Science and Community in the Response to HIV, STIS and Co-infections in Asia and the Pacific
Objectives

• Present key scientific and policy content from the IAS 2017 conference held in Paris, France
• Facilitate discussions on new insights from IAS 2017
• Discuss how to effectively translate these key scientific and policy content into practice
CD8+ T Cell Responses

- Detailed characterisation of HIV-1 specific CD8+ T cell responses in a cohort of women initiating ART during hyperacute HIV-1 infection (Fiebig stage I) in South Africa
- Does very early ART suppress the development of immune responses or help to preserve CD8+ T cell immune responses?
- A large proportion of individuals treated in Fiebig stage I have detectable anti-HIV immune responses

- Early ART was associated with more functional HIV-1-specific CD8+ T cells that expressed higher levels of the IL-7 receptor and secreted higher levels of interferon-γ
- Shows that early treatment preserves immune function and is likely to be beneficial
- Understanding of immune responses in early treated people may be useful for future intervention studies
South African Child

- Child acquired HIV-1 perinatally, was started on suppressive antiretroviral therapy for about one year, stopped treatment, and has had undetectable viral replication for the subsequent 8.75 years of ART
- Pre-treatment viral load 151,000 copies/mL; ART initiated in week 8; viral load <50 copies/ml at week 24
- ART stopped after 40 weeks. In the 8.75 years of follow up persistently undetectable HIV RNA <20 copies/mL
- Child differs from ‘elite controllers’ who are characterised by protective HLA class I alleles and strong HIV-1-specific T cell responses
Viral features:
- Small amounts of detectable HIV DNA, around 5 copies per million peripheral blood mononuclear cells, both at 1 year and 9.5 years
- No replication-competent virus detected using two co-culture methods

Host features:
- CCR5 expression on T cells low (surface density) compared to uninfected children and adults; similar to elite controllers
- Immune activation low and similar to uninfected children and adults, but lower than elite controllers

The case complements a series of prior case reports of individuals with spontaneous long-term control of HIV-1, showing that sustained drug-free remission of HIV is possible
Basic Sciences Highlights

Promising developments

• More evidence that sustained drug-free remission of HIV is possible
• New concepts in immunology, several derived from non-human primate studies, which might impact on HIV transmission and vaccine design
• A preventative vaccine generated immune responses against HIV in human subjects

Challenges

• Limited understanding of the mechanisms of drug-free remission
• Even with a very small reservoir, viral rebound may occur
• Once again, disappointing results from a therapeutic vaccine trial
Overview

New Fixed Dose Combinations
- Bictegravir/FTC/TAF
- Doravirine/3TC/TDF
- Darunavir/COBI/FTC/TAF

Dual Therapy
- Feasibility of dual therapy
- DTG/3TC
- DRV/r/3TC
- Other treatment simplification strategies

Late Treatment Intensification
- Epidemiology
- Maraviroc treatment intensification

Drug Resistance
- Epidemiology

Hepatitis C Co-Infection
- Glecaprevir/Pibrentasvir
- Treatment in West Africa
Dual Therapy

Do we need triple therapy for everyone for life?

• Requirements for dual therapy agents:
  – Potent, long half life, once daily, minimal side-effects, low primary resistance rates
• Treatment-naïve patients: dual ART with robust drugs is a realistic ART option for individuals with low to moderate viral load and good immune status
• Some guidelines now include dual therapy as an alternative option, when other therapies cannot be used
• Switching studies for treatment experienced patients - only two types of reduced drug regimens have matched the efficacy of triple therapy:
  – Boosted protease inhibitor + lamivudine
  – Dolutegravir + rilpivirine
• Rather than only assessing dual therapy by viral suppression, evaluation should also be based on residual viremia, persistent inflammation and immune activation, penetration in reservoirs, toxicity, and cost
Dual Therapy

**DTG/3TC**

- 120 participants in single-arm phase II study (ACTG A5353)
- Eligibility criteria: treatment naïve, viral load < 500,000 cpm, no major resistance mutations
- Interim analysis at 24 weeks
- **High rate of virologic suppression regardless of baseline viral load**
- 3 cases of virological failure, including one patient with emergent integrase resistance (M184V)

### Baseline HIV-1 RNA

<table>
<thead>
<tr>
<th>Virologic success</th>
<th>&gt; 100,000 cpm N=37</th>
<th>≤ 100,000 cpm N=83</th>
<th>Total N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 cpm [95% CI]</td>
<td>33 (89%) [75%,97%]</td>
<td>75 (90%) [82%,96%]</td>
<td>108 (90%) [83%,95%]</td>
</tr>
<tr>
<td><strong>Virologic non-success</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 50 cpm</td>
<td>3 (8%)</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Discontinued study treatment for other reasons while HIV RNA ≥ 50*</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

- Data from larger, comparative studies with longer follow-up are needed to confirm these findings - two phase III studies are ongoing

Taiwo MOAB0107LB
Dual Therapy

Other treatment simplification strategies

Short cycle therapy
- Treatment for 4 or 5 days a week, with a break at weekends
- Six trials in virologically suppressed adults or adolescents reviewed, each with <100 participants
- Results: excellent virological efficacy, reduced toxicity, saved costs, strong preference of patients for the strategy

Dose reduction
- Thailand has had positive experiences with dose reduction:
  - Efavirenz, from 600mg to 400mg once daily
  - Atazanavir, from 300mg to 200mg once daily, taken with 100mg ritonavir
- Improvements in tolerability may lead to improvements in long-term outcomes
- New data on efavirenz 400mg in pregnant women and post-partum:
  - safe, good virological suppression, reassuring pharmacokinetic data
- These data may allow WHO guidelines to be revised, allowing greater use of 400mg efavirenz by pregnant women
WHO guidelines say treat all regardless of CD4 count, but what is actually happening?

Cohort data from 2002 to 2015: 16 low-income countries, 11 lower-middle countries, 9 upper-middle countries, 19 high-income countries

Median CD4 count at treatment initiation has increased over time, but remained below 350 in 2015 in all income brackets

In 2015, >25% of people in all income brackets began treatment with CD4 below 200, i.e. severe immunodeficiency

"Substantial additional efforts and resources are needed to increase testing coverage with the aim of achieving earlier diagnosis, linkage to care, and initiation of ART globally."
Rates of pre-treatment drug resistance (PDR) have been increasing worldwide, especially in Eastern and Southern Africa.

High levels of pre-treatment drug resistance:
- Result in treatment failure with significant impact on the individual
- Make realisation of 90-90-90 targets challenging
- 6 of 11 surveyed countries in Africa, Latin America and Asia have >10% PDR to efavirenz or nevirapine among adults with HIV
  - Guatemala, Nicaragua, Argentina, Namibia, Zimbabwe, Uganda
- For infants (<18 months), rate has reached nearly 50% in surveyed countries
Drug Resistance

Epidemiology

- New World Health Organization guidance recommends that countries with PDR >10% use dolutegravir in first-line ART (or use genotype resistance testing prior to ART)
- Cost-effectiveness modelling: dolutegravir has lower cost and averts more disability-adjusted life years (DALYs) than resistance testing
- Many countries need to revise ART regimens, improve surveillance of drug resistance, strengthen laboratory capacity

Countries implementing WHO PDR surveys
Almost all studies of hepatitis C treatment have been conducted in high income countries - very little research in resource-limited settings.

Do different health systems have an impact on outcomes?

TAC ANRS 12311 trial assessed the feasibility, efficacy and safety of interferon-free direct-acting antivirals (DAA) treatment in Cameroon, Ivory Coast and Senegal.

110 treatment-naïve adults, 10% with compensated liver cirrhosis

12 week therapy:

- 89% sustained virological response (SVR12), similar to studies in high-income countries and 78% in those with cirrhosis; treatment safe and well tolerated.
- “This is very good proof that when treatment is available, patients are adherent and keen on taking treatment – this is the time to advocate for larger access to DAAs in Africa.” – Karine Lacombe, Saint-Antoine Hospital, Paris.
Cameroon was presented as an example of good practice
- The government treats hepatitis C as a public health priority
- Co-operative agreement with pharmaceutical companies to obtain DAAs at reduced prices
- Ten treatment centres established
  - a demonstration project evaluating feasibility, efficacy and cost effectiveness is on its way
- Challenges: implementing screening programmes, sustainable financing mechanisms
Promising developments

• New fixed dose combinations will increase treatment options for patients and allow for increasingly individualised therapy.
• Approaches to simplify treatment, such as dual therapy, dose reduction and short cycle therapy, may improve the quality of life for people with HIV and lower costs.
• Success of providing direct-acting antivirals for hepatitis C in West Africa.

Challenges

• Late diagnosis and poor linkage to care means that a quarter of people with HIV have severe immunodeficiency when they start treatment.
• The increasing prevalence of drug resistance makes it harder to control the epidemic.
Overview

Self-Testing
- PopART Zambia
- Other African Studies
- eSTAMP USA

Treatment as Prevention
- Swaziland
- Opposites Attract

Oral PrEP
- Roll out of PrEP
- On Demand Regimen
- On demand or daily?
- PlusPills

New PrEP Agents
- Dapivirine Vaginal Ring
- Injectable Cabotegravir
- Rilvipirine & MK-8591
Self-Testing

Other African Studies

- Numerous studies of self-testing (HIVST) in sub-Saharan Africa presented at IAS 2017
- Estimated size of the African self-testing market by 2020:
  - 3-5 million users with tests distributed through community channels
  - 11-15 million users with investment in distribution through pharmacies and healthcare facilities
- Secondary distribution to male partners by women attending antenatal services: randomised study in Uganda
  - Partners tested: 74% vs 36%
- **Self-testing feasible and acceptable for female sex workers in Zimbabwe and Zambia**
  - Linkage to care may be lower than in facility-based testing
  - No increase in intimate partner violence
Treatment as Prevention

Swaziland

- Convincing evidence that massively expanding HIV treatment coverage reduces new HIV infections (incidence) across the population
- The study “shows that our efforts can pay off and is a proof of concept.”
  - Linda Gail-Bekker, International AIDS Society
- Swaziland: population 1.5 million, 79% rural, 32% living with HIV
- Significant expansion of HIV testing, prevention and treatment services between 2011 and 2016:

![Graph showing annual HIV tests, PLHIV starting ART, cumulative PLHIV on ART, and cumulative VMMC numbers between 2011 and 2016.](Nkambule_MOAX0204LB)
Swaziland

- Swaziland HIV Incidence Measurement Survey (nationally representative sample of the population) conducted in 2011 and 2016
- Progress to 90-90-90 targets: 85-87-92
- Remaining challenges:
  - Undiagnosed infection in 15-24 year olds (33.9% vs 12.9% in >25 years)
  - Unsuppressed viral load in 15-24 year olds on treatment (23.6% vs 6.7% in >25 years)
  - Undiagnosed infection in men (22.5% vs 11.4% in women)

![Graph showing HIV incidence and suppressed viral load reduction](image)
Highlights

Promising developments

• Swaziland demonstrates that the ‘theory’ of treatment as prevention works in practice, at a population level
• Data to support a wider range of PrEP options, both agents and dosing schedules
• Self-testing helps individuals who do not engage with other testing services to learn their HIV status

Challenges

• Engaging younger people and men with HIV testing services and the treatment cascade
• Scaling up PrEP in the many countries where it is not currently available
IAS TOOLKITS

TRACK D: IMPLEMENTATION SCIENCE

IAS 2017 HIGHLIGHTS

PRODUCED BY THE INTERNATIONAL AIDS SOCIETY

OCTOBER 2017
Overview

Differentiated Service Delivery
- Why do we need DSD?
- Paediatric Services
- Implementation Challenges
- Urban vs Rural
- Integrated Services for PWID

Costs and Funding
- $90 $90 $90
- US Funding Decisions

Economic Incentives
- Introduction
- Punto Seguro
- Couples Testing

Stigma
- Stigma in Healthcare
- Reducing Stigma
- Providing Stigma-Free Services
Differentiated Service Delivery

Why do we need DSD?

• Progress towards HIV epidemic control:
  – 19.5 million individuals accessing ART worldwide
  – 1.8 million new HIV infections each year
  – 1 million deaths from HIV-related disease each year

• Our successes are due to the public health approach (consistent package of care, decentralised delivery model) enabling scale-up of services

• Challenges to reaching 90-90-90 goals:
  – Expanding ART coverage
  – Achieving high quality care
  – Improving efficiency

• There are structural, psychosocial and behavioural obstacles to successful engagement in care

• DSD can address these challenges and reduce gaps in outcomes
Differentiated Service Delivery

Why do we need DSD?

- DSD is a client-centred approach that simplifies and adapts HIV services
  - Tailor services to recipients of care: modulate the frequency, location and content of service provision
- For example, multi-month prescribing (MMP): people with less complex care needs are prescribed several months ARVs at a time
  - Monthly clinic visits can be difficult to manage for patients: transport costs, time away from education/work, etc.
  - Frees up staff capacity for patients who are starting treatment, have co-morbidities, or are unwell
Vietnam is working to develop integrated OTP and ART services, at the same time as reducing the role of compulsory treatment centres for PWID.

71% of HIV-positive clients at methadone maintenance clinics are on ART.
- 94% in Ho Chi Minh City.

Challenges:
- different cultures of OTP and ART
- stigma of ART providers towards PWID
- services may be in the same building but with separate staff and separate doors.
Unaffordable drug prices are a major barrier to achieving the 90-90-90 goals.

Large increases in treatment coverage will require medicine prices to be cut.

Countries and donors should aim for a new $90-$90-$90 target on HIV, viral hepatitis and TB drug prices – Andrew Hill, University of Liverpool.

Analysis of prices paid for the raw materials and manufacturing costs of drugs:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CALCULATED TARGET (ESTIMATED ANNUAL PRICE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>$126</td>
</tr>
<tr>
<td>TDF/FTC/EFV</td>
<td>$78</td>
</tr>
<tr>
<td>TDF/3TC/EFV</td>
<td>$82</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>$42</td>
</tr>
<tr>
<td>TB: RHZE</td>
<td>$38</td>
</tr>
</tbody>
</table>

This shows that each disease can be treated for $90 per year, as long as generics are used and prices are effectively negotiated.

Patents have expired on TDF, 3TC, and EFV worldwide – this combination should be available in all countries for less than $90 per year.

Generic drugs, government commitment, price negotiation, civil society mobilisation and advocacy are important tools to reduce treatment costs.
Economic Incentives

Punto Seguro

- Punto Seguro ("safe point") programme targeting a vulnerable population: young male sex workers in Mexico City
- Cash transfers to encourage male sex workers to attend monthly prevention talks and STI testing
  - 1,628 individuals chose to participate
- After one year, higher retention rates and more condom use
- ‘Incentives’ can include transport, food, credit support and income generation and should be adapted to the social context and the population’s needs
- Small incentives help bring vulnerable populations to services - stronger evidence for engagement with care and behaviour change, than for biological markers (HIV incidence, HIV viral load)
Economic Incentives

Couples Testing

- Cluster randomised trial in Zimbabwe: use of incentives to encourage participation in couples HIV testing and counselling
- 68 rural communities
- Non financial incentives worth $1.50 - a grocery item such as bar of laundry soap, petroleum jelly, cooking oil
- Incentive for couples testing versus standard community mobilisation
- Participation in testing:
  - People tested per day: 70 vs 56
  - Proportion couple testers: 55.7% vs 10.0%
  - HIV prevalence: 8.8% vs 6.5%
- Economic analysis: incentives added little to the cost of the intervention, the main cost in both arms was human resources
  - Cost per person tested: $7.96 vs $8.18
- Cost per HIV-positive diagnosis: $93.10 vs $128.10
Stigma in Healthcare

- Stigma against key populations negatively impacts engagement and retention in healthcare settings
- There have been significant advances in the measurement of stigma and in monitoring tools – these need to be scaled up
- Better feedback between key populations and care providers leads to accountability & continuous quality improvement
- Promising strategies to reduce healthcare stigma, e.g. PEPFAR Gender & Sexual Diversity training, conducted with all implementing partners globally
Reducing Stigma

- Integrated stigma mitigation interventions for female sex workers and men who have sex with men in Senegal
- Interventions: peer-led community groups, training of healthcare workers in service provision for key populations, peer-to-peer anonymous referral system to health services and prevention
- Interim data up to month 15:
  - Large reductions in *anticipated* healthcare stigma
  - Some reductions in *experienced* healthcare stigma
  - Low uptake of ART in HIV-positive MSM - results reinforce the need for stigma mitigation interventions to be combined with HIV prevention and treatment interventions for key populations

Anticipated and experienced stigma for MSM
Implementation Science Highlights

Promising developments
• The client centred approach of differentiated service delivery is more responsive to the needs of different groups of patients and may boost their engagement with care
• Economic incentives can help engagement with existing services and technologies

Challenges
• Less commitment to the global HIV/AIDS response from its largest donor
• Stigma against key populations in healthcare settings remains an important barrier to access to care
• Attention needs to be given to appropriate implementation of differentiated service delivery models