Principles of HIV Transmission and Infection (AIDS Vaccine 2013)

• My brief:
  - How HIV transmission and infection occurs
  - Potential routes to block infection

Disclaimer: I am a basic lab scientist and so I am going to focus on the microscopic details of the virus and the human immune system....
Some questions you may want answered.....???

• How many viral particles does it take to cause infection?
• Which cells does HIV infect in men and women?
• Do the viruses that cause infection have any special properties?
• Are there things that might increase the risk of infection?
• Can an HIV-infected person be infected again (so called superinfection)?
• Are some people resistant to HIV infection?
• Can we able to stop HIV from binding to target cells?
• How do current biomedical prevention modalities work?
• How did RV144 work?
• Are we ever likely to make a vaccine against HIV?
RISKS OF TRANSMISSION
(Wawer et al., JID 2005)
Laith J. Abu-Raddad\textsuperscript{a,b,c,*}, Ruanne V. Barnabas\textsuperscript{c,e,f,*}, Holly Janes\textsuperscript{c,g}, Helen A. Weiss\textsuperscript{i}, James G. Kublin\textsuperscript{c}, Ira M. Longini Jr\textsuperscript{j,k}, and Judith N. Wasserheit\textsuperscript{d,e,f,h} the HIV Viral Load Working Group
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Declines in HIV incidence with increased ART coverage in KZN, South Africa

High Coverage of ART Associated with Decline in Risk of HIV Acquisition in Rural KwaZulu-Natal, South Africa

Frank Tanser,1,2 Till Bärnighausen,1 Erofili Grapsa,1 Jaffer Zaidi,1 Marie-Louise Newell1,3

The landmark HIV Prevention Trials Network (HPTN) 052 trial in HIV-discordant couples demonstrated unequivocally that treatment with antiretroviral therapy (ART) substantially lowers the risk of transmission to the HIV-uninfected partner. However, it has been vigorously debated whether robust coverage could be achieved in sub-Saharan African settings where stable, cohabiting couples are often not the norm. The considerable operational challenges exist to the successful and sustainable delivery of ART to large numbers of patients. We used data from one of Africa’s largest population-based cohort studies (in rural KwaZulu-Natal, South Africa) to follow up a total of 16,667 uninfected individuals uninfected at baseline, observing individual HIV seroconversions over the period. With on ART was 88% less likely to acquire HIV than someone not on ART. For example, an individual living in a community with high ART coverage (90% of all HIV-infected individuals on ART) was 38% less likely to acquire HIV than someone in a low (<10%) coverage area.

Source: Tanser F et al, Science 2013
Genetic Bottleneck during HIV Transmission

Donor Recipient

Mucosal barrier

Transmission
The transmitted virus

- Transmission is associated with a severe genetic bottleneck.
- In ~70-80% of cases only a single virus moves across (Keele et al., 2008; Abrahams et al., 2009; Nofemela et al., 2010; Hallaard and others)
- Not derived from dominant population in the genital tract implying a selective process (Boernas et al., 2011)

Boernas et al., PNAS 2011
Is the transmitted virus different?

- Overall, not that different but there are some subtle differences....
- Transmitted viruses have fewer glycosylation sites (Ping et al., JV 2013)
- Enhanced cell-free infectivity, higher Env content, improved dendritic cell interaction (Parrish et al., PNAS, 2013).
- More resistant to innate factors such as IFN (Seph Borrow)
Figure 3: Hypothetical HIV superinfection transmission pattern
A sequence of a typical heterosexual sexual network involving initial transmission with an original viral strain followed by superinfection with a new viral strain. The sequence can result in the newly superinfected partner transmitting one or both of their two strains or a new recombinant strain to a subsequent partner. Although this demonstrates a heterosexual pattern, a similar pattern would be anticipated for men who have sex with men and intravenous drug users.
Figure 4: Representative clinical and virological aspects of HIV superinfection

Putative representative graph indicating the HIV viral load, CD4 cell count, CD8 cytotoxic T-lymphocyte response, and anti-HIV neutralising antibody (NAb) response of a typical case. The spike shown in viral load during superinfection is similar to what is found during acute infection, which might or might not result in superinfection. As also shown after superinfection.
Women who later became HIV-1-infected had higher pre-infection genital inflammation.
INFECTION TIME LINE

MINUTES TO HOURS
Crossing the barrier and viral attachment

HOURS-DAYS
Primary local propagation in initial target/founder population

DAYS
Secondary local expansion influx and activation of additional target cells
Viral dissemination to draining lymph nodes

DAYS-WEEKS
Self-sustaining propagation
Systemic dissemination

MATERIALS

Regional lymph node

Vaginal lumen

Microbicides

- Entry/fusion inhibitors (such as maraviroc)
- Reverse transcriptase inhibitors (NNRTIs such as dapivirine) (NiRTIs such as tenofovir)
- Integrase inhibitors
- Protease inhibitors

Robin J. Shattock\textsuperscript{1} and Zeda Rosenberg\textsuperscript{2}

Cold Spring Harb Perspect Med 2012;4:a007385
Entry inhibitors which are not being commonly used to treat HIV infection should be reserved for HIV prevention...

Entry inhibitors should be used to prevent HIV infection

ARV used to treat infected people
HIV requires the CD4 receptor and a co-receptor to infect cells.
HIV-1 Envelope Glycoprotein

CD4

CCR5

gp120

gp41

T-Cell Surface
Entry inhibitors being tested for HIV prevention

**CCR5**
- **Antagonist**
  - Selzentry (Maraviroc)

**gp41**
- **inhibitor**
  - D-peptide, PIE12-trimer

**Sugar Binding**
- Cyanovirin, Griffithissin, BanLec

**Antibodies**
- VRC01, PG9/16
4 sites of vulnerability on the HIV-1 envelope defined by neutralizing mAbs

- PG9 V2/glycan >12 mAbs
- PGT128 V3/glycan >25 mAbs
- VRC01 CD4bs >25 mAbs
- MPER 2F5/4E10 >5 mAbs

Long CDRH3 (>25 aa) to penetrate glycan shield

Heavily mutated (30%)

Bind lipids, autoreactive

Burton et al., Science 2012
Neutralizing antibodies PREVENT HIV infection in animal models

Moldt et al., PNAS 2012
HIV is a Moving and Evasive Target

Infinite number of viruses

? Role of Abs in immunity

Evolving neutralization profiles and viral escape

Gary Nabel, VRC
Significant advances in HIV prevention in the last few years

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
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<tbody>
<tr>
<td>Antiretroviral treatment for prevention</td>
<td>96% (73-99)</td>
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<tr>
<td>HPTN 052 Africa, Asia, Americas</td>
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<tr>
<td>PrEP for discordant couples</td>
<td>73% (49-85)</td>
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<tr>
<td>Partners PrEP Uganda, Kenya</td>
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<tr>
<td>PrEP for heterosexual men and women</td>
<td>63% (21-84)</td>
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<tr>
<td>TDF2 Botswana</td>
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<td>Medical male circumcision</td>
<td>54% (38-66)</td>
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<tr>
<td>Orange Farm, Rakai, Kisumu</td>
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<tr>
<td>PrEP for MSMs</td>
<td>44% (15-63)</td>
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<tr>
<td>iPrEX Americas, Thailand, South Africa</td>
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<tr>
<td>Sexually transmitted diseases treatment</td>
<td>42% (21-58)</td>
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<tr>
<td>Mwanza Tanzania</td>
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<tr>
<td>Microbicide</td>
<td>39% (6-60)</td>
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<td>CAPRISA 004 South Africa</td>
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<tr>
<td>HIV vaccine</td>
<td>31% (1-51)</td>
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<td>RV144 Thailand</td>
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Two correlates of protection identified:

IgG Antibodies Binding to V1V2

IgA Antibodies Binding to Env

Placebo

Vaccine, medium response

Vaccine, low response

Vaccine, high response
Beyond Neutralization: HIV Inhibition at Mucosal Surfaces

1. HIV-1 enters the mucous layer
2. HIV-1 interacts with Stratified squamous epithelium
3. Langerhan or dendritic cell
4. CD4+ T cell
5-9. HIV-1 interaction with: CD4, CCR5, α4β7

10-11. Macrophage FcR-mediated phagocytosis of virions and ADCC of virus infected CD4+ T cells

Mucosal layer

HIV-1-infected cell

Columnar epithelium

Mucosal layer
