HIV Pathogenesis

Clinical Implications

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Learning Objective

At the conclusion of this session, participants should be able to apply recent advances in our understanding of HIV pathogenesis to the clinical care of HIV infected patients.

HIV Pathogenesis: Clinical Implications

• HIV Transmission
• HIV Lifecycle and Host Cell Interactions
• HIV and the Host Immune Response

Case

• 30 yo F presents with fever and sore throat
• Reports she had unprotected vaginal intercourse with a new male partner three weeks ago
• Exam shows oral ulcers and a maculopapular rash
• HIV ELISA: negative; HIV RNA 10 million copies/mL
• Diagnosed with acute HIV infection

HIV Transmission: Estimates

• Sexual: ~ 1 in 1000 coital acts
  – Male receptive anal intercourse: 1 in 10 to 1 in 1600
  – Male to female vaginal intercourse: 1 in 200 to 1 in 2000
  – Female to male vaginal intercourse: 1 in 700 to 1 in 3000
• Mother to infant: ~ 1 in 4 (in absence of antiretroviral therapy (ART))
• Blood transfusion (contaminated unit): ~ 95 in 100
• Needle sharing: ~ 1 in 150
• Needle-stick injuries in health-care workers: ~ 1 in 300

Risk Factors for Sexual Transmission

• High viral load (VL)
• Sexually transmitted infections/genital ulcer disease
• Uncircumcised male partner
Sexual Transmission of HIV

Clinical Implication: Advances in Microbicide Research

- Vaginal microbicides aim to prevent transmission of HIV by blocking the virus from crossing the vaginal mucosa
- Multiple microbicides have been tested, with no evidence of efficacy
- Results of a phase II study of PRO 2000 were recently presented
  - Synthetic polyanionic polymer
  - Prevents the binding of HIV to cells
  - Compatible with the use of latex condoms

Microbicides and Gels

- Phase 2B study of PRO 2000 (N=3,087 women from Africa and US)\(^1\)
  - 4 arms: PRO 2000, Buffered gel, Placebo gel, Control
  - Buffered and placebo gel not effective
  - PRO 2000 associated with a 30% reduction in HIV transmission compared with placebo (p=0.10)

<table>
<thead>
<tr>
<th></th>
<th>No. HIV Infections</th>
<th>Women-Yr F-Up</th>
<th>Incidence Rate (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>PRO 2000</td>
<td>36</td>
<td>1332</td>
<td>2.7 (1.9 – 3.7)</td>
</tr>
<tr>
<td>Buffered Gel</td>
<td>54</td>
<td>1334</td>
<td>4.3 (2.7 – 5.8)</td>
</tr>
<tr>
<td>Placebo Gel</td>
<td>51</td>
<td>1305</td>
<td>3.9 (2.9 – 5.1)</td>
</tr>
<tr>
<td>No Gel</td>
<td>53</td>
<td>1318</td>
<td>4.0 (3.0 – 5.3)</td>
</tr>
</tbody>
</table>

Hazard Ratio vs Placebo Hazard Ratio vs Buffered

- PRO 2000 0.70 (0.46 – 1.08), \(P=0.10\)
- Buffered Gel 1.10 (0.75 – 1.62), \(P=0.63\)
- Placebo Gel 1.05 (0.72 – 1.55), \(P=0.78\)

Microbicides and Gels

Clinical Implication: Effect of Antiretroviral Therapy on Transmission

- Risk of sexual transmission between serodiscordant couples is related to the VL in the positive partner
  - Transmission risk from a person on ART whose VL is consistently <50 is thought to be extremely low
  - Swiss Federal Commission stated that risk is negligibly low
- However, HIV can be found in semen of patients whose plasma VL is undetectable

- A case report of transmission from a patient whose VL was <50 indicates that risk is not zero

HIV Pathogenesis: Clinical Implications

- HIV Transmission
- HIV Lifecycle and Host Cell Interactions
- HIV and the Host Immune Response
HIV Lifecycle

**HIV Lifecycle: Entry**
- HIV envelope (gp120) binds to the CD4 molecule and to either the CCR5 coreceptor (R5-tropic virus) or the CXCR4 coreceptor (X4-tropic virus).
- Binding induces a conformational shift in the HIV envelope, which mediates fusion of the viral membrane with the host membrane and entry of virus into the cell.

**HIV Entry Inhibitors**

**Control of HIV by Transplantation with CCR5-negative Stem Cells**
- 1% of the Caucasian population has a homozygous CCR5 delta 32 deletion.
  - Confers natural resistance to HIV acquisition.
- Case report:
  - 40 yo M with HIV infection & AML underwent stem cell transplantation from a CCR5 delta 32 homozygous donor.
  - After the transplant, the patient stopped ART and has had no detectable viremia for at least 20 months.

**Clinical Implications**
- Studies of approaches to modify CCR5 levels on CD4 cells or on stem cells are being studied, e.g., RNAi.
- Whether such approaches will select for emergence of X4-tropic HIV is uncertain.

**HIV Lifecycle: Integration**
- Following entry, HIV RNA is reverse transcribed into DNA.
- The viral DNA is integrated into the host genome.
- HIV integrase catalyzes this integration process.
Case (continued)

- 30 yo F diagnosed with acute HIV infection
- Over the next 2 years, her CD4 cell count drops to <350/mm³
- Started on antiretroviral therapy with tenofovir, emtricitabine and efavirenz and achieves an undetectable HIV RNA
- She asks you “Doc, will this treatment cure my infection?”

What prevents eradication of HIV in patients on suppressive antiviral therapy?

1. Virus attached to the surface of CD4 cells cannot be detached by current therapy
2. Persistence of unintegrated HIV in the cytoplasm
3. Long-lived latently infected CD4 cells
4. Decline of immune responses against the virus
5. Non-adherence

Establishment of the latent reservoir

- HIV
- Infection of activated CD4 cell and integration of virus into the genome
- Reversion of activated T cell to a resting, memory CD4 cell
- Latently-infected resting memory CD4 cell
  1. Long-lived
  2. No expression of viral gene products
  3. Not seen by the immune system
  4. Established during acute infection

Long half-life of the latent reservoir

- Possible mechanisms:
  - Intrinsic stability of memory CD4+ T cells
  - Ongoing low level viral replication leading to replenishment of the latent reservoir
- Most patients on combination ART have persistent low-level residual viremia (usually 1-10 copies/mL)
- Does this residual viremia represent ongoing HIV replication that replenishes the latent reservoir or is it simply episodic release of virus from stable reservoirs?
- Studies of intensified ART may help answer this question
No Decrease in Residual Viremia after ART Intensification with Raltegravir (RAL)

- Does intensification of ART by adding RAL decrease low level viremia?
- 9 subjects with detectable low-level viremia on a single copy assay added RAL to their regimen for 30 days
- HIV RNA measured weekly before, during and after intensification
- Result: No decrease in HIV RNA
- Larger studies of RAL intensification for longer periods ongoing (e.g. ACTG 5244).

HIV RNA Level Pre- and Post-Intensification

<table>
<thead>
<tr>
<th>Pre-Intensification</th>
<th>Intensification</th>
<th>Post-Intensification</th>
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<tbody>
<tr>
<td>0.04 l</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>P=0.89</td>
<td>P=0.38</td>
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Jones J. et al. 16th CROI; Montreal, Canada; 2009. Abst. 423b.

Intensive ART: No Decline in Latent Reservoir

- ACTG A5173 was a single arm study in treatment-naive patients of intensive multi-target therapy with Enfuvirtide + TDF/FTC + SQV/r for 96 wks to determine impact on latent HIV reservoir (N=19)
  - 9 subjects maintained VL <50 and continued on the intensive regimen for at least 48 weeks
  - No evidence for decay in the frequency of latently infected cells (95% CI for half-life: 11 months to infinity)
  - Conclusion: an intensive multi-target induction strategy was not effective at decreasing the number of latently-infected cells

Gandhi R. et al. 16th CROI; Montreal, Canada; Abst. 424.

HIV Pathogenesis: Clinical Implications

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- HIV and the Host Immune Response

Natural history of Untreated HIV infection: Viral load and CD4 Count

Acute HIV Chronic HIV Late HIV

Adaptive Immune Response to HIV

1. Neutralizing antibodies (Nab)
2. CD8+ cytotoxic T lymphocytes (CTL)
3. CD4+ T helper cells (Th)

Courtesy of Bruce Walker and Eric Rosenberg
Failure of the Immune System to Control HIV

- In most infected patients, immune system fails to control viral replication
- Possible explanations:
  - Rapid viral mutation leading to escape from neutralizing antibodies and CD8+ CTL
  - HIV-mediated CD4 cell loss and dysfunction, leading to inadequate help for B cells and CD8+ CTL
  - Intrinsic defects in CD8+ CTL, including decreased cytokine production, decreased proliferation, decreased polyfunctionality, lack of effector function

Case (continued)

- 30 yo F diagnosed with acute HIV infection
- Two years later, she initiates antiretroviral therapy and achieves an undetectable HIV RNA and a normal CD4 cell count
- She asks you “Is my immune system normal now?”

During HIV Infection, When Are the Majority of the Body’s CD4 Cells Lost?

1. During the first few weeks after acquisition of HIV (acute infection)
2. During the chronic phase of HIV infection, when the patient is asymptomatic
3. During the late stage of infection, when the patient develops opportunistic infections and other complications of AIDS
4. Equally throughout the course of infection

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Acute HIV Infection: The Die is Cast

- HIV infection is characterized by loss of CD4 cells
- Most CD4 cells reside in the GI associated lymphoid tissue (GALT). Only 1 - 2% of total body T cells are in the peripheral blood.
- Early in infection there is dramatic depletion of CD4 cells within GALT.
- Damage to GI tract may lead to abnormal microbial translocation and persistent immune activation.

Immune Activation and Disease Progression

Immune Activation and Disease Progression

- Animal models suggest that persistent T cell activation is associated with development of immunodeficiency
  - Sooty mangabeys, the natural host of SIV, have high levels of viremia but do not develop persistent immune activation and remain healthy
  - Rhesus macaques infected with SIV develop viremia, persistent immune activation and develop clinical immunodeficiency
- CD8 cell activation predicts HIV disease progression in patients who are not on ART
- Persistent T cell activation is associated with impaired CD4 cell count recovery in patients on ART


T Cell Activation Persists in Patients on ART

- 99 HIV-infected adults with suppressed VL for a median of 21 months were compared to HIV-uninfected controls

Imune Activation and CD4 Cell Decline

- HIV elite controllers are patients who are not on therapy but maintain undetectable VL
- Controllers have higher T cell activation than HIV-uninfected patients and ART-suppressed patients
- 10% (3/30) of elite controllers had CD4 cell counts <350 and 7% had AIDS
- In controllers, higher T cell activation associated with lower CD4 cell counts
  - Consistent with hypothesis that activation influences CD4 cell count decline and immunodeficiency


Chronic Inflammation and Atherosclerosis

- Carotid IMT, a measure of atherosclerosis, is higher in HIV-infected patients than in HIV-negative controls, even after adjustment for CV risk factors
- Even HIV elite controllers (who had not received ART and did not have viremia) had higher carotid IMT than HIV-negative individuals
- IMT in controllers was similar to IMT in ART-untreated HIV-infected patients
- CRP levels higher in HIV-infected patients, including controllers, than in HIV-negative individuals
- Suggests chronic inflammation, perhaps related to immune activation, may contribute to accelerated atherosclerosis in HIV-infected patients

Hsue P AIDS 2009 23, e-pub

Clinical Implications

- Immune modulators may have a role in preventing HIV disease progression in patients not yet on ART
- Residual immune activation in patients with virologic suppression may be associated with non-AIDS related complications, such as atherosclerosis
- Interventions to reduce residual viremia and abnormal inflammation should be studied

Summary: Clinical Implications of Pathogenesis Research (1)

- HIV Transmission
  - Microbicide studies are ongoing, with a glimmer of hope for the agent PRO 2000
- HIV Lifecycle and Host Cell Interactions
  - Viral entry has been effectively targeted to inhibit HIV replication; new approaches to modify CCR5 levels on stem cells are being explored
  - HIV integration into the genome results in a long-lived latent reservoir, which prevents eradication of HIV; approaches to activate HIV from the latent reservoir should be studied
Summary: Clinical Implications of Pathogenesis Research (2)

- HIV and the Immune Response
  - HIV elicits a vigorous immune response, but in most patients this response cannot control viral replication
  - HIV causes persistent immune activation, perhaps through early damage to the GI tract and ensuing microbial translocation
  - Persistent immune activation may contribute to CD4 cell decline and to non-AIDS related morbidity. Interventions to modulate activation and inflammation should be explored.

Questions or comments

The Johnson Treatment

Extra Slides

HIV Lifecycle: Cellular antiviral factors
(Host restriction factors)

- Host cellular proteins can interfere with HIV replication
- HIV has developed counteracting gene products to overcome these cellular antiviral factors

New host restriction factors: Tetherin and CAML

- HIV replication involves budding of newly-produced virus from the cell surface
- 2 different proteins—tetherin and CAML—prevent HIV from budding from the cell
- The HIV protein Vpu seems to counteract the effects of these two antiviral host factors

Discovering New Host Restriction Factors

- Using a strategy to inhibit gene expression, 273 human proteins involved in HIV replication discovered
  - Only 36 of these HIV dependency factors had been previously identified
  - Some may be good therapeutic targets
Clinical implications

- Disrupting the interaction between host cellular defenses and the virus may be a novel mechanism for inhibiting HIV replication

- Caveat: Unclear if the currently identified host restriction factors can be therapeutically exploited without causing undue toxicity