Retroviruses

• Introduction
• Molecular Biology/Replication
• Retroviruses in Human Populations
• Emergence/Spread
• Lessons
HIV-1 pandemic and risk

Total: 36.7 million [34.0 million–39.8 million]
Retroviruses

•Molecular Biology/Replication
Retroviruses

A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.

A different paradigm for replication

Transition from RNA World?
Reverse Transcriptase and Retroelements are all around you

- Avian Retroviruses
- Human
  - Primate
  - Rodent
- Porcine
- Fish
- Plant
- Fruit fly
- Roundworm retrovirus
- Bacterial retroplasmids
Retrovirus classification

Retroviruses
Classification by RT Sequence into Seven Families

- **Spumavirus**  exog. infection from primates, no oncogenes
  - MLV  endo/exo oncogene  numerous mammals

- **Lentiviruses**  HIV-1,-2, SIV, EIAV, CAEV, VISNA

  - **D-type viruses**  Primates-MPMV, SAIDS
  - **B-type viruses**  endog/exogen milk-borne agent-mouse
    Some T cell lymphoma in mice
  - **ALV-related**  endog/exogen avian oncogene
  - **BLV-HTLV**  exog, no oncogenes, neoplasms

Line length not to scale  AND THERE IS NO UNIFORM TIME SCALE
Lentivirus Relationships

HIV-2
  SIV-smm
  SIV-syk
  HIV-1
  SIV-cpz
  SIV-agm
    SIV-mnd
  VMV
    CAEV
    EIAV
    BIV
  FIV

1 % difference
Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120
Retroviruses Conventions

The viral genome is RNA

The integrated genome is called the provirus

Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120
Retroviruses Glossary

- **gag:** group antigen
- **pol:** polymerase
- **env:** envelope
- **tat:** Transactivator
- **rev:** Regulator of Expression of Virion proteins

- U3: unique sequence in 3’ region
- U5: Unique sequence in 5’ region
- R: Repeat sequence
- PBS Primer binding site for initiation of RT
- Ppt: polypurine tract primer for RT
- TAR: Tat activating sequence
- RRE: Rev responsive element
- Provirus: copy of retrovirus that is integrated into host genome
HIV Virion
HIV replication

HIV Replication

- Attachment/Entry
- Reverse Transcription
- Integration
- Reverse Transcription
- RNA Processing
- Translation
- Assembly
- Maturation
HIV attachment and Entry

HIV Attachment and Entry

- **Virus Factors**
  - Attachment: Env glycoprotein gp120
  - Entry: Env glycoprotein gp41

- **Host Cell Factors**
  - Receptor
    - CD4
  - Co-receptor (major)
    - CXCR4
    - CCR5
HIV Coreceptor Blockade

- Crystallographic Structure
- Model Inhibitors

- Multiple binding domains predicted
- Binding disrupts structure generally
- Does not require blocking CCR5-gp120 interaction
- Potential for simultaneous inhibition
- Resistance emerges by reducing affinity for drug

Maeda, JBC, 2006
A spring-loaded mechanism that drives the membranes together to overcome a high energy barrier to
Uncoating

HIV Replication

- Attachment/Entry
  - Reverse Transcription
  - Integration
  - Transcription
  - RNA Processing
  - Translation
  - Assembly
  - Maturation

Maturation

Assembly

Translation

RNA Processing

Uncoating

CYTOPLASM

HIV virion

Attachment
Post-Entry Events

HIV Post – Entry Events

- Uncoating is a fundamental step in virus replication
  - Restricts replication
  - Source of host range restriction
- Requires interactions between viral and cellular factors
- Virus
  - Gag
- Cell
  - Trim 5 – alpha
## HIV Post - Entry Events

### Host Trim5 Alpha

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>Human</th>
<th>Chimp</th>
<th>Monkey</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Infection</td>
<td>Infection</td>
<td><strong>NO INFECTION</strong></td>
</tr>
<tr>
<td>SIV Chimp</td>
<td><strong>INFECTION</strong></td>
<td>Infection</td>
<td>Poor infection</td>
</tr>
<tr>
<td>SIV Monkey</td>
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</tbody>
</table>
Reverse transcription
Trim 5-alpha

Positive Selection in Trim 5-alpha

- Trim 5 alpha undergoes genetic change faster than many genes
- Working hypothesis
  - human populations undergo waves of pandemics
  - Humans that survive have trim 5alpha variant that excludes infection

Generals are Always Fighting The Last War
Evolution can solve this problem but it will take time
Integration

Figure 4

Reverse Transcription

Integration
Enzymatic Activities

Reverse Transcriptase
Enzymatic Activities

• RNA-dependent DNA Polymerase
• RNase H
• DNA-dependent DNA Polymerase
• Error rate on order of 1-4 / 100,000 bases synthesized
• Recombination occurs during reverse transcription permitting reassortment of sequences
• Replication rapid and error prone

MUTANTS ARE LIKELY TO EXIST PRIOR TO THE THERAPY
Error-Prone HIV Replication is a Pathogenic Determinant

- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral “fitness”) may vary greatly.
- The virus population can respond rapidly to a selective pressure.
Transcription
Integration

Multistep reaction

Strong inhibitors

Hazuda 2005
Translation of HIV $gag/pol$ and $env$ Paradigm: Process Polyprotein Precursors
HIV Particle Maturation

Immature Particle
Noninfectious

HIV Protease

Mature Particle
Infectious
Retroviruses

• Retroviruses in Human Populations
Lentivirus relationships

HIV-2
SIV-smm

SIV-syk

HIV-1
SIV-cpz

SIV-agm

SIV-mnd

VMV
CAEV

EIAV
BIV

FIV 1 % difference
HTLV-I ATL

• Long Latency (>30 years)
  • Small pediatric series in SA
• Epidemiology
  – Approximately 1% of HTLV-I infected adults
• Associated syndromes
  – Infectious
    • TB, MAC, Leprosy
    • PCP
    • Strongyloides
    • Scabies esp. Norwegian scabies
      – Noninfectious-hypercalcemia+lytic bone lesions
• Therapy-Chemotherapy, Ifn, anti-Tac
FIG. 2. Evolutionary relationships of SIVcpz and HIV-1 strains based on maximum-likelihood phylogenetic analyses of full-length envelope protein sequences (adapted from ref. 10). SIVcpz strains from *P. t. troglodytes* and *P. t. schweinfurthii* are highlighted in red and blue, respectively. Representative strains of HIV-1 groups M, N, and O were included for comparison. Asterisks indicate internal branches with estimated posterior probabilities of 95% or higher. The scale bar denotes 10% replacements per site.
Bushmeat trade in Africa

Bushmeat Trade in Central and West Africa

Poacher

Chophouse

Bushmeat market
HIV expansion

Korber, Science 2000
HIV Spread

- **Biologic**
  - Blood and body fluid
  - Iatrogenic
    - Blood transfusion
    - Vaccination – needles not vaccine
  - Mother to Child

- **Non-Biologic**
  - Political
  - Economic
  - Multiple Epidemics
HIV Spread

- Modes of Transmission
  - Political

Consequences of large political upheaval are population movement and potential for malnutrition and immunodeficiency.
HIV and population expansion

Zoonotic Transmission of HIV Coincides with Population Expansion in Africa

http://www.populstat.info/
HIV Spread

- Modes of Transmission
  Trans Africa Highway
HIV evolution

Central Africa (subtype D)

Trinidad and Tobago 1993-1996

Pandemic clade

USA, Canada, Argentina, Colombia, Brazil, Ecuador, Netherlands, France, UK, Germany, Estonia, Gabon, South Africa, South Korea, etc.
Cumulative U.S. AIDS cases as of 2/83 \( N = 1000 \)

Cumulative U.S. AIDS Cases
as of 2/83 \( N \sim 1,000 \)

Each point = 30 cases
Cumulative U.S. AIDS cases as of 5/85 N = 10,000

Each point = 30 cases
Cumulative AIDS cases as of 7/89 N = 100000

Cumulative U.S. AIDS Cases as of 7/89 N ~ 100,000

Each point = 30 cases
Cumulative AIDS cases as of 12/95 N = 500,000
New cases of AIDS

New cases of HIV/AIDS—USA

- Geographic spread from metropolitan areas
  - ~12% of cases in locations with population <50,000
- Women
  - comprise > 25% of all AIDS cases
- Age
  - 11% of AIDS cases are 50+ years old
  - c.50% of persons living with HIV are >50 yo

JAMA 2008
HIV Therapy and Beyond
If you get the AIDS virus now, you and your license could expire at the same time.
Gardner Continuum of Care

HIV Care Continuum Shows Where Improvements are Needed

In the US, 1.2 million people are living with HIV. Of those:

- **Diagnosed**: 86%
- **Engaged in Care**: 40%
- **Prescribed ART**: 37%
- **Virally Suppressed**: 30%

Sources: CDC National HIV Surveillance System and Medical Monitoring Project, 2011.
Key Advances in HIV Therapy

- **PrEP**
  - Adherent prophylaxis is effective

- **SMART Study**
  - Continuous therapy essential to avoid AIDS and other complications

- **START Study**
  - Earlier therapy is initiated, greater preservation of therapy
Next Advances in HIV Therapy

• Vaccines
• Cures
Retroviruses

• Lessons
Summary

- Viruses are bad and should be avoided
- Except when they save the planet
- And maybe if it saves you from the next virus
- Epidemics are not single events
- Epidemics evolve
- Antivirals are useful
  - Instituted as early as possible
  - Adherence is essential