HIV service had depressive symptoms

Shoptaw WESY0503; Reyes-Diaz, MOAC0101
Haas, MOSY0205; Galea, MOAC0104
Key populations
Young men who have sex with men (MSM)

- Substantial HIV epidemics among young MSM in Latin America require interventions
- Latin America: HIV prevalence among MSM aged 15-24 ranges from 5-10%; HIV incidence: approx 3%/yr
- Conditioned by low levels of HIV testing and condom use, changes in technology (eg apps) that facilitate greater frequency of casual partnerships, changes in sexual culture eg chemsex
- Structural barriers to HIV/STI services: stigma, legal requirements for parental consent
- Low access to PrEP and variable awareness of PrEP
- Latin American MSM Internet Survey (LAMIS) found only 0.6% of young MSM had used PrEP but half were quite likely or very likely to use it if available
PrEP

Impact of PrEP: EPIC-NSW

- Population and prospective cohort studies show a high level of effectiveness of PrEP in men who have sex with men.
- New South Wales: EPIC-NSW implementation study, 19,690 person-years of follow-up
- 30 infections, incidence of 1.52 per 1000 PY (95% CI 1.07-2.18)
- All seroconverters had stopped taking PrEP
- Incidence strongly associated with baseline rectal STI and methamphetamine use
- Slightly higher incidence in under-25s, trend towards higher incidence in men of Asian origin
- Implications for HIV elimination in Australia:
  - Further expansion: modelling indicates PrEP coverage > 75% is needed for HIV elimination
  - Improved PrEP access for migrants and visitors to Australia
  - Addressing why and how people stop and restart PrEP is critical to reducing incidence
  - Long-acting forms of PrEP required

Grulich, TUAC0201
New interventions

New prevention products in the pipeline (2)

• **Long-acting injectable antiretrovirals for prevention**: long-acting cabotegravir (CAB LA) – integrase inhibitor, injectable half-life 45-60 days
  - HPTN 083 & 084: phase 2b/3 studies evaluating the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)
  - Randomized, placebo-controlled studies
  - 5-week induction phase: oral CAB or TDF/FTC
  - Phase 2: two injections 4 weeks apart, then every 8 weeks, 3.5 years follow-up
  - Completion of recruitment projected in April 2020
  - HPTN 084: 3200 women at higher risk of HIV infection in southern and eastern Africa
  - Does a long-acting injectable have a prolonged sub-therapeutic pharmacokinetic tail if dosing is interrupted / terminated?

Long-acting cabotegravir: dosing schedule in HPTN 083 & 084
HIV self-testing
Peer distribution

Burundi: HIVST introduced December 2018

- Peer outreach has the potential to reach key populations who may not be in touch with facility-based health services
- Peer outreach workers distribute Oraquick HIVST; 2321 kits distributed December 2018-March 2019
- 22% of HIV diagnoses in FSW June 2018-March 2019 by HIVST, 35% in MSM
- Challenge: delay between reactive and confirmatory result
- HIVST improves uptake of HIV testing among key populations who rarely or never tested
- More widespread implementation of HIVST with high-risk populations could accelerate progress toward 95-95-95 goals
Highlights

• Gender-affirmative care is essential for testing and PrEP access for transgender people
• High HIV incidence in young men who have sex with men in Latin America and Asia highlights the case for wider PrEP provision
• PrEP: population cohort studies show very high effectiveness
• New antiretroviral prevention products using injectables or implants have the potential to extend dosing intervals, improve convenience
• A large pipeline of broadly neutralising antibodies is beginning to be evaluated for prevention
• Phase III HIV vaccine studies now underway
• HIV self-testing has the potential to improve case detection and engage men and key populations in HIV care
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TRACK D:
SOCIAL, BEHAVIOURAL AND IMPLEMENTATION SCIENCE

IAS 2019 HIGHLIGHTS

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Overview

- Implementation science
  - Using data in programme design
  - DREAMS impact
- Funding and sustainability
  - The funding gap
  - Health investment
  - ARV tendering
- Community involvement
  - PrEP programme design
  - Prevention trials
- Stigma
  - Laws & sex work
  - PrEP uptake
- Improving engagement in care
  - Reaching the untested
  - PrEP discontinuation
South Africa’s cost for preferred adult 1st-Line (1L) ARV regimens has decreased significantly over time. The steady decrease in cost has allowed South Africa to quadruple the number of adult 1st line patients since 2011, with a marginal impact on ARV drug budget.
Community involvement
PrEP programme design

A peer-based online social network intervention to facilitate PrEP adoption among young Black/Latinx men who like men in New York City

METHODS

- Recruited & randomized YMLM Peer Influencers (PIs)
- Participants completed online eligibility survey → joined Facebook/Instagram groups
- PIs conducted online campaign x 6-weeks, posted arm-specific contents
- PIs recruited participants from existing online networks
- Follow-up surveys at 6 and 12 weeks.

RESULTS

N=155 enrolled

Feasibility:
- Rapid recruitment/enrollment
- >90% Retention at 12 weeks
- >85% liked, commented, loved ≥ 1 post
- Each post viewed by ~40-50% of participants

Acceptability:
- 82% would continue participating,
- 78% reported high satisfaction
- 75% would recommend friends to participate

Involving the community is critical for programmatic success

Patel, MOPDD0203
Highlights

Promising developments

- Accurate and timely data is the core of good programming and drives improved outcomes – evidence from DREAMS of large-scale application
- Involvement of the community is critical for programmatic success
- Numerous examples of successful interventions to engage men in testing and care

Challenges

- Engagement of men in testing, prevention and treatment still lags behind
- Sustainability of the HIV response requires prioritization of interventions
- Stigma and legal context are mutually reinforcing, and exacerbate risk – legal and policing reform is essential for risk reduction