RECENT ADVANCES IN HIV PREVENTION & TREATMENT RESEARCH

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Far too many people become HIV infected & die from the effects of HIV/AIDS.
MILESTONES IN 30 YEARS OF HIV RESEARCH
(WE HAVE COME A LONG WAY, YET MUCH MORE NEEDS TO BE DONE)

1st Decade (1980-1990)

- HIV biology and pathogenesis
- SIV
- Identification VIH-2
- HIV-1 Diversity
- HIV-1 Sequence
- CD4 Receptor
- HIV-1 Identification

2nd Decade (1990-2000)

- HIV biology and pathogenesis
- ~25 million infections
- Co-receptors
- Origin of HIV
- Recombinants VIH-1
- HIV Reservoirs
- HIV-1 O
- HIV-1 subtypes
- HIV-1 N

3rd Decade (2000-2010)

- HIV biology and pathogenesis
- ~35 million infections
- CD4 Depletion in gut
- HIV controllers
- HIV Restriction factors
- HIV-1 P
- Immune activation
- Microbial Translocation

PREVENTION & TREATMENT MILESTONES

1981: AIDS
1983: African Epidemic

- Therapy & Prevention Research
  - 1984/5: HIV Testing
  - 1988: AZT Therapy
  - 1989: ARV Resistance
  - 1994: HIV Quantification
  - 1996: PMTCT
  - 1996: HAART
  - 2006: Circumcision (Risk Reduction)
  - 2010: ARV as prevention
  - Cure Proof of concept

Ref: Modified from Francoise Barre-Sinoussi, (ASSHH July 2013)
FUNDAMENTAL PRINCIPLES OF INTERVENTIONS FOR PREVENTION & TREATMENT OF SEXUALLY TRANSMITTED HIV

INFECTIOUSNESS (HIV positive)
- Blood viral load
- Genital tract viral load
  - Inflammatory STDs
- Viral clade
- Acute infection

SUSCEPTIBILITY (HIV Negative)
- Genital ulcers
- Inflammatory STI’s
- Cytokine profile
- Lack of circumcision
- Cervical ectopy
- HLA haplotype
- Hormonal contraception?

HIV TRANSMISSION

HIV TREATMENT INTERVENTIONS
- HIV Testing
- Behaviour Change
- STI Treatment

HIV PREVENTION INTERVENTIONS
- HIV Testing
- Behaviour Change
- Safe Sex
- STI Treatment

Ref: Modified from Cohen (ART for Prevention)
HIV PREVENTION
FOUR PREVENTION OPPORTUNITIES

**UNEXPOSED**
- Behavioral, Structural
- HCT
- Circumcision
- Condoms & Safe Sex

**EXPOSED (precoital/coital)**
- Vaccines
  - ART PrEP
  - Microbicides

**EXPOSED (postcoital)**
- Therapeutic Vaccines
- ART PEP

**INFECTED**
- Treatment of HIV reduce Infectivity
  - e.g. PMTCT, TasP

HIV PREVENTION

HIGHLY ACTIVE COMBINATION OF HIV PREVENTION TOOLS

- VACCINES
- PMTCT
- PrEP
- TasP
- HIV CURE
- MICROBICIDES
- EDUCATION / BEHAVIOUR CHANGE
- CONDOMS
- STI TREATMENT
- COUNSELING & TESTING
- MMC
- DRUG/ALCOHOL TREATMENT
- HARM REDUCTION
HIV PREVENTION (PRECOITAL/COITAL)
MICROBICIDE RESEARCH: 1992 - 2012

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

MTN 003 – VOICE (2009-2013)
Daily use
Tenofovir gel & tablet

FACTS 001 (2011-2014)
Tenofovir gel
SA study to confirm CAP 004
ongoing

MTN 020 (2012 – 2015)
Intravaginal
Dapivirine ring
ongoing

1992-2012
10 products in large scale clinical trails

1 proof of concept

Adherence is critical for efficacy

1992 - 2012
N9 sponge (1987-1990)
NIH


COL-1 (1996-2000)

SAVVY (2004-2006)
FHI

ARV BASED PRODUCTS
(prevent establishment of HIV infection)

POLYANIONS
(prevent attachment of virus)

SURFACHTANTS
(disrupt membrane)

Carraguard (2004-2008)

HPTN 035 (2004-2009),
MDP 301 (2005-2009)

CONF 001 (2006-2007)
FHI Cellulose Sulphate

N9 INCREASED RISK

SAFE, NOT EFFECTIVE

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ADDRESSING ADHERENCE: NEW FORMULATION & DELIVERY SYSTEMS

Delivery Systems: Systems Currently in Clinical Trials (Phase I to III)

Vaginal Gels

- Tenofovir
  - FACTS 001
    (Exiting participants, Data end 2014/2015)

Rectal Gels

- Tenofovir
  - CHARM
  - Project Gel
  - MTN 017
  - MTN 013

Silicon Rings

- Dapivirine
  - ASPIRE (MTN 020)
    - Maraviroc + Dapivirine
  - MTN 013/ IPM 026 (Completed)
# EVIDENCE FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) EFFICACY WITH ORAL TENOFOVIR-BASED REGIMENS, 2014

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>N</th>
<th>EFFICACY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>Men having sex with men</td>
<td>2499</td>
<td>44% (15%-63%) Daily oral FTC/TDF</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, South Africa, Thailand, US</td>
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<tr>
<td>TDF2 Study</td>
<td>Young men &amp; women</td>
<td>1200</td>
<td>62% (21%-83%) Daily oral FTC/TDF</td>
</tr>
<tr>
<td>Botswana</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Partners PrEP Study</td>
<td>Heterosexual couples</td>
<td>4758</td>
<td>67% (44%-81%) Daily oral TDF 75% (55%-87%)</td>
</tr>
<tr>
<td>Kenya, Uganda</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thai IDU Study</td>
<td>IDU; 17 drug treatment centers</td>
<td>2413</td>
<td>49% (10%-72%) Daily oral TDF</td>
</tr>
</tbody>
</table>

**Adherence:**
In every PrEP trial adherence was imperfect – range (<30%-81%). Correlates of low adherence: younger age, not partnered, stigma, low risk perception, less sex, alcohol use, non-adherence to study visit

Modified from Jared Baeten, PrEP & Treatment as Prevention: Finding the Balance, STI & AIDS World Congress 2013 Vienna, July 2013
Long-acting injectables

- **TMC278LA**: (Janssen/BMGF) NNRTI
- **S/GSK1265744**: (744 LA, ViiV) Integrase inhibitor

Major strength of the injectable approach
- Long half-life-weeks to months
S/GSK744 LONG-ACTING INJECTABLE FORMULATION

- HIV-1 integrase inhibitor
- Developed via joint venture between GSK/Shionogi/ViiV
- Evaluated clinically as an oral formulation
  - Generally safe & well tolerated
  - 30 mg/d, 10 days = 2.6 log median reduction in viral load
- LA formulation evaluated in P1 (Spreen et al, IAC 2012)
  - IM or SC single dose of 100-800 mg
  - No drug related AEs; No grade 3-4 AEs
  - Mean terminal t_{1/2} 21-50 d (Oral 30-40 h)
  - 800 mg IM sustained plasma levels above that required to produce >2.5 log reduction in viral load as monotherapy

Ref: Long Acting Formulation Strategies for HIV Prevention Products: Addressing the Challenges of Adherence? Joe Romano, June 2, 2013, NWJ Group, LLC
**TREATMENT AS PREVENTION (TasP)**

- Proof of Concept of the impact of ART on HIV transmission: Reduction in MTCT of HIV during pregnancy, delivery, breast feeding when women are on ART

- Numerous observational, community & RCT studies show that a decrease in viral load is associated with significant reduction in HIV transmission (Quinn et al 2000, Attia S et al 2009, Cohen MS et al 2010)

- HIV viral load in the infected person is a key determinant of the risk of HIV transmission
RECENT SUCCESS: HPTN 059- significant reduction in HIV transmission when ART started immediately with CD4 count between 350 & 550 per ul. (Cohen MS, et al. 2011)

BENEFITS:
- Early initiation of ART has clinical benefits- tolerability, CD4 cell recovery & overall prognosis decreases immune reconstitution inflammatory syndrome, impact on HIV & TB morbidity
- Successes dependant on sustained high adherence- poor adherence: treatment failure & drug resistance- numerous personal, societal & structural barriers to high adherence
- Impact on HIV transmission- people on ART, adherent to Rx unlikely to infect sexual partner & reduce MTCT
- Implementation trials in progress- earlier HIV testing & immediate offer of treatment e.g. PopART

RISKS OF TasP & IMPACT ON TREATMENT CASCADE:
Challenges at both individual & health systems level

<table>
<thead>
<tr>
<th>INDIVIDUAL</th>
<th>HEALTH SYSTEMS</th>
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<tbody>
<tr>
<td>Toxicity</td>
<td>Treatment delivery to larger numbers of people – overburden of resources</td>
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<tr>
<td>Decreased adherence- drug</td>
<td>budgets</td>
</tr>
<tr>
<td>resistance</td>
<td>Programme to expand support for retention, adherence &amp; supply chain,</td>
</tr>
<tr>
<td>Disclosure &amp; stigma</td>
<td>laboratory testing</td>
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Targeted operations research critical to address these at all levels

Ref: Granich et al, 2009
PUTTING PrEP & TasP TOGETHER

<table>
<thead>
<tr>
<th>ART FOR HIV PREVENTION</th>
<th>PrEP FOR HIV PREVENTION</th>
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<tr>
<td><strong>96%</strong> (HPTN 052, near - perfect adherence)</td>
<td><strong>~90%</strong> (When tenofovir detected)</td>
</tr>
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</table>

Two incredibly powerful HIV prevention strategies – when used, can prevent HIV

- WHO Guidelines - Recommendations for use in context of demonstration project, July 2012
- CDC Guidelines - Clinical Practice Guidelines, 2014

Ref: Modified from, Jared Baeten, STI & AIDS World Congress 2013, Vienna, July 2013, PrEP & Treatment as Prevention: Finding the Balance
POST EFFICACY PrEP DEMONSTRATION STUDIES

**HPTN (NIH):**
- **HPTN 066:** PK for intermittent PrEP
  - Will the “intermittent” groups: Have the same coverage of sex events? Need fewer tablets for coverage? Report fewer side effects?
- **HPTN 067:** PK & behavioral study of alternative FTC/TDF dosage schedules including event-driven
  - Harlem, USA (MSM), Bangkok, Thailand (MSM), Cape Town, South Africa (♀)
- **HPTN 073:** Uptake of FTC/TDF by black MSM
  - Willingness
  - Will it be used as prescribed
  - Will client centred care coordination enhance uptake & adherence
- **HPTN 069:** Maraviroc an alternative to FTC/TDF
  - Safety & tolerability in MSM & women

**PopART (NIH):** Cluster randomised trial- immediate vs. delayed ART

**MaxART:** Swaziland (Stop AIDS now) - feasibility, acceptability, scalability & clinical outcomes

**ANRS 12249 Africa Centre:** Impact on HIV incidence at population level

**iPrEX OLE:** Access & follow-up in MSM
ADVANCES IN HIV TREATMENT RESEARCH
HIV REPLICATION CYCLE: TARGETS FOR ANTIRETROVIRAL THERAPY (ART)

>20 different ARV drugs used in Combination that improves health & prolongs life of HIV infected individuals

Ref: Modified from Carl W. Dieffenbach, The Future of HIV Cure Research & the NIH, 1 July 2013
WHY DO WE NEED LIFELONG ART?
HIV INFECTION PERSISTS ON ART...

For every HIV infected person initiating therapy, 2 individuals are newly infected—challenges with sustainability—HIV infected population is likely to grow overtime

Despite successes in HIV therapy full health & immune status not restored

Co-morbidities still experienced such as CVDs, bone disorders & cognitive impairment

Presence of an inducible HIV-1 latent reservoir during HAART (Chun 1997, J Wong 1997)

Interruption of ARV therapy leads to the re-emergence of viral replication & progression to AIDS

Therefore it is critical that strategies for a safe, affordable & scalable cure for HIV address individual & public health challenges of lifelong ARV therapy

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Viral Latency

1. Mechanism that establishes latency
2. Effect of ART on Host immune system & consequences of HIV persistence

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Ref: Palmer et al., Proc Natl Acad Sci USA. 2008; 105: 3879-84
Malderelli et al., Plos Pathogens 2007: 3: 484
HIV PERSISTENCE DURING ART

Figure 2 | Mechanisms of HIV persistence during antiretroviral therapy. The left panel illustrates how latent HIV infection can be established in T cell and myeloid cell reservoirs. The primary mechanism is probably infection of activated memory CD4+ T cells. Most of these cells die, but a minority revert to a resting state. The centre panel illustrates the fate of these now resting ‘latently infected’ memory CD4+ T cells. These cells either die slowly, become a source of new infections, persist as long-lived cells or expand through homeostatic mechanisms. The right panel depicts some immune mechanisms that contribute to persistence. These include mechanisms that maintain cells in a resting state (for example, the upregulation of programmed cell death protein 1 (PD1)). Immune dysfunction during therapy probably reduces the efficient clearance of infected cells.
HIV CURE RESEARCH
(ELIMINATE HIV)

HYPOTHESIS:
 Can immediate ART at PHI* lead to enhanced “post-treatment” viral control, or limit the size of HIV reservoir to increase the chance of viral “remission/cure”?

ASSUMPTION:
 The size of the HIV reservoir increases with time after PHI
 Immediate ART following PHI limits viral reservoir feeding

*PHI: Primary HIV infection

Ref:
Hurst et al, CRIO 2014 Abstract 403 LB
POTENTIAL CURES FOR HIV INFECTION

Functional Cure
(Control of viremia without drugs)

Sterilizing Cure
(No detectable infectious virus)

Efficacy endpoints:
- Absence of rebound upon cessation of ARVs
- Elimination of all HIV infected cells

Ref: Modified from Carl W. Dieffenbach, The Future of HIV Cure Research & the NIH, 1 July 2013
EVIDENCE OF FUNCTIONAL CURE

**BERLIN PATIENT:**
Received stem cells (bone marrow transplant) from a donor with genetic mutation-made patient highly resistant to HIV infection

**ANRS47 VISCONTI COHORT:**
14 HIV + patients treated approximately 10 weeks PHI for 3 years, 7.5 years of control off treatment (Saez-Cirion et al Plos Pathogen 2013)

**MISSISSIPPI BABY:**
Born to HIV infected mother - treated with ART therapy within 30 hours of birth remains negative after stopping treatment at 18 months. No detectable virus at 3 years (Persaud D et al NEMJ 2013; 369: 1828-1835)

**HIV ELITE CONTROLLERS (<0.3%):**
Treatment naïve infected people naturally control HIV infection (undetectable viral load, low level of reservoir - efficient suppressive CD8 responses; restricted infection of their CD4 cells & macrophages; genetic factors) - (Natures Review: Immunology 2012)
“FUNCTIONAL CURE” OF HIV INFECTION

1. Early ARV Treatment of HIV Infection
2. Preservation of Substantial Level of HIV-Specific Immune Response
3. Prolonged Suppression of Detectable Viremia with ARV
   +/− Intensification of ARV Therapy
   +/− HIV-Specific Immunotherapy
4. Continual Attrition of HIV Reservoir
5. Discontinuation of Therapy
6. Prolonged Suppression of Viral Rebound by Preserved and Amplified Anti-HIV Immune Responses

Ref: Carl W. Dieffenbach, The Future of HIV Cure Research & the NIH, 1 July 2013
FUTURE HIV CURE STRATEGIES?  
A COMBINED APPROACH…  
(IAS WORKING GROUP ON HIV CURE)

Other ongoing or planned studies

1. Very early therapy to prevent Host responses
2. Direct-acting anti-latency drugs
3. Anti-inflammatory drugs
4. Therapeutic vaccination
5. Immune-based therapy
6. Cell therapy

Requires a multidisciplinary, integrated approach – scientists, community, public-private partnerships, interaction between basic & clinical science, data exchange platform

Ref: Modified from Francoise Barre-Sinoussi, ASSHH July 2013)
Paediatric HIV: NIH funded IMPAACT PIII5- 54 HIV infected infants treated 48 hours of birth. ART stopped after 2 years - viral suppression achieved. Babies will be monitored for viral rebound. Primary endpoint- undetectable HIV in plasma 48 weeks post-treatment follow-up 5 years after birth.

Therapeutic Vaccine (European Union): Vaccine tested in 36 HIV positive participants- safe & drop in HIV viral load in some participants- drop is effective when HIV therapy is initiated - reformulation to be tested.

CHERUB: Collaboration on HIV eradication- a UKBRC initiative (HEATHER studies - stopping ART algorithm, River Study- ART plus therapeutic vaccine) – (S.Fidler, pers Comm)

Martin Delaney Collaborations:
- DARE: Immunological mechanisms controlling latency
- Defective HIV: Gene editing & transplantation
- HIV Care: Reactivation of latent HIV gene expression - new & old target

amfAR: Chart the previous location of viral reservoirs
Understand how HIV persists
Record virus in reservoirs
Eliminate virus
ETHICAL CONSIDERATION:
HIV CURE BIOMEDICAL STRATEGIES RAISE MANY QUESTIONS

For most patients in care, living with ART has become a routine part of daily life - will they be willing to stop therapy or change therapy?

New HIV Cure research raises the question of uncertainty management
  o Are there individual benefits for the patients?
  o What are the possible risks for the patients?

Are clinical trials for HIV Cure research acceptable?
  o For which kinds of patients?
  o Which protocols are acceptable?
  o What are the motivations & fears to participate?

IAS Cure Working Group has developed a multidisciplinary research agenda to address these challenges

Ref: Modified Francoise Barre-Sinoussi, (ASSHH July2013)
CONCLUSION:
HIV PREVENTION & TREATMENT

What we now know
- Behavioural, biomedical or structural interventions are needed for prevention & treatment of HIV
- None of the interventions alone are sufficient to impact on the epidemic
- Treatment impacts prevention & vice versa
- Reducing HIV incidence requires a combined & integrated approach of both HIV prevention & treatment
CONCLUSION

HIV CURE IS CRITICAL- FOR PREVENTION & RESTORATION OF HEALTH OF THOSE INFECTED

- Safe, affordable & scalable cure will improve health & quality of life of HIV infected & reduce transmission risk to those not infected

- Recent advances & future research will lead towards a combination of safe, scalable & affordable strategies to eradicate HIV - requires effective partnerships - potential participants, community, ethicists, multidisciplinary group of scientists, public-private partnerships
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