Retroviruses and AIDS
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- History of retroviruses
- Biology of HIV/AIDS and some advances in the last decade
AIDS death rate males age 25-44

FIGURE 1. Death rates* from leading causes of death among men aged 25-44 years, by year — United States, 1982-1994†

*Per 100,000 population.
History

- Vallee and Carre 1904 equine infectious anemia was a “filterable” agent
- Ellermann and Bang 1908 leukemia in the chicken was a “filterable” agent
- Peyton Rous 1911 sarcoma in chickens caused by “filterable” agent
- Bittner 1942 mammalian RNA tumor virus Mouse Mammary Tumor Virus (MMTV)
- 1970 Baltimore and Temin simultaneously discover Reverse Transcriptase in retroviruses
- 1976 Bishop and Varmus discover the src gene has a counterpart in normal cells
History Cont.

- 1980 a retrovirus associated with human leukemia HTLV-I
- 1983 a retrovirus associated with acquired immune deficiency syndrome HTLV-III, ARV or LAV now HIV
1975 Nobel Prize in Medicine

- David Baltimore
- Howard Temin 1934-1994
- Prize was shared with Renato Dulbecco
Bishop and Varmus

Recipients of the 1989 Nobel Prize in Medicine
HOW TO WIN THE NOBEL PRIZE

{An Unexpected Life in Science}

J. MICHAEL BISHOP
Harold also wrote a memoir in 2009
Varmus in his Nobel lecture said:

- In describing the formation of RSV DNA
- “These problems were solved by the unexpectedly elegant configuration of viral DNA, as worked out mainly by Peter Shank, Steve Hughes, and Hsing-Jien Kung in our group.”
Nobel Prize in Medicine 2008

Luc Montagnier  Francois Barre-Sinoussi
shared with Harald vur Hausen
Retrovirus Structure

- Positive polarity RNA *ca.* 7-11 kb
- RNA capped and polyadenylated *but doesn’t* function as mRNA
- Enveloped particles *ca.* 100 nM dia
- *Only diploid viruses*, 2 identical RNAs per virion
- Replication via a complex process of reverse transcription
- Found in every vertebrate species where they have been looked for
- 8% of the human genome is derived from retroviral sequence
HIV-1
Structure of a simple retroviral genome

Reverse transcription doesn’t just copy the RNA
Why does the retrovirus go through such a complex process?

- All retroviruses do exactly the same thing
- It is the only way then can replicate if they integrate randomly into the cell
- The U3 region encodes the viral promoter
- What the process of reverse transcription does is duplicates the promoter and put it “upstream” of the genome
Retroviral replication phase I

Infection of target cell

1. HIV gp120 binds to CD4 on target cell.
2. Fusogenic domain in gp41 and CXCR4, a G-protein–linked receptor in the target-cell membrane, mediate fusion.
3. Nucleocapsid containing viral genome and enzymes enters cells.
4. Viral genome and enzymes are released following removal of core proteins.
5. Viral reverse transcriptase catalyzes reverse transcription of ssRNA, forming RNA-DNA hybrids.
6. Original RNA template is partially degraded by ribonuclease H, followed by synthesis of second DNA strand to yield HIV dsDNA.
7. The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the viral integrase enzyme.

RT lacks a proofreading exonuclease
RNA Pol II lacks a proofreading exonuclease
AIDS first reported in MMWR May 1981

- Based on astute clinical observations
- *Pneumocystis* Pneumonia --- Los Angeles
- Reported on five young men (29-36)
- All patients MSM
- Two had died
- All had past or current CMV infections and mucosal candidal infections
Current Status
Global HIV Burden

Adults and children estimated to be living with HIV

- North America and Western and Central Europe: 2.4 million (1.5 million – 3.5 million)
- Eastern Europe & Central Asia: 1.5 million (1.3 million – 1.8 million)
- Caribbean: 280,000 (210,000 – 340,000)
- Middle East & North Africa: 240,000 (150,000 – 320,000)
- Latin America: 1.7 million (1.4 million – 2.0 million)
- Sub-Saharan Africa: 25.8 million (24.0 million – 28.7 million)
- Asia and the Pacific: 5.0 million (4.5 million – 5.6 million)

Total: 36.9 million (34.3 million – 41.4 million)

UNAIDS
2015/6 AIDS data

- Infected 36.7M, The majority in Sub-Saharan Africa *i.e.* 1 in 20 are infected
- *Ca.* 18.2M on therapy (*ca.* 20M or more eligible)
- New infections *ca.* 2.1M
- Deaths 1.2M
- *Ca.* 12M orphans in Africa
- Overall 60M infections and 25M deaths
HIV and the development of AIDS

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Seroconversion
Acute phase
Chronic phase
Anti-HIV antibody
Death

CD4^+ T-cell count in blood (cells/mm^3)

Viral load in blood (HIV RNA copies/ml plasma)

Weeks
0 1 2 3 4 5 6 7 8 9 10 11

Years

CD4^+ T cells
HIV viral load
Where did HIV come from?

- The CIA?
- The smallpox eradication program?
- The polio vaccine trials in the Belgian Congo?
- Molecular analysis now shows that HIV-1 originated from a simian virus infecting chimpanzees (SIV\textsubscript{cpz}) and has been transferred to humans multiple times.
- HIV-2 originated from a distinct simian virus infecting sooty mangabey (SIV\textsubscript{smn}).
- Sequence divergence suggest HIV-1 has infected humans for \textit{ca.} 100 years originating in Leopoldville, now Kinshasa.
HIV groups and clades

Clades

B US and Western Europe A,C Africa, Asia C and E
Clades

- Differ by 20% amino acid in Env
- Differ by 15% in Gag
- Major implication for vaccine trials
1970s and ‘Patient 0’ HIV-1 genomes illuminate early HIV/AIDS history in North America

- Concludes that the clade B virus in the US came from Africa to Haiti around 1967 and New York around 1970
- New York rather than San Francisco or LA was the epicenter for the US epidemic and that the virus moved west around 1976
The early patterns of HIV-1 subtype B spread in the Americas

HIV-1 shown in DNA form
The unusual genes of HIV classified as regulatory or accessory

- Regulatory genes *tat* and *rev* are essential for replication
- Accessory genes *vif*, *vpr*, *vpu* and *nef* are dispensable for growth under some circumstances
Tat interacts with TAR to allow extension of the initial transcript.
Rev leads to export into the cytoplasm access to splicing machinery
Both Nef and Vpu down regulate CD4
It has been known for quite some time that Vpu increases viral release in some cells.

Recently it has been shown that Vpu antagonizes the function of a cellular protein previously called CD317 with no known function.

CD317 now called Tetherin appears to grab retroviruses as they are exiting the cell and prevents release.

Innate immunity
Tetherin function

**Diagram:**

- **a** Budding virus
- **b** Budding virus stuck
- **c** Reuptake

- Envelope
- Tetherin molecules
- Cell membrane
- Degradation
Another effect of Nef
Yet Another function of Nef?

- Two recent reports in *Nature*:
  - Suggest yet another function of Nef

- Both reports suggest that cellular proteins, SERINC3 and SERINC5 (serine incoporator) are incorporated into HIV envelope in the absence of functional Nef and decrease viral replication

- Intact Nef prevents incorporation of SERINC3 and SERINC5 and leads to higher levels of viral replication

- Innate immunity?

- Speculated that SERINVC3 and 5 may limit the size of the pore formed by fusion of the viral and cellular membranes
Vpr originally termed rapid

- A small protein which is present within the virion
- Vpr has two known functions
  - Arrests cells in the G2 phase of the cell cycle
  - Assists nuclear entry of the preintegration complex
APOBEC3G
Innate immunity

- Apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 (APOBEC3)
- Humans contain 5-7 such genes
- Cytidine deaminase function
- Vif excludes APOBEC3G from the virion and thus preserves newly synthesized viral DNA
- Vif minus mutants fail to replicate in CD4⁺ T cells or macrophage
- APOBEC3G inhibits replication of many retroviruses
HIV vaccine approaches

- recombinant protein (gp120)
- synthetic peptides (V3)
- naked DNA
- live-recombinant vectors (viral, bacterial)
- whole-inactivated virus
- live-attenuated virus
Efficacy testing of a clade B HIV vaccine
MRKAd5 trivalent vaccine

- Vaccine: 1:1:1 admixture of 3 Ad5 vectors
  - Encoded transgenes: codon-optimized, near-consensus clade B HIV-1 sequences
- Placebo: vaccine dilution buffer without Ad5
49 HIV infections in the vaccine group and 33 among those who received placebo (Oct 17, 2007).

But in individuals with the highest levels of Ad5 antibody, 21 infections in vaccinees compared to 9 in placebo!
The RV 144 Trial combined 2 failed vaccines

- ALVAC Canarypox expressing Gag-Pol and Env at 0, 4, 12 and 24 weeks
- AIDSVAX recombinant gp120 at weeks 12 and 24
- Called a prime – boost method
- Very large trial ca. 16,000 low to moderate risk individuals
RV 144 Results

- Over 3 years 125 people became infected
- 74 in the placebo arm
- 51 in the vaccine arm
- Efficacy 31%
- This is the first human trial to demonstrate any positive effect
Recently the NIH announced the first new vaccine trial in seven years

- The new trial called HVTN 702 is based on the RV 144 trial
- It will be conducted in South Africa and hopes to enroll 5,400 men and women
- In South Africa ca. 1000 people become HIV-1 infected every day
- NIH hopes to have preliminary results by 2020
- Still a work in progress
The huge success of US combination chemotherapy
Targets for antiviral drugs

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HIV drugs

- **NRTIs**
  - Abacavir
  - Didanosine (ddI)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Zidovudine (ZDV)
  - Tenofovir (TDF)
  - And others

- **NNRTIs**
  - Efavirenz (EFV)
  - Nevirapine

- **PIs**
  - Atazanavir (ATV)
  - Darunavir (DRV)
  - Indinavir (IDV)
  - Ritonavir (RTV)
  - And others

- **Fusin inhibitors**
  - Enfuvirtide (ENF)
  - Maraviroc

- **Integration inhibitors**
  - Raltegravir (Isentress)
## Individualized therapy

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**NRTI Mutations**: V75I, F77L, Y115F, F116Y, Q151M, M184V

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<td>Nevirapine</td>
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**NNRTI Mutations**: K103N, V108I

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- Lower Clinical Cutoff (in bold)
- Upper Clinical Cutoff (in bold)
- Biological Cutoff
- Evidence of Susceptibility
- Evidence of Partial Drug Susceptivity
- Evidence of Drug Sensitivity
- Evidence of Drug Resistance
HIV co-receptors

Figure 20-12c
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CCR5 deletion mutants

- A significant proportion of the European Caucasian population have a 32-bp deletion in both copies of CCR5 (1-3%) 
- These individuals are highly resistant HIV infection w/out other major phenotypes 
- Even heterozygous individual appear to progress less rapidly to AIDS 
- The only other known consequence of the deletion is increased susceptibility to West Nile virus
Dr. Gero Hutter, a German hematologist, was treating an American AIDS patient in Berlin.

The patient had leukemia as well as AIDS.

Hutter knew that a number of Europeans carried the 32bp deletion in CCR5.

The patient required a bone marrow transplant for his leukemia.

Hutter found a suitable CCR5 deleted donor.

Following transplant, the patient was taken off his HIV medications.

For the several years following the transplant, HIV has not been detected in the patient.
The “Berlin Patient”

Timothy Ray Brown
The NEW ENGLAND JOURNAL of MEDICINE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

HPTN 052 Trial Led to a Revolution

■ 1,763 discordant heterosexual couples
■ Infected partner w/ CD4 levels of 350-550
■ Early therapy or delayed therapy at CD4 250
■ 39 HIV infections w/ 28 coming from the infected partner
■ Only one of the 28 infections was in the treatment group
■ 96% protection!
Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Recent advances in chemotherapy

- Development of a single pill once a day (ATRIPLA) was approved by the GFDA in 2006
- Recently it has been reported that a single monthly injection can replace daily oral therapy

This paper reports that there is a conserved open reading frame in the antisense orientation present only in clade M HIV-1 isolates.
The Future?

- WHO goals 90-90-90 by 2020
- 90% people HIV tested
- 90% HIV positive people on therapy
- 90% on therapy have repressed viral load
- Plus reduction in new infections to 500,000