Overview of HIV-1

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www.hivresearch.org
Outline of Progress in HIV-1

- Background and Epidemiology
- HIV Virology, Transmission, and Pathogenesis
- Acute HIV infection
- HIV Diagnostics
- Pre- and Post-exposure prophylaxis
- HIV Prevention—turning the tide
HIV identified 1984

Origins

Early expectations – vaccine in 2 years
(M.Heckler-NIH Director)

Search for cure and prevention strategies continues in 2011
Epidemiology

Global pandemic

Centered in Sub-Saharan Africa

(70% of infections)
Adults and Children with HIV, 2009
33.4 million (31.1-35.8) million

North America
1.4 million
[1.2–1.6 million]

Caribbean
240 000
[220 000–260 000]

Latin America
2.0 million
[1.8–2.2 million]

Western and Central Europe
850 000
[710 000–970 000]

Middle East and North Africa
310 000
[250 000–380 000]

Sub-Saharan Africa
22.4 million
[20.8–24.1 million]

Eastern Europe and Central Asia
1.5 million
[1.4–1.7 million]

East Asia
850 000
[700 000–1.0 million]

South and South-East Asia
3.8 million
[3.4–4.3 million]

Oceania
59 000
[51 000–68 000]

UNAIDS / WHO, AIDS Epidemic Update 2009
AIDS Orphans in the Agape House

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Question

How many new HIV infections occurred in 2009 worldwide?

a) 27,000
b) 270,000
c) 2,700,000
d) 27,000,000
New HIV Infections, 2009
2.7 million (2.4-3.0 million)

UNAIDS / WHO, AIDS Epidemic Update 2009
Over 7400 new HIV infections a day in 2009

More than 96% are in low and middle income countries

About 1000 are in children under 15 years of age

About 6300 are in adults aged 15 years and older of whom:
  — almost 50% are among women
  — about 45% are among young people (15-24)
HIV Virology, Transmission, and Pathogenesis
HIV Virus Structure

Trans-membranous glycoprotein (gp41)

Spike of envelope glycoprotein (gp120)

Host cell protein

Lipid bilayer

Matrix protein (p17)

Reverse transcriptase

RNA with protein surround (p7 nucleocapsid)

Ribonucleic protein (p24)
HIV/AIDS

HIV-1 Clades

GLOBAL DISTRIBUTION OF HIV-1 SUBTYPES AND RECOMBINANTS

Source: Francine E. McCutchan, Henry M. Jackson Foundation (Rockville, Maryland). McCutchan and colleagues are indebted to the many international collaborators who helped develop the data used to generate this map.
HIV life cycle and mechanisms of anti-virals
Transmission Routes

- Unprotected sexual intercourse with an infected partner
- Vertical transmission (from mother to child)
  - in utero
  - during delivery
  - breastmilk
- Injection drug use (rare: infected blood/blood products)

HIV INFECTION
Agape House kids
Risk of Specific Exposures

Per Contact Transmission Rate

- Transfusion: 95%
- Untreated Perinatal: 15 - 30%
- Occupational:
  - Needle Stick: 0.3%
  - Mucous Membrane: 0.01 - 0.1%
Lessons from Occupational Exposure Literature

- Relative Risk of Infection associated with:
  - Deep injury OR: 16.1
  - Visible blood OR: 5.2
  - Needle in vein/artery OR: 5.1
  - Source is terminally ill OR: 6.4
**Figure 2.** HIV RNA levels 1 year after untreated infection are relatively stable and predict subsequent disease progression. Data are from the Multicenter AIDS Cohort Study [21].
Acute HIV Infection
Symptoms of Acute HIV Infection

- **Systemic:**
  - Fever
  - Weight loss

- **Central:**
  - Malaise
  - Headache
  - Neuropathy

- **Pharyngitis:**

- **Mouth:**
  - Sores
  - Thrush

- **Lymph nodes:**
  - Lymphadenopathy

- **Esophagus:**
  - Sores

- **Muscles:**
  - Myalgia

- **Liver and spleen:**
  - Enlargement

- **Skin:**
  - Rash

- **Gastric:**
  - Nausea
  - Vomiting
# Frequency of Signs and Symptoms in Acute HIV-1 Infection

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Fever</td>
<td>&gt;80-90%</td>
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<tr>
<td>Fatigue</td>
<td>&gt;70-90</td>
</tr>
<tr>
<td>Rash</td>
<td>&gt;40-80</td>
</tr>
<tr>
<td>Headache</td>
<td>32-70</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>40-70*</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>50-70*</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>50-70</td>
</tr>
</tbody>
</table>


*highest in younger patients, Vanhems. JAIDS 2002;31:318-321.
Natural History of HIV Infection

Modified from Faucii, 2000
HIV Vaccine Strategies

- DNA
- Peptides
- Subunits
- Live Vectors
- Dendritic Cells

- Virus-like Particles/Pseudovirions
- +/- Adjuvants
- Combinations
- Whole killed HIV
- Live attenuated HIV (therapeutic history)
STEP Study

3000 high risk, uninfected participants
Ad5 vectored vaccine x 3
Stopped early because no evidence of efficacy
More infections amongst vaccinees
Risk related to pre-existing Ad titer, circumcision

HR = 1.2 [95% CI 0.6-2.2]  
HR = 2.3 [95% CI 1.2-4.3]
Modest results, but first sign of protection in humans

N=16,402 Thai volunteers at community risk

Canarypox vector $x$ 4 + gp120 $x$ 2

Modified intention to treat efficacy 31.2%
(95% CI, 1.1 to 52.1; $P = 0.04$)

No effect on viral load
HIV/AIDS Vaccine Mechanisms

- Prevent infection
- Lower initial peak viremia
- Lower set point or eliminate HIV
- Stop progression or transmission
When Will An HIV Vaccine Be Available?

A. A vaccine is available now
B. Next year
C. 5 years
D. 10 years
E. Don’t know
Search for a Microbicide

CAPRISA 004 (July 2010)

- Tenofovir intravaginal gel pre and post coitus
- 39% efficacy (95% CI: 6-60%)
- Effect on HSV 2

Future Directions

- Dosing Frequency
- Route
- Other agents

What to do with partial efficacy?

- Impact on prevention research
Behavioral-Social Considerations

Social Stigma
Global Economics
Political Instability
Societal Structure
Vaccine Induced Seropositivity

AIDS Orphan, Telegraph 2010
References

- UNAIDS Report on the Global AIDS Epidemic

- DHHS Guidelines for Use of ART in Adults and Adolescents

- Military HIV Research Program
  www.hivresearch.org/home.php

- International AIDS Vaccine Initiative
  www.iavi.org/Pages/home.aspx


- RV 144 Thai Trial Paper: Rerks-Ngarm et al, NEJM, 2009
HIV Diagnostics
Rapid Immunoassay – RIA

Uni-Gold Recombigen OraQuick Advance HIV-1/2

Positive HIV-1

Reactive Control

Results in 10 -12 minutes

Positive HIV-1/2

Reactive Control

Results in 20 minutes
Monitoring

Aim for maximal virologic suppression ("detectable is unacceptable")

- HIV RNA < 400 copies / mL after 24 weeks
- HIV RNA < 50 copies / mL after 48 weeks

Maintain adequate CD4 count

- Increases 50-150 cells / mm³ until steady state
Post-exposure prophylaxis
Websites to Access the Guidelines

- http://www.aidsetc.org
Occupational Risk Exposures in Health Care Personnel

- Percutaneous injury (needlestick, cut)
- Contact of mucous membrane or nonintact skin

OR

- WITH:
  - Blood
  - Tissue
  - Other body fluids that are potentially infectious (cerebrospinal, synovial, pleural, pericardial, peritoneal, or amniotic fluids; semen or vaginal secretions)
NOT Considered Infectious for HIV, unless *Visibly Bloody*

- Feces
- Nasal Secretions
- Saliva
- Sputum

- Sweat
- Tears
- Urine
- Vomitus
Risk of HIV Infection following Occupational Exposure to HIV-Infected Blood

- Approximately 0.3% following percutaneous exposure
- Approximately 0.09% following mucous membrane exposure
Factors Associated with Increased Risk

- Visible contamination of device (such as needle) with patient’s blood
- Needle having been placed directly into vein or artery
- Hollow-bore (vs solid) needle
- Deep injury
- Source patient with terminal illness
- High viral load (not established in occupational exposure)
Toxicity of PEP Regimens

- PEP should be given for a full 4 weeks
- Side effects of ARV drugs are common, and a major reason for not completing PEP regimens
- Therefore, to the extent possible, regimens that are tolerable for short-term use should be selected
Initiating PEP

- PEP should be started as soon as possible, preferably within hours, rather than days, following exposure.
- When uncertain as to which drugs to choose, start the basic regimen rather than delay.
- PEP should be administered for 4 weeks, if tolerated.
Initiating PEP (2)

- Re-evaluate exposed HCP within 72 hours of exposure, especially as additional information about the exposure or source patient becomes available
- If the source is found to be HIV negative, PEP should be discontinued
- Rapid HIV testing of the source patient can facilitate decisions regarding PEP when the source patient’s HIV status is unknown
Selecting the PEP Regimen

- Selection of number (2 or ≥3) of drugs is based on assessment of risk for HIV infection.
- Selection of which agents to use is based largely on potential toxicity of PEP drugs and on likelihood of efficacy (especially in the case of resistant virus).
  - Few data on efficacy of individual ARV agents in PEP.
Which Drugs to Use?

- Consultation with an expert is recommended

- Regimens should be chosen to minimize potential drug toxicities and maximize the likelihood of adherence

- Consideration should be given to the history of the source person, including history of and response to ART and disease stage
Which Drugs to Use? (4)

Expanded ≥3-drug PEP regimens:

- Preferred:
  - LPV/RTV (Kaletra) + basic 2-drug regimen

- Alternative:
  - ATV* ± RTV
  - FPV ± RTV
  - IDV** ± RTV
  - SQV + RTV
  - NFV***
  - EFV***

  + basic 2-drug regimen

* If ATV is coadministered with TDF, RTV must be included in the PEP regimen.
** Avoid in late pregnancy.
*** Avoid in pregnancy.
Current ARV Medications

**NRTI**
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine ( FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

**NRTI**
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)

**PI**
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

**Integrate Inhibitor (II)**
- Raltegravir (RAL)

**Fusion Inhibitor**
- Enfuvirtide (ENF, T-20)

**CCR5 Antagonist**
- Maraviroc (MVC)
HIV Prevention—turning the tide
Adult male circumcision

- Reduction in transmission from HIV+ women to HIV – men by 50-60%
  
  
  

- No effect on transmission from HIV+ men to HIV- women
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pittisutthithum M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEC Investigators*

NEJM 361:2209 (03 Dec 09)
RV 144 Primary Population Efficacy

A  Intention-to-Treat Analysis

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<tr>
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<th>Placebo</th>
<th>Vaccine</th>
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<tbody>
<tr>
<td>No. at Risk</td>
<td>8380</td>
<td>7757</td>
</tr>
<tr>
<td>Cumulative No. of Infections</td>
<td>7643</td>
<td>3441</td>
</tr>
<tr>
<td>Probability of HIV-1 Infection (%)</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
</tr>
<tr>
<td>P-value</td>
<td>0.08</td>
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No. at Risk
Placebo  8380  7757  7643  3441  7325
Vaccine  8282  7707  7665  3471  7447
Cumulative No. of Infections
Placebo  32  52  67  75
Vaccine  17  37  50  56

B  Per-Protocol Analysis

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<tr>
<td>No. at Risk</td>
<td>6196</td>
<td>6083</td>
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<tr>
<td>Cumulative No. of Infections</td>
<td>6220</td>
<td>6089</td>
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<tr>
<td>Probability of HIV-1 Infection (%)</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
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<tr>
<td>P-value</td>
<td>0.16</td>
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No. at Risk
Placebo  6196  6083  6220  6089  6002
Vaccine  6176  6040  6068  5958  5874
Cumulative No. of Infections
Placebo  16  31  44  59
Vaccine  5  22  32  36

C  Modified Intention-to-Treat Analysis

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<tr>
<td>No. at Risk</td>
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<tr>
<td>Cumulative No. of Infections</td>
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<td>Probability of HIV-1 Infection (%)</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
<td>0.2, 0.4, 0.6, 0.8, 1.0</td>
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<td>P-value</td>
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No. at Risk
Placebo  8138  7797  7643  3441  7325
Vaccine  8137  7797  7665  3471  7447
Cumulative No. of Infections
Placebo  30  50  65  74
Vaccine  12  32  45  51
Tenofovir gel protects women from male to female infection

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<th>Months of follow-up</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
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<tr>
<td>Cumulative HIV endpoints</td>
<td>37</td>
<td>65</td>
<td>88</td>
<td>97</td>
<td>98</td>
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<tr>
<td>Cumulative women-years</td>
<td>432</td>
<td>833</td>
<td>1143</td>
<td>1305</td>
<td>1341</td>
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<tr>
<td>HIV incidence rates (Tenofovir vs Placebo)</td>
<td>6.0 vs 11.2</td>
<td>5.2 vs 10.5</td>
<td>5.3 vs 10.2</td>
<td>5.6 vs 10.2</td>
<td>5.6 vs 9.1</td>
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<tr>
<td>Effectiveness (P-value)</td>
<td>47% (0.064)</td>
<td>50% (0.007)</td>
<td>47% (0.004)</td>
<td>40% (0.013)</td>
<td>39% (0.017)</td>
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Coming steps

- Pre-exposure prophylaxis
- Improved antiretroviral microbicides
- Test and treat
- Extend the impact of RV 144
- New generation HIV vaccines