HIV: A 60 Year Retrospective

1959 Serum from Bantu Male @ Kinchasa DRC => ZR59
Suggests single trans-species jump in 1940-1950 and radiation after WWII
YBF30 is a sequence outlier isolated from a patient in Cameroon
Disease Progression

Pathological conditions associated with HIV-1 infection:

Acute phase:
- Malaise, headache, myalgia, weakness, fever, rash, pharyngitis, lymphadenopathy, oral ulcers, maculopapular rash, neutropenia

Asymptomatic phase:
- Often, some patients may present specifically with one or more of the following symptoms: fatigue, mild weight loss, generalized lymphadenopathy, night sweats, or body aches and pains, shingles

Symptomatic phase and AIDS:
- CD8+ T cells become generalized, lymphadenopathy, and lesions may appear: hairy leukoplakia, aphthous ulcerations, thrush, esophagitis, molluscum contagiosum, basal cell carcinomas of the skin, laryngeal carcinoma, angioedema, reactivation of herpes simplex virus

Less than 200 CD4+ T cells per mm³
- Fungal infections: cryptococcosis, candidiasis, histoplasmosis
- Bacterial infections: mycobacterium avium, tuberculosis
- Fungal infections: aspergillosis, cryptococcosis, histoplasmosis
- Herpes and varicella zoster

Viral infections and malignancies: human cytomegalovirus, respiratory viruses, dental or genitai HSV, lymphoma, hairy cell leukemia, HHV, HHV-8, Kaposi's sarcoma, HHV-1, mononucleosis, HHV-6

Neurological symptoms: encephalitis, myelitis, myelopathy, spinal cord demyelination, peripheral neuropathies, as well as dementia, stroke, myelopathy, motor neuron disease, and multiple sclerosis

Symptomatic polynuropathy/myelopathy: polyneuropathy, AIDS dementia complex (ADC)

Clinical Picture

Varicella zoster

Pneumocystis carinii

Hairy leukoplakia

Oral candida
Modes of Horizontal Transmission

(11-60% depending on severity of maternal infection and ±breastfeeding)
• 36.1 million worldwide are infected
• Another 21.8 million have died
• 13.2 million children currently are “AIDS Orphans”
• 14,000 new infections daily (5.3 million in 2000)
• 70% of cases in sub-Saharan Africa where seroprevalence can exceed 25%
• Caribbean, Southeast Asia and Eastern Europe are other trouble areas
HIV belongs to the lentivirus subclass of retroviruses

- 2 copies of the +RNA strand; goes through a dsDNA intermediate
- icosahedral capsid
- enveloped
- 80-130 nm virion

Virus Taxonomy

<table>
<thead>
<tr>
<th>Family name</th>
<th>Reo</th>
<th>Birnaviruses</th>
<th>Caliciviruses</th>
<th>Picornaviruses</th>
<th>Flaviviruses</th>
<th>Togaviruses</th>
<th>Retroviruses</th>
<th>Coronaviruses</th>
<th>Filoviruses</th>
<th>Paramyxoviruses</th>
<th>Arena</th>
<th>Parvoviruses</th>
<th>Pappovaviruses</th>
<th>Adenoviruses</th>
<th>Hepadnaviruses</th>
<th>Herpesviruses</th>
<th>Iridoviruses</th>
<th>Baculoviruses</th>
<th>Poxviruses</th>
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<tbody>
<tr>
<td>Virion polymerase</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
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</tr>
<tr>
<td>Virion diameter (nm)</td>
<td>60-80</td>
<td>60</td>
<td>35-40</td>
<td>28-30</td>
<td>40-50</td>
<td>60-70</td>
<td>80-130</td>
<td>80-60</td>
<td>80</td>
<td>100</td>
<td>90-120</td>
<td>90-140</td>
<td>130-300</td>
<td>30-300</td>
<td>50-300</td>
<td>18-26</td>
<td>45-55</td>
<td>70-90</td>
<td>90</td>
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<tr>
<td>Genome size (total in kb)</td>
<td>23-37</td>
<td>7</td>
<td>8</td>
<td>7.2</td>
<td>8.4</td>
<td>10</td>
<td>12</td>
<td>3.5</td>
<td>9</td>
<td>16-21</td>
<td>12.7</td>
<td>13-16</td>
<td>13.5-21</td>
<td>13.6</td>
<td>16-20</td>
<td>10-14</td>
<td>6</td>
<td>5-8</td>
<td>36.38</td>
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</tbody>
</table>
Anatomy of a Retrovirus

-NEF Attenutation
Viral Replication Cycle

- $10^9$ copies/day in fulminant AIDS
- Every single-base mutation of the genome occurs at least once per day per patient
RT Inhibitors

Nucleoside:

- Zidovudine (AZT)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)

Non-Nucleoside:

- Nevirapine
- Delavirdine
- Loviride
- Efavirenz
Protease Inhibitors

Indinavir

Nelfinavir

Ritonavir

Saquinavir

Amprenavir
Retroviral Drug Resistance in New Patients

Temporal Changes in the Prevalence of Drug Resistance at Base Line.*

<table>
<thead>
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<tbody>
<tr>
<td>High-level drug resistance (phenotype assay)†</td>
<td></td>
<td>9/264 (3.4)</td>
<td>14/113 (12.4)</td>
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<tr>
<td>Any antiretroviral drug</td>
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<td>6/264 (2.3)</td>
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<tr>
<td>NNRTIs</td>
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<td>8/113 (7.1)</td>
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<td>PIs</td>
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<td>9/113 (8.0)</td>
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<tr>
<td>Multidrug resistance</td>
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<td>3/264 (1.1)</td>
<td>7/113 (6.2)</td>
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<tr>
<td>Major drug-resistance mutations (genotype assay)</td>
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<td>17/213 (8.0)</td>
<td>20/88 (22.7)</td>
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<tr>
<td>Any antiretroviral drug</td>
<td></td>
<td>15/176 (8.5)</td>
<td>12/82 (15.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td>3/176 (1.7)</td>
<td>6/82 (7.3)</td>
<td>0.03</td>
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<tr>
<td>PIs</td>
<td></td>
<td>2/213 (0.9)</td>
<td>8/88 (9.1)</td>
<td>0.001</td>
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<tr>
<td>Multidrug resistance§</td>
<td></td>
<td>8/213 (3.8)</td>
<td>9/88 (10.2)</td>
<td>0.05</td>
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</tbody>
</table>

*Both resistance assays were performed at ViroLogic. NNRTI denotes nucleoside reverse-transcriptase inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.
†P values are two-sided and were determined by Fisher’s exact test.
‡Data are numbers (and percentages) of samples containing virus with a 50 percent inhibitory concentration (IC₅₀) that was more than 10 times that of a reference virus.
§These results did not change when T215D, T215N, T215S, T215C, and T215E mutations were excluded from the analysis (i.e., all subjects with a revertant mutation detected at position 215 had at least one additional major drug-resistance mutation).
HIV Vaccine

• >50 preparations have entered clinical trials (HIV Vaccine Trials Network)
• 1997 Clinton’s HIV vaccine challenge: 10 years
• NIH currently spends >500 million/year on trying to find an HIV vaccine
• NOTHING! (punctuated equilibrium)
• Do aspects of the immune response facilitate HIV pathogenesis?

Broadly Neutralizing Antibodies

• mAB b12: convex recombining site
• 447-52D: V3 GPGR motif and main-chain (MHC)
• mAb 2G12: domain-swap binds oligomannose
• 2F5, 4E10: TM epitopes
Where Else to Attack?
HIV Association with Targets

- CCR5 Homozygous Mutants are HIV resistant and otherwise healthy
- RANTES promoter overexpression mutants are HIV resistant
SNARE proteins Mediate Membrane Fusion Inside Cells
Energy from Helix Coiling Drives Fusion
The Model for Viral Fusion
Preventing HIV Entry

- PRO542 (Progenics): gp120 tetramer to IgG Fc that blocks CD4-gp120 interaction
- BMS-806 (Bristol-Myers Squibb): small molecule that targets the CD4 binding site on gp120
- TNX-355 (Tanox): an anti-CD4 antibody
- SCH-C, SCH-D (Schering-Plough) and UK-427,857 (Pfizer): block CCR5
- AMD3100, AMD070 (AnorMED): block CXCR4
Other Ideas

- TRIM5a: a species restriction factor that is an E3! (*J. Vir.* 79(14): 8870-8877 2005)
- Target HIV immunomodulators (Vpr, Vpu, etc.)
- Block inflammatory response
The Future of the Arms Race?
