HIV OVERVIEW

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DURBAN, SOUTH AFRICA

EDCTP STAKEHOLDER MEETING
LISBON, PORTUGAL
3-4 SEPTEMBER 2013
OUTLINE

- HIV Origin and Classification
- HIV Spread & Global Evolution
- Evolution of Laboratory Tests to Identify HIV Infections
- Global HIV Epidemic
- HIV Therapeutics- Adherence & Drug Resistance
- HIV Prevention- Biomedical, Behavioural & Structural
- Integration- HIV Prevention/ Treatment /Care
- Global HIV Prevention, Treatment & Care Priorities
- EDCTP II Priorities in HIV Prevention & Treatment
HUMAN IMMUNODEFICIENCY VIRUS (HIV)

“It all started as a rumour- then we realized we are dealing with a disease-then we realized that it was an epidemic and now we have accepted it as a tragedy”

-Anonymous Ugandan epidemiologist 1992
HIV & ITS ORIGINS

- HIV is a zoonotic disease transmitted from animal (non-human) to humans

- HIV- “lentivirus” a subgroup of retroviruses
  - Lentivirus is a genus of viruses of the Retroviridae family (long intervals between infection and onset of serious symptoms)

Ref: Tebit DM, Arts EJ. Tracking a century of global expansion and evolution of HIV to drive understanding and to combat disease. Lancet Infect Dis 2011; 11: 45-56
THE NATURAL HISTORY OF HIV INFECTION:
TYPICAL OF LENTIVIRUSES

HIV-1 is now a clinical disease

SPREAD OF HIV FROM CONGO BASIN TO THE REST OF THE WORLD & GLOBAL EVOLUTION

Ref: Tebit DM, Arts EJ. Tracking a century of global expansion and evolution of HIV to drive understanding and to combat disease. Lancet Infect Dis 2011; 11: 45-56
GLOBAL DISTRIBUTION OF HIV-1 SUBTYPES AND RECOMBINANTS

Ref: Joris Hemelaar, The origin and diversity of the HIV-1 pandemic. 2012
GLOBAL HIV EPIDEMIC (1990 – 2011)

## HIV Treatment Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930s-1984</td>
<td>FDA approved first AIDS antibody screening test</td>
</tr>
<tr>
<td>1985</td>
<td>Emergence of HIV-1 to first report of AIDS and HIV-2</td>
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<tr>
<td>1986</td>
<td>HIV (Human Immunodeficiency virus) adopted</td>
</tr>
<tr>
<td>1985</td>
<td>Reports that Retrovirus, SIVcpz, passed to humans</td>
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<tr>
<td>1992</td>
<td>First antiretroviral drug, Zidovudine</td>
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<tr>
<td>1995</td>
<td>First combination drug therapy for HIV treatment</td>
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<tr>
<td>1996</td>
<td>Saquinavir, a new type of protease inhibitor drug to treat HIV</td>
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<tr>
<td>1996</td>
<td>WHO estimated 15% and 20% new infection worldwide resulting from blood transfusion</td>
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<tr>
<td>1999</td>
<td>Robert Gallo discovered that some natural compounds, chemokines can block HIV and halt progression to AIDS</td>
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<tr>
<td>2000</td>
<td>A highly resistant form of HIV strain linked to rapid progression to AIDS identified in New York City</td>
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<tr>
<td>2001</td>
<td>First report of a Leukaemia patient from San Francisco cured of HIV</td>
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<tr>
<td>2007</td>
<td>Confirmation of the cured leukaemia patient and second report of toddler functionally cured of HIV</td>
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<tr>
<td>2011-2013</td>
<td>CDC recommended ART post-exposure prophylaxis for people exposed to HIV</td>
</tr>
<tr>
<td>2013</td>
<td>Maraviroc, CCR5 receptor antagonist approved by FDA as an antiviral drug</td>
</tr>
</tbody>
</table>

### References

3. Antiretroviral Post-exposure Prophylaxis after sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV, CDC guideline - retrieved 2011
TARGET SITES FOR ANTIRETROVIRAL DRUGS IN THE HIV LIFE CYCLE

2. Attachment Inhibitors
KD-247, Griffithsin

3. Fusion Inhibitors
Maraviroc, Enfuvirtide

4. Reverse Transcription Inhibitors

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>NRTI</th>
</tr>
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<tbody>
<tr>
<td>Atevirdine</td>
<td>Abacavir</td>
</tr>
<tr>
<td>Delaviren</td>
<td>Amivudine</td>
</tr>
<tr>
<td>Efaviren</td>
<td>Amdoxovir</td>
</tr>
<tr>
<td>Emiviren</td>
<td>Apricitabine</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Didansine</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Elcuvitabine</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Entecavir</td>
</tr>
</tbody>
</table>

5. Integrase Inhibitors
Elvitegravir, Raltegravir, GSK1349572, MK-2048

6. Assembly

7. Maturation Inhibitors
Atazanavir, Fosamprenavir, Daruavir, Ritonavir
Lopinavir, Nelfinavir, Squinavir, Tipranavir, Indinavir

From 1987 (Zidovudine) to 2008-30 HIV therapeutic single or combination drugs were approved by the FDA- targeting 5 HIV enzymes.

**Critical in the HIV replication cycle**
WHEN TO START THERAPY:
Balance now favours earlier ARV therapy

Ref: Practical strategies to engage HIV patients in timely care. www.clinicaloptions.com/hiv
**RESISTANCE:**

ABILITY OF HIV TO ENTER CELL AND REPLICATE DESPITE PRESENCE OF ARV DRUGS

**REASONS:**

- Poor adherence to treatment or infected with mutant virus
  - Result
  - High rate of viral replication ($10^9$ to $10^{10}$ virons/person/day)
  - Errors in HIV due to high rate of replication - HIV Polymerase
  - Selective pressure and mutant viral strains

**OUTCOME:**

- Increase in viral load
- On-going damage to immune system
- Single or multiple-class drug resistance - limited access to therapy
- Progression of HIV disease

**Progression of HIV disease**

High rate of viral replication ($10^9$ to $10^{10}$ virons/person/day)
COMBINATION OF FACTORS MAY CONTRIBUTE TO POOR ADHERENCE

INDIVIDUAL FACTORS
- Socio-demographics
  - Economics
  - Education
  - Cultural beliefs, values and practices
- Social support
  - status disclosure, friends, partner & family support
- Cognitive Factors
  - cognitive impairment,
  - forgetfulness
- Psychological Factors
  - Depression, anxiety
- Substance Abuse
  - Alcohol
- State of disease

HEALTH SYSTEMS
- Adequate education & counselling
- Effective linkage to care
- Effective communication & decision making with patient
- Access- insurance, transport
- Convenience/ confidentiality
- Adherence counselling & follow -up

ADHERENCE
ART REGIMEN & TREATMENT EXPERIENCE
- Complexity of regimen
- Toxicity
- Side effects

Every effort required to mitigate risks of developing ARV resistance

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HIV PREVENTION INTERVENTIONS

Community & Policy Makers:
- Support commitment in addressing the epidemic
- HIV Prevention adequate support & resources
- Focused program for key populations
- Address stigma & gender-based violence
- Integrating HIV & reproductive health care for women
- Health Systems strengthening
- Address stigma

Individual:
- Commitment
- Adherence & acceptability of intervention
- VCT
- HIV status disclosure
- Reduce Stigma
BIOMEDICAL PREVENTION STRATEGIES

- **PMTCT**
- **TREATMENT AS PREVENTION (TaSP)**
- **ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP)**
- **MICROBICIDES: TOPICAL PRE-EXPOSURE PROPHYLAXIS**
- **TREATMENT OF STI’S**
- **MALE CIRCUMCISION**
- **VACCINES**

- Reduces HIV acquisition by 50-60%.
- Extensively rolled out
- High rate of effectiveness in reducing community HIV incidence 73% (Gray et al AIDS, 2012).
- SA: MMC increase 36.0%(2008)-40.5(2012)

- Overwhelming biological evidence
- Remain important for public health intervention to prevent HIV

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GLOBAL PROGRESS IN REDUCING PMTCT

In 2011, 330 000 [280 000–390 000] children acquired HIV infection

- a 43% decline since 2003 (560 000)
- a 24% drop since 2009 (430 000)

More than 90% of the children who acquired HIV infection in 2011 live in sub-Saharan Africa

In sub-Saharan Africa, the number of children newly infected fell by 24% from 2009 to 2011

Ref: UNAIDS 2012
FOUR-PRONGED STRATEGY FOR PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION

Prevention of HIV in Women, (Especially Young Women)

Prevention Unintended Pregnancies in HIV+ Women

Prevention MTCT from an HIV+ Woman to Her Infant B & B+ program

Support for HIV+ Mother and Family

Research Priority- implementation & sustainability of B & B+ PMTCT programs (WHO) in resource poor settings

Ref: James McIntyre (On the road to) zero vertical transmission, 6th SA AIDS Conference 2013
HIV TREATMENT AS PREVENTION (TaSP)

- High HIV viral load is the single greatest risk factor for all modes of HIV transmission

- Treatment as prevention is based on the fact that ARV treatment can reduce plasma and genital viral loads to undetectable levels

- Reduced viral loads results in reduced infectiousness

HPTN 095

CONCEPT:

- Provision of early ARV Treatment to HIV infected partner in an HIV discordant relationship in order to reduce viral load and therefore infectiousness (Cohen et al, 2011)

1763 discordant couples in Africa & America effect of ART (HIV +ve) on HIV –ve: 96% (CI: 73%- 99%)

Cohen et al 2011, NEJM
ORAL PRE-EXPOSURE PROPHYLAXIS (PrEP)

CONCEPT: Use of oral Antiretroviral Therapy (ART) in HIV negative individuals prior to sex to prevent HIV Infection

SUCCESSES:

- Daily use of oral combination prophylaxis with Tenofovir (TDF) and Truvada (TDF/FTC) among HIV –ve MSM. (iPrEx Study)

2499 Men who have sex with men.
Effect of Daily TDF-FTC on HIV: 42% (CI: 15%-63%)
Grant et al, 2010 NEJM

- Daily use of oral Tenofovir or Truvada reduced HIV infection among uninfected partners of HIV-discordant couples. (Partners in PrEP study)

4,758 HIV discordant couples in Kenya & Uganda
Effect of TDF on HIV: 67% (CI: 44%-81%)
Effect of FTC/TDF on HIV: 75% (CI: 55%-87%)
Baeten et al, 2012, NEJM
ORAL PRE-EXPOSURE PROPHYLAXIS

- Daily use of Truvada reduced HIV infection among young heterosexuals in Botswana. (CDC)

  1219 heterosexual men & women in Botswana. Effect of TDF-FCT on HIV: 63% (CI: 21.5 - 83.4)
  
  *Thigpen et al, 2012, NEJM*

- Daily use of oral Tenofovir in IDU’s in Thailand. (CDC)

  2411 men and women IDU’s.
  Effect of TDF on HIV: 49% (CI: 9.6-72.2)
  
  *Lancet on line: 12 June 2013*

- FDA approved Truvada for use in HIV negative MSM with pre-conditions on eligibility and safety ([http://www.fda.gov/newsevents/312210.htm](http://www.fda.gov/newsevents/312210.htm))

- CDC Interim guidance on PrEP for Injecting drug users.

Ref: [http://www.cdc.gov/mmWr/preview/mmwrhtml/mm6223a2.htm?s_cid=mm6223a2_w](http://www.cdc.gov/mmWr/preview/mmwrhtml/mm6223a2.htm?s_cid=mm6223a2_w)
CONFLICTING RESULTS WITH THOSE IN OTHER HIGH-RISK POPULATIONS

- Use of daily oral Truvada among women in Sub-Saharan Africa showed no effect on HIV incidence (Lut van Damme, et al 2012, NEJM)

- Use of daily oral Tenofovir or Truvada among young women show no effect on HIV incidence in VOICE Trial 2012 (MTN 003) (Marrazzo JM, Ramjee G et al) CROI 2013.

LESSONS LEARNT

- ARVs do not work for HIV treatment or prevention unless taken as prescribed.

- High **Adherence** is key

- Individual risk perception is critical

- Important to understand the cultural context in which new biomedical strategies are used

- For young women greater understanding of biological risk factors is critical. Genital tract inflammation is likely to play a critical role
Hormonal contraception- oral pills, injectables, patches, rings, implants- effective methods of pregnancy prevention

Recent conflicting evidence from observational studies suggests that progesterone- only injectable contraception use increases risk of HIV acquisition

Risk could be attributable to changes in immune function or changes in genital tract environment. Different forms of contraceptives may change immune functions in different ways

Use of oral contraceptive pills and HIV acquisition (seven studies that met minimum quality criteria only) For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. OR=odds ratio. HR=hazard ratio. IRR=incidence risk ratio. *Analysis showed significant findings.

Ref: Chelsea Polis, Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence, 2013
Use of injectable contraceptives and HIV acquisition (all 16 studies) For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. IRR=incidence risk ratio. OR=odds ratio. HR=hazard ratio. DMPA=depot-medroxyprogesterone acetate. *Analysis showed significant findings

Ref: Chelsea Polis, Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence, 2013
Contraception & HIV: Way Forward

- Observational studies- inconclusive results.

- Need for RCT to determine whether progestin-only injectable contraceptives do indeed increase risk of HIV-1 acquisition.

- Population attributable risk of Depo Provera suggest that removing Depo Provera without substantial evidence may increase unintended pregnancy rates which could result in other complications.

- Integration of HIV prevention and Reproductive Health Services for women is critical.
MICROBICIDE RESEARCH: 1992 – 2012
Microbicides- Products designed for vaginal or rectal administration to prevent HIV acquisition

ARV BASED PRODUCTS
Prevents establishment of HIV infection

SURFACTANTS
(disrupts membrane)

POLYANIONS
.prevents attachment of virus)

1992-2012
10 Products in large scale clinical trails

CAPRISA 004 (2007-2010)
Tenofovir gel
39% EFFECTIVE

MTN003 – VOICE (2009-2013)
Daily use
Tenofovir gel & tablet

FACTS 001 (2011-2014)
Tenofovir gel
SA study to confirm CAP004 on-going

MTN 020 (2012 – 2015)
Intravaginal
Dapivirine ring
on-going

N9 INCREASED RISK

N-9 sponge (1987-1990)
NIH


COL-1 (1996-2000)

SAVVY (2004-2006)
FHI

ADHERENCE IS CRITICAL FOR EFFICACY

1 proof of concept
Further evidence needed for licensure

SAFE, NOT EFFECTIVE

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## VACCINES

<table>
<thead>
<tr>
<th>Year Completed</th>
<th>Product/Clade/Trial Name</th>
<th>Countries</th>
<th>Number of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>AIDSVAX B/B VAX003</td>
<td>Canada, Netherlands, Puerto Rico, US</td>
<td>5,417</td>
<td>No effect</td>
</tr>
<tr>
<td>2003</td>
<td>AIDSVAX B/E VAX004</td>
<td>Thailand</td>
<td>2,546</td>
<td>No effect</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Step</td>
<td>Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US</td>
<td>3,000</td>
<td>Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.</td>
</tr>
<tr>
<td>2007</td>
<td>MRK-Ad5 B Phambili</td>
<td>South Africa</td>
<td>801</td>
<td>Immunizations halted based on Step result; additional data presented in May 2013.</td>
</tr>
<tr>
<td>2009</td>
<td>ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime-Boost/RV 144</td>
<td>Thailand</td>
<td>16,402</td>
<td>Modest effect (31.2%) Not licensure trial</td>
</tr>
<tr>
<td>2013</td>
<td>DNA and Ad5 A/B/C HVTN 505</td>
<td>US</td>
<td>2,500</td>
<td>Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.</td>
</tr>
</tbody>
</table>

FOLLOW-ON TRIALS BASED ON RV144: STRATEGY INCLUDES DEVELOPMENT AND RESEARCH TRACKS

RV144 FOLLOW-UP: Thailand

Research Studies:
- RV144i immune correlates studies
- RV305 protein boost in volunteer-subset from RV144
- RV306 expanded immunogenicity of RV144 regimen
- RV328 AIDSVAX B/E study

Partners/Funders:
US Army, Thai government, NIH, Sanofi Pasteur, BMGF

LICENSURE TRIAL: Thailand

Population: MSM, high-risk

Products: ALVAC (Sanofi Pasteur) + gp120/adjuvant (such as MF59)

Partners/Funders: US Army, Thai government, NIH, Sanofi Pasteur, BMGF, Novartis

LICENSURE TRIAL: South Africa

Population: Heterosexual, high-risk

Products: ALVAC (Sanofi Pasteur) + gp120/MF59 (Novartis)

Partners/Funders: NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

RESEARCH TRIAL

Population: Heterosexual, high-risk

Products: DNA + NYVAC (Sanofi Pasteur) + protein/adjuvant (such as MF59) vs. NYVAC (Sanofi Pasteur) + protein/adjuvant

Partners/Funders: NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

Ref: This schematic comes from the Pox-Protein Public Private Partnership (P5), a collaboration spanning four continents established in 2010 to build on the results of RV144. P5 partners include the US NIAID, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the US Military HIV Research Program, Sanofi Pasteur and Novartis Vaccines and Diagnostics.
SUMMARY OF EVIDENCE: BIOMEDICAL HIV PREVENTION

Treatment for prevention (discordant couples)
96% (CI: 73.99)

Oral Pre-Exposure Prophylaxis (discordant couples)  
(Tenofovir and Truvada)
Truvada: 73% (CI: 49.85) & Tenofovir: 62% (CI: 34-78)

Oral PrEP (heterosexual couples)  
(Truvada)
63% (CI: 21.98)

Medical Male Circumcision
54% (CI: 38.66)

Oral Pre-Exposure Prophylaxis for IDU’s
49% (CI: 9.6-72.2)

Oral Pre-Exposure Prophylaxis for MSM
44% (CI: 15.63)

STD Treatment (Random cohort of 1000 adults)
42% (CI: 21.58)

Topical Microbicide (heterosexual women)
39% (CI: 16.60)

HIV Vaccine (Thai RV 144)
31% (CI: 1.51)

The search for the most effective HIV prevention prophylaxis for all is still elusive

Effect size is directly proportional to adherence
BEHAVIOURAL HIV PREVENTION STRATEGIES

HIV Counselling & Testing

Delaying Sexual Debut

Clean Needle Exchange Programs

Barrier Methods (Male & Female Condoms)

Eliminating Stigma

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HPTN 043:
- A four-fold increase in testing was observed in HIV mobile voluntary counseling and testing
- Data suggests knowing the status decreases risky behaviour

Evidence suggests that clean needle syringe exchange program can reduce HIV transmission among IDU’s
- HIV sero-prevalence declined by a mean annual 18.6% for 36 cities with NSPs compared to an 8.1% increase in 67 cities without NSPs (Wodak, 2005)

High seroconversion rate was observed among women who had reported to have had sex at 15 years or younger (12.0 per 100 person-years, 95% CI 8.0 to 18.0) (Wand and Ramjee et al 2012).

Correct and consistent use of male condom use can reduce HIV acquisition by up to 97% (Pinkerton & Abramson, 1997)
- HIV incidence in consistent condom users: 0.9 per 100 person-years (95% CI, 0.4-1.8)
- HIV incidence in non consistent condom users: 6.8 per 100 person-years (95% CI, 4.4-10.1)(Davis and Weller, 1999)

Development of the AIDS-Related Stigma Scale (Kalichman et al 2005)
- Disclosure of HIV testing may eliminate stigma

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Microfinance is one of the few interventions that can both mitigate AIDS impact and prevent new infections (Pronyk et al 2005)

A South African based study provided evidence for the effect of a microfinance based structural intervention on the prevention on HIV infection and intimate-partner violence (Pronyk et al 2006)

Intervention more effective between partner (Lurie et al, 2003)


Decentralizing and integrating HIV health services with effective linkage to care are shown to contribute to improved health outcomes (Pfeiffer et al 2010)

Windows who had participated in this study had 15% fewer new HIV infections and a change in men’s gender-related behaviour was observed (Jewkes et al 2008)

Stepping Stones: a participatory HIV prevention programme to improve sexual health through building stronger, more gender equitable relationships (Jewkes et al 2006)

Poor access to health care

High risk behaviour for economic survival e.g. sex workers or transactional sex (Baba-Djara et al 2013)
HIV INCIDENCE AND AIDS MORTALITY AMONG ADULTS IN SUB-SAHARAN AFRICA, 2003–2020, UNDER DIFFERENT INTERVENTION SCENARIOS (MODELING)

Integration of HIV prevention & care activities for long-term reduction in HIV incidence & significant decline in AIDS mortality

**EDCTP: RESEARCH PRIORITIES FOR HIV PREVENTION, TREATMENT & CARE IN AFRICA**

<table>
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<tr>
<th>IMPLEMENTATION RESEARCH</th>
<th>OPERATIONAL RESEARCH</th>
<th>HUMAN RESOURCES</th>
<th>THERAPEUTICS DRUG DEVELOPMENT</th>
<th>PREVENTION</th>
</tr>
</thead>
</table>

European & Developing Countries Partnerships to prevent & treat HIV & related co-morbidities through an integrated and a multidisciplinary research program including development of world class African scientists.
THANK YOU