Key Messages from IAS 2019

Kenneth Ngure MPH, PhD  
GC Member – Africa  
School of Public Health  
Jomo Kenyatta University (JKUAT)
IAS TOOLKITS

TRACK A: BASIC SCIENCE

IAS 2019 HIGHLIGHTS

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OCTOBER 2019
### Overview

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<th>Cellular and tissue reservoirs</th>
<th>Macrophages</th>
<th>Naïve CD4+ T cells</th>
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<td>Latency-reversing agents</td>
<td>AZD5582</td>
<td>STING agonist</td>
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<td>Remission</td>
<td>San Francisco patient</td>
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<td>Hormonal influences on HIV</td>
<td>MPA and vaginal microbiome</td>
<td>Oestrogen and HIV reservoir</td>
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<td>Primary infection</td>
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<td>HIV-specific CTL responses</td>
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Hormonal influences on HIV

Vaginal microbiome, immune activation and hormonal contraceptives

- The vaginal microbiome can be categorized into two broad types, those with *Lactobacillus* and those where *Lactobacillus* is displaced for anaerobic and facultative bacteria.

- Analysis of mucosal specimens of CAPRISA-004 participants using hormonal contraceptives by mass spectrometry-based proteomics to characterise microbiome.

- Depo-Provera (DMPA) use was associated with increased vaginal immune activation but only in women with *Lactobacillus* dominant microbiome.

- DMPA recipients with lactobacillus-dominant vaginal microbiome had 3-fold higher risk of HIV acquisition (p=.0686).

- The microbiome environment influences DMPA-associated immune activation and the risk of acquiring HIV.

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Noël-Romas TUPDA0104  Burgener TUPL0102
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.

Tentative evidence to predict post-treatment control: Genes driving IFN-gamma and type 1 interferon responses are highly enriched in post-treatment controllers at the time of treatment interruption.

Fewer viral escape mutations in Fiebig stage 2 compared to stage 5 or chronically infected, enhances opportunity for CD8 control.
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
- Islatravir (MK-8591)
- Fostemsavir
- GS-6207 (capsid inhibitor)

TB diagnosis, prevention and treatment
May 2018: Tsepamo 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 31 March 2019:
- Surveillance expanded to capture 72% of all births in Botswana 2014-2019
- Published in NEJM to coincide with IAS 2019
Dolutegravir

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>0.10% (0.06, 0.17)</td>
<td>0.04% (0.01, 0.11)</td>
<td>0.03% (0.0, 0.15)</td>
<td>0.08% (0.06, 0.10)</td>
</tr>
<tr>
<td>Prevalence difference (95% CI)</td>
<td><strong>Ref</strong></td>
<td>0.20% (0.01, 0.59)</td>
<td>0.26% (0.07, 0.66)</td>
<td>0.27% (0.06, 0.67)</td>
<td>0.22% (0.05, 0.62)</td>
</tr>
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Zash, MOAX0105LB
Dolutegravir

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.

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)*.
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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
Key populations
Sexual and reproductive health integration

Tutu Teen Truck: HIV testing, PrEP and contraception

- ECHO study in 7829 women desiring contraception (63% < 25 years) showed very high efficacy of 3 modes (Depo Provera, copper intrauterine device or levonorgestrel implant) in sub-Saharan Africa.
- BUT: very high HIV incidence (3.81% per year), very high STI incidence despite syndromic management.
- High need for integration of HIV prevention, sexual and reproductive health rights (SRHR) services.
- POWER study: delivery of PrEP, contraception and HIV testing to adolescent girls and young women through mobile service
  - Initiation of PrEP and contraception correlated in this population
  - Adolescent girls and young women who were using contraception were significantly more likely to initiate PrEP on the same day compared to those who declined PrEP
- High-quality contraceptive services can be delivered in HIV contexts.

Photo: Desmond Tutu HIV Foundation

Onono, MOAX0103LB; Deese, LBPEB16; Rousseau, TUPEC479
**PrEP**

**Sexually transmitted infections (STIs) in the era of PrEP**

- **Is PrEP associated with increases in STIs?**
  - Concurrent increases in STIs; rates of bacterial STIs increasing over time; however, rises **pre-date** PrEP use.
  - Some but inconsistent evidence of risk compensation.
  - PrEP availability is uncovering the hidden epidemic of STIs in some populations.

- **Implications for STI control:**
  - Improve and move beyond syndromic STI management.
  - Integrate point of care STI tests and revise WHO syndromic algorithms for women.
  - Make sensitive STI diagnostic tests affordable e.g. Xpert.
  - Increasing investment in PrEP programmes could benefit STI control.
  - Expedited partner treatment.
  - Evaluate innovative STI interventions such as post-exposure, on-demand doxycycline in PrEP users.
  - Invest in STI vaccines – especially important with growth of gonococcal resistance.
PrEP

DISCOVER trial: TAF/FTC as PrEP

- DISCOVER: randomised comparison of TDF/FTC (Truvada) vs TAF/FTC (Descovy).
- TAF/FTC non-inferior but a trend towards fewer infections in the TAF arm – why?
- Post-hoc analysis:
  - No differences in sexual behaviour or adherence between arms.
  - Faster achievement of optimal drug concentrations in the TAF/FTC arm.
  - Higher proportion in TAF arm achieved TFV-DP levels in PBMCs >EC90 by week 4 (98% vs 64%).
  - F/TAF achieved EC90 within 1–2 hrs of first dose vs 3 days of daily doses of F/TDF.

Simulation Based on Observed TFV-DP at Steady State

- F/TAF
- F/TDF

Spinner, TUAC0403LB
PrEP
Dapivirine ring: MTN-025/HOPE

- MTN-025/HOPE – open-label extension study of dapivirine ring for HIV prevention, to assess adherence and safety
- Population: HIV-negative women previously enrolled in MTN-020 ASPIRE.
- Enrolled in Malawi, South Africa, Uganda, Zimbabwe.
- 12-month follow-up, 1,456 women.
- 73% of women accepted ring at all follow-up visits.
- Observed HIV incidence lower than the placebo group in ASPIRE.

Placebo based on MTN-020/ASPIRE EXPECTED

HIV-1 incidence = 4.4 (95% CI 3.2-5.8)

MTN025/HOPE OBSERVED

HIV-1 incidence = 2.7 (95% CI 1.9-3.8)

39% reduction 95%CI 14-65%

Baeten, TUAC0203
New interventions
New prevention products in the pipeline

- **Broadly neutralising antibodies (bnAbs):** antibodies that have been shown to neutralize a wide range of HIV isolates.
- First generation products: monoclonal antibodies targeting CD4 binding site of HIV gp120.
  - VRC01 being evaluated in 2 phase 2b randomised trials (Antibody-Mediated Prevention, AMP studies):
    - HVTN 704 / HPTN 085: 2,700 men who have sex with men and transgender women in the Americas
    - HVTN 703 / HPTN 081: 1,900 women in sub-Saharan Africa
- Next generation products: monoclonal antibodies targeting multiple sites:
  - VRC07-523LS - 5- to 8-fold increased potency *in vitro* compared to VRC01.
- Trispecific antibodies: Combining multiple bnAbs with specificities against different epitopes into a single molecule has the potential to:
  - Improve efficacy
  - Simplify prevention and treatment regimens
  - Streamline the regulatory pathway to a licensed drug
- The goal of these studies is to identify the best regimens for moving to a licensure trial.
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 and 084: phase 2b/3 studies evaluating the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV-negative men who have sex with men/transgender women (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: 3,200 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 and 084**

![Dosing schedule diagram](image-url)
New interventions
Islatravir implant

Islatravir (formerly MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI) with long half-life (120-177 hrs in PBMCs), achieves similar concentrations in plasma and rectal, vaginal tissues.

- High barrier to resistance due to multiple sites of action.
- Safety and tolerability of two islatravir-eluting implants (54 and 62mg) tested in 12-week placebo-controlled phase 1 study in 16 HIV-negative subjects.
- Both implants had concentrations above PK threshold at 12 weeks; 62 mg implant will continue to release through 52 weeks.
- Potential advantages of implants: removable, consistent and predictable drug delivery.
- BUT an implant requires a surgical procedure, is regulated as both drug and device, difficulty in moving to generic marketplace.
HIV self-testing

Engaging men in HIV testing and care

• Rapid oral or blood-based HIV self-testing kits are now available in many settings.
• HIV self-tests have potential to improve uptake of testing and engagement in care among harder-to-reach groups.
• Implementation study of multi-venue community-based HIV self test (HIVST) distribution targeting men in KwaZulu-Natal.
• Choice of 2 HIVST options: oral-fluid or blood-based testing.
• 4,495 test kits distributed, 92% to men.
• Take-away self-testers: 4% HIV positive, 81% linked to care, 73% started ART.
• Rapid HIVST distribution with non-intensive staff support is a feasible, acceptable approach to identify HIV+ men and link them to care and ART in South Africa.

Shapiro, WEAC0202
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.
- 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.
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TRACK D:
SOCIAL, BEHAVIOURAL AND IMPLEMENTATION SCIENCE

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Overview

- Implementation science: Using data in programme design
- DREAMS impact

- Funding and sustainability: Health investment
- The funding gap
- ARV tendering

- Community involvement: PrEP programme design
- Prevention trials

- Stigma: Laws and sex work
- PrEP uptake

- Improving engagement in care: Reaching the untested
- PrEP discontinuation
In 2017, the majority (>60%) of DREAMS districts showed a decline in new HIV diagnoses among adolescent girls and young women attending antenatal clinics.

In 2018, new diagnoses among adolescent girls and young women continued to decline in 85% of these communities/districts implementing DREAMS.

Eight DREAMS-supported districts progressed from a less than a 25% decline in new HIV diagnoses among AGYW in 2017 to a greater than 25% decline in 2018 (including communities in Lesotho and South Africa).
Community involvement
Engaging end-users in the research process

iPrevent study in Cape Town, South Africa

"Don't disrupt my life" (i.e. consider products that are discrete)

"Youth don't go well with clinics" (i.e. consider products that can be accessed elsewhere)

product designers
film-makers
survey designers
analysts and interpreters

Hartmann, TUAD01
Stigma

Impact on PrEP uptake

Qualitative research in Kenya to understand slow uptake to PrEP

Example of product stigma:

“I have kept it a secret because the bottle is similar to that of ARVs. Someone who doesn’t know about PrEP could think you have HIV…”

(20 year old, female PrEP user)
The End