Lecture 6

The diversity of infectious disease agents (II)
Outline:

• Phylogenetics introduction

• Eukaryotic microparasites (especially *Plasmodium spp.)*

• Types of viruses

• Origins and evolution of viruses

• Major killers: HIV/AIDS

• Major killers: Influenza virus
Outline:

- Major killers: other respiratory viruses
- Major killers: Measles virus (and other “childhood” illnesses)
- Major killers: rotavirus (the most important pathogen you’ve never heard of)
- Vectored versus non-vectored pathogens
- Zoonoses
Introduction to phylogenetic trees...

- It’s all about ancestors and offspring, lineages branching
- The ancestor could be distant great grandmother or a human immunodeficiency virus
- The ancestral form of some gene (a “marker”) is inherited in two offspring lineages
- Let’s assume that we’re looking at virus from a “patient 0” who then infects two others
Phylogenetics interlude

- Mutations happen when genetic material is copied.
- Changes accumulate independently along each branch (within each new infectee).
- If one of these patients now infects two new victims, they inherit those changes.
Eventually, a series of branching events, plus mutations along each branch, lead to 4 current HIV infected patients.

Their viruses display genetic diversity that reflects their evolutionary history.
Phylogenetics interlude

- Unfortunately, we almost never have access to that history

- What we **can** do, is go out into nature and sample genetic markers

- Then we work **backwards** to infer the most likely series of events that gave rise to what we observe
Phylogenetics interlude

- In this case, we would infer a tree that correctly recapitulated the chain of infections...
Phylogenetics interlude

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Ancestor

1 change

1 change

2 changes

1 change

1 change

Evolutionary change
Accurate reconstruction of a known HIV-1 transmission history by phylogenetic tree analysis

THOMAS LEITNER*, DAVID ESCANILLA†, CHRISTER FRANZÉN‡, MATHIAS UHLEN§, AND JAN ALBERT*§

TRUE TRANSMISSION HISTORY AND SAMPLING TIMES

INFERRED TREE FROM GENE SEQUENCES
The three domains of life

ARCHEA

BACTERIA

EUCARYA

0.1 CHANGES/SITE
Leading infectious killers

Millions of deaths, worldwide, all ages, 1998

- Acute respiratory infections (including pneumonia and influenza): 2.3 (Over age five: 1.8, Under age five: 0.5)
- AIDS*: 3.5 (Over age five: 3.0, Under age five: 0.5)
- Diarrhoeal diseases: 2.2 (Over age five: 1.5, Under age five: 0.7)
- TB: 1.5 (Over age five: 1.0, Under age five: 0.5)
- Malaria: 1.1 (Over age five: 0.3, Under age five: 0.8)
- Measles: 0.9 (Over age five: 0.4, Under age five: 0.5)

* HIV-positive people who died with TB have been included among AIDS deaths.

Source: WHO 1999
### Table 2.1 Major killers on the world scale

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Annual deaths/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>Virus</td>
<td>More than 2 million; mainly in the tropics</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bacterium</td>
<td>&quot; 1.5 million; &quot;</td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan</td>
<td>&quot; 1 million; &quot;</td>
</tr>
<tr>
<td>Measles</td>
<td>Virus</td>
<td>1 million; mostly children in the tropics</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Bacterium</td>
<td>400 000; mostly newborn children</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>Bacterium</td>
<td>350 000</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Bacterium</td>
<td>160 000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Viruses; bacteria</td>
<td>3.5 million; mostly children</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Viruses; bacteria</td>
<td>2.2 million; mostly children</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Viruses; bacteria</td>
<td>140 000</td>
</tr>
</tbody>
</table>
There are a handful of important protozoan pathogens of humans, of which *Plasmodium* is by far the most important.

Others include:

- *Trypanosoma*
- *Leishmania*
- *Entamoeba*
- *Giardia*
- *Schistosoma*
<table>
<thead>
<tr>
<th>Fungi</th>
<th>Ascomycetes</th>
<th>Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Histoplasma capsulatum, Coccidioides immitis, Pneumocystis carinii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protozoa</td>
<td></td>
<td>Entamoeba histolytica, Giardia intestinalis, Leishmania donovani, Plasmodium falciparum, Trypanosoma brucei, Toxoplasma gondii, Cryptosporidium parvum</td>
</tr>
<tr>
<td>Worms</td>
<td>Nematodes</td>
<td>Trichuris trichura, Trichinella spiralis, Enterobius vermicularis, Ascaris lumbricoides, Ancylostoma duodenale, Strongyloides stercoralis</td>
</tr>
<tr>
<td></td>
<td>Intestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tissues</td>
<td>Onchocerca volvulus, Loa loa, Dracuncula medinensis</td>
</tr>
<tr>
<td></td>
<td>Flukes</td>
<td>Schistosoma mansoni, Clonorchis sinensis</td>
</tr>
</tbody>
</table>
Major killers: malaria

- Forty-one percent of the world's population live in areas where malaria is transmitted (e.g., parts of Africa, Asia, the Middle East, Central and South America, Hispaniola, and Oceania).

- An estimated 700,000-2.7 million persons die of malaria each year, 75% of them African children.

- In areas of Africa with high malaria transmission, an estimated 990,000 people died of malaria in 1995 – over 2700 deaths per day, or 2 deaths per minute.
Major killers: malaria

* In 2002, malaria was the fourth cause of death in children in developing countries, after perinatal conditions (conditions occurring around the time of birth), lower respiratory infections (pneumonias), and diarrheal diseases. Malaria caused 10.7% of all children's deaths in developing countries.

* In Malawi in 2001, malaria accounted for 22% of all hospital admissions, 26% of all outpatient visits, and 28% of all hospital deaths. Not all people go to hospitals when sick or having a baby, and many die at home. Thus the true numbers of death and disease caused by malaria are likely much higher.
The buck stops with viruses

So, naturalists observe, a flea
Has smaller fleas that on him prey;
And these have smaller still to bite ’em;
And so proceed *ad infinitum*

-Jonathan Swift 1733

A chlamydial body infected with crystalline arrays of phage particles
The **probably multiple origins of viruses** are lost in a sea of conjecture and speculation, which results mostly from their nature: no-one has ever detected a fossil virus as a particle;

As a result, we are limited to studying viruses that are isolated in the present, or from material that is at most a few decades old. The new science (or art) of virus molecular systematics is, however, shedding a great deal of light on the distant relationships of, and in some cases on the presumed origins of, many important groups of viruses.
Origins and evolution of viruses

This is as a result of the sequencing of all or part of the genomes of representatives of many of the known varieties of viruses, including the largest (pox- and herpesviruses) and the smallest (gemini- and other ssDNA viruses). If viral genomes are compared with each other and with cellular sequences, presumed patterns of evolution / divergence of the genomes can be reconstructed.

Geminiviridae, for example, presumably have a common origin - and one that may be traceable back to beyond 200 Myr BP, if one takes into account geographical diversity, and genetic divergence of vectors and of plant hosts (see Rybicki, 1994).

Potyviridae are also a putatively ancient family of viruses
Origins and evolution of viruses

If one were to go far back into evolutionary time, a case could be made for descent from a single ancestor of at least the replicase-associated functions of all viruses with positive-sense and negative-sense single-strand RNA genomes;

likewise, large DNA viruses like pox- and herpesviruses and Phycodnaviridae could be presumed to have "degenerated" from cellular organisms, given that their enzymes share more sequence similarity with sequences from cells than with other viruses or anything else.

Retroviruses, pararetroviruses, retrotransposons and retroposons all probably share a common origin of the reverse transcription function, which in turn may be a living relic of the enzyme that enabled the switch from a presumably RNA-based genetics to DNA-based heredity.
Origins and evolution of viruses

It is very quickly apparent from sequence studies that there can have been no single origin of viruses as organisms.

For instance, there is no obvious way one can relate viruses of the size and complexity of the Poxviridae [double-stranded linear DNA, 130-375 kb, 150-300 genes] with viruses like the tobamoviruses [ss linear RNA, 6-7 kb, 4 genes], or either of these with the Geminiviridae [ss circular DNA, 2.7 - 5.4 kb, 3-7 genes].

Thus, there can be no simple "family tree" for viruses; rather, their evolutionary descent must resemble a number of scattered "bushes". Viruses as a class of organism must be therefore be considered to be polyphyletic in origins: that is, having a number of independent origins, almost certainly at different times, usually from cellular organisms.
What they have in common is a role as the ultimate "stripped-down" parasites:

organisms which can **only undergo a life cycle inside the cells of a host organism**, using at the very least the metabolic enzymes and pathways and **ribosomes** of that host to produce **virion components which get assembled into infectious particles**.
Ancient co-speciation of simian foamy viruses and primates

William M. Switzer\textsuperscript{1}, Marco Salemi\textsuperscript{2}, Vedapuri Shanmugam\textsuperscript{1}, Feng Gao\textsuperscript{3}, Mian-er Cong\textsuperscript{1}, Carla Kuiken\textsuperscript{1}, Vinod Bhullar\textsuperscript{1}, Brigitte E. Beer\textsuperscript{5}, Dominique Vallet\textsuperscript{6}, Annie Gautier-Hion\textsuperscript{6}, Zena Tooze\textsuperscript{7}, Francois Villinger\textsuperscript{8}, Edward C. Holmes\textsuperscript{9} & Walid Heneine\textsuperscript{1}

Although parasite–host co-speciation is a long-held hypothesis, convincing evidence for long-term co-speciation remains elusive, largely because of small numbers of hosts and parasites studied and uncertainty over rates of evolutionary change\textsuperscript{1–5}. Co-speciation is especially rare in RNA viruses, in which cross-species transfer is the dominant mode of evolution\textsuperscript{6–9}. Simian foamy viruses (SFVs) are ubiquitous, non-pathogenic retroviruses that infect all primates\textsuperscript{10,11}. Here we test the co-speciation
hypothesis in SFVs and their primate hosts by comparing the phylogenies of SFV polymerase and mitochondrial cytochrome oxidase subunit II from African and Asian monkeys and apes. The phylogenetic trees were remarkably congruent in both branching order and divergence times, strongly supporting co-speciation. Molecular clock calibrations revealed an extremely low rate of SFV evolution, \(1.7 \times 10^{-8}\) substitutions per site per year, making it the slowest-evolving RNA virus documented so far. These results indicate that SFVs might have co-speciated with Old World primates for at least 30 million years, making them the oldest known vertebrate RNA viruses.
Figure 1 Congruence of host/parasite phylogenies. Phylogenetic relationships of (a) primate COII (500 base pairs) and (b) SFV pot sequences (425 base pairs) inferred by maximum-likelihood analysis. Support for the branching order was determined by 1,000 bootstrap replicates run on neighbour-joining trees using the maximum-likelihood substitution model and the zero branch length test (significance is indicated with $P$ values on the branches; asterisks indicate $P < 0.001$). Only bootstrap values 70% or greater are shown. Branch lengths are drawn to scale except for the Atelés (Asp) COII sequence; the bar indicates 0.1 nucleotide substitutions per site. Primate taxon codes are provided in Supplementary Information.
### Table 1: Estimates of branching times (Myr ago) within the Catarrhini, using host and parasite phylogenies

<table>
<thead>
<tr>
<th>Branch point</th>
<th>SFV pol</th>
<th>COI</th>
<th>Fossil estimate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cercopithecida</td>
<td>22.9–24.4</td>
<td>23.6–27.7</td>
<td>–</td>
</tr>
<tr>
<td>Hominoidae(≡split Homonidae/Hylobatidae)</td>
<td>12–16</td>
<td>26.1</td>
<td>–</td>
</tr>
<tr>
<td>MRCA Hylobatidae</td>
<td>10.1–10.8</td>
<td>8.3–15.1</td>
<td>–</td>
</tr>
<tr>
<td>MRCA Ponginae</td>
<td>4.7–5.5</td>
<td>1.4–10.7</td>
<td>–</td>
</tr>
<tr>
<td>Split Homininae/Ponginae</td>
<td>n.a.†</td>
<td>18.5–23.5</td>
<td>~14</td>
</tr>
<tr>
<td>Split Pan/Gorilla</td>
<td>9.8–10.8</td>
<td>10.6–16.4‡</td>
<td>–</td>
</tr>
<tr>
<td>Split Pan/Homo</td>
<td>n.a.§</td>
<td>4.7–8.9</td>
<td>~5–6</td>
</tr>
<tr>
<td>MRCA Pan</td>
<td>5.9–6.6</td>
<td>1.2</td>
<td>–</td>
</tr>
<tr>
<td>Split Cerocebus torquatus/M. sphinx</td>
<td>–</td>
<td>1.4</td>
<td>–</td>
</tr>
</tbody>
</table>

Values for SFV and COI represent 95% confidence intervals; n.a., not available; MRCA, most recent common ancestor. The split of the Cercopithecoida from the Hominoidea 25–30 Myr ago was used as a calibration point for the molecular dating of both SFV and COI sequences. Estimates and confidence intervals of the SFV and COI divergence times were determined on the maximum-likelihood tree topology by using the nonparametric rate smoothing algorithm implemented in the r8s program. Values given without a range are the upper limit estimates.

*The fossil estimates for the Catarrhini are from refs 18 and 19.
†Homininae and Ponginae do not form a monophyletic clade in the SFV tree.
‡Includes Homo sapiens sequence.
§A human-specific foamy virus has yet to be identified.
# Types of viruses

## Table 1. Viral Diversity

<table>
<thead>
<tr>
<th>Genetic Material</th>
<th>Families</th>
<th>Example Families</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>20</td>
<td><em>Herpesviridae</em></td>
</tr>
<tr>
<td>ssDNA</td>
<td>5</td>
<td><em>Parvoviridae</em></td>
</tr>
<tr>
<td>RNA/DNA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td><em>Retroviridae</em></td>
</tr>
<tr>
<td>dsRNA</td>
<td>6</td>
<td><em>Reoviridae</em></td>
</tr>
<tr>
<td>–ssRNA</td>
<td>7</td>
<td><em>Orthomyxoviridae</em></td>
</tr>
<tr>
<td>+ssRNA</td>
<td>18</td>
<td><em>Paramyxoviridae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Filoviridae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Picornaviridae</em></td>
</tr>
</tbody>
</table>

<sup>a</sup>Viruses that reverse transcribe RNA into DNA.
<table>
<thead>
<tr>
<th>Viruses</th>
<th>DNA viruses</th>
<th>RNA viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenoviruses</td>
<td>Human adenoviruses (e.g., types 3, 4, and 7)</td>
</tr>
<tr>
<td></td>
<td>Herpesviruses</td>
<td>Herpes simplex, varicella zoster, Epstein-Barr virus,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytomegalovirus, HHV8</td>
</tr>
<tr>
<td></td>
<td>Poxviruses</td>
<td>Variola, vaccinia virus</td>
</tr>
<tr>
<td></td>
<td>Paroviruses</td>
<td>Human parovirus</td>
</tr>
<tr>
<td></td>
<td>Papoviruses</td>
<td>Papillomavirus</td>
</tr>
<tr>
<td></td>
<td>Hepadnaviruses</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td></td>
<td>Orthomyxoviruses</td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td>Paramyxoviruses</td>
<td>Mumps, measles, respiratory syncytial virus</td>
</tr>
<tr>
<td></td>
<td>Coronaviruses</td>
<td>Cold viruses, SARS</td>
</tr>
<tr>
<td></td>
<td>Picornaviruses</td>
<td>Polio, coxsackie, hepatitis A, rhinovirus</td>
</tr>
<tr>
<td></td>
<td>Reoviruses</td>
<td>Rotavirus, reovirus</td>
</tr>
<tr>
<td></td>
<td>Togaviruses</td>
<td>Rubella, arthropod-borne encephalitis</td>
</tr>
<tr>
<td></td>
<td>Flaviviruses</td>
<td>Arthropod-borne viruses (yellow fever, dengue fever)</td>
</tr>
<tr>
<td></td>
<td>Arenaviruses</td>
<td>Lymphocytic choriomeningitis, Lassa fever</td>
</tr>
<tr>
<td></td>
<td>Rhabdoviruses</td>
<td>Rabies</td>
</tr>
<tr>
<td></td>
<td>Retroviruses</td>
<td>Human T-cell leukemia virus, HIV</td>
</tr>
</tbody>
</table>

Figure 10-3 part 1 of 3 Immunobiology, 6/e. © Garland Science 2005
# Types of viruses

## Table 1. Viral Diversity

<table>
<thead>
<tr>
<th>Genetic Material</th>
<th>Families</th>
<th>Example Families</th>
<th>Example Genus</th>
<th>Example Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>20</td>
<td><em>Herpesviridae</em></td>
<td><em>Rhadinovirus</em></td>
<td>Human herpesvirus 8</td>
</tr>
<tr>
<td>ssDNA</td>
<td>5</td>
<td><em>Paroviridae</em></td>
<td><em>Dependovirus</em></td>
<td>Adeno-associated virus 2</td>
</tr>
<tr>
<td>RNA/DNA(^a)</td>
<td>5</td>
<td><em>Retroviridae</em></td>
<td><em>Lentivirus</em></td>
<td>HIV-1</td>
</tr>
<tr>
<td>dsRNA</td>
<td>6</td>
<td><em>Reoviridae</em></td>
<td><em>Rotavirus</em></td>
<td>Human rotavirus group A</td>
</tr>
<tr>
<td>(--ssRNA)</td>
<td>7</td>
<td><em>Orthomyxoviridae</em></td>
<td><em>Influenzavirus A</em></td>
<td>Influenza A virus</td>
</tr>
<tr>
<td>(+ssRNA)</td>
<td>18</td>
<td><em>Picornaviridae</em></td>
<td><em>Enterovirus</em></td>
<td>Zaire Ebola virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Paramyxoviridae</em></td>
<td><em>Morbilivirus</em></td>
<td>Measles virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Filoviridae</em></td>
<td><em>Ebolavirus</em></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Viruses that reverse transcribe RNA into DNA.
dsDNA

HHV-8
• The story of Human Herpesvirus 8 (HHV-8) is closely tied to the history of Kaposi's Sarcoma.

• Early in the 1980's, a number of gay and bisexual men developed Kaposi's Sarcoma, which had previously been a rare skin cancer seen primarily in the Mediterranean and Africa. Investigation into these new cases of KS and pneumocystic pneumonia led, in part, to the identification of the Acquired Immunodeficiency Syndrome (AIDS) and the HIV virus. Kaposi's Sarcoma is a cancer that often shows up as purple discoloration on the skin, but in severe cases can also involve the internal organs.

• The Discovery of HHV-8
From the beginning of the AIDS epidemic, it was suspected that there might be another infectious agent besides HIV that causes KS. KS was a common problem among HIV-seropositive men who have sex with men before the era of more effective HIV medications. In the 1980's, around 30-40% of homosexual men with AIDS developed KS at some point in their illness. In contrast, KS was a rare occurrence in women or homophiliacs with HIV. This suggested that there was an additional factor among gay and bisexual men that increased their chances of developing KS. In 1994 scientists identified a previously unknown virus in KS biopsies.
This virus was named human herpesvirus 8 (also known as Kaposi's sarcoma-associated herpesvirus-KSHV). It belongs to the important family of human herpesviruses that includes varicella-zoster (chickenpox/shingles), epstein-barr virus (mononucleosis), and herpes simplex 1 and 2 (oral and genital herpes). After identification of HHV-8, researchers have been able to identify it in virtually all types of Kaposi's sarcoma tumors, including those seen before the AIDS epidemic.
A typical shingles episode in an adult.

A severe case of chickenpox in an adolescent.
Varicella-Zoster Virus (VZV) is one of most common viruses to infect humans. It is found all over the world, and there do not seem to be any immune populations. The initial infection manifests itself as chickenpox (AKA varicella), and reactivation of the virus appears as shingles (AKA zoster).

In the initial stage, VZV has an incubation period of about 14 days, after which pustular lesions appear in waves for about five days. These lesions can be painful but are usually classified as just "itchy." After five days no new spots appear (except in immunosuppressed individuals), and the old spots eventually crust over and disappear.

The virus, however, does not. It becomes latent in sensory ganglia cells until a time when the host become immunosuppressed for whatever reason. The virus then reactivates in a single ganglia and manifest as an isolated patch of lesions which may be very painful. (why do you think it becomes latent?)

VZV is one of the most infectious viruses known, so there is very little that can be done to prevent infection. In fact, since chickenpox is, for some unknown reason, much more severe in adolescents and adults, before a vaccine was developed many families would intentionally expose their young children to an infected individual. Now there is a very good vaccine, the varicella vaccine, which is given as part of the universal pediatric vaccination schedule.
Other notable dsDNA viruses

Vaccinia virus (cowpox)

Myxoma virus (myxomatosis)

Papilloma virus (cervical cancer)

Human adenovirus (childhood respiratory and gastrointestinal infections)
Adenoviruses

- A group of viruses that infect the membranes (tissue linings) of the respiratory tract, the eyes, the intestines, and the urinary tract, adenoviruses account for about 10% of acute respiratory infections in children and are a frequent cause of diarrhea.

- Adenoviral infections affect infants and young children much more frequently than adults. Child-care centers and schools sometimes experience multiple cases of respiratory infections and diarrhea that are caused by adenovirus.

- The majority of the population will have experienced at least one adenoviral infection by age 10. Although adenoviral infection in children can occur at any age, most take place in the first years of life.

- Since there are many different types of adenovirus, repeated adenoviral infections can occur.
ssDNA

• Adeno-associated virus (AAV) is the smallest of known human viruses. (less than 5kb)

• There is no disease which has been to date associated with AAV. It causes very mild immune response and can infect non-dividing cells.

• It incorporates into the host cell's genome, but there is no evidence that it can cause malignant transformation. Because of these features it presents a very attractive subject for creating vectors for gene therapy.

• Not many other human pathogens are ssDNA
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Not many other human pathogens are ssDNA
RNA/DNA reverse-transcribing viruses

Hepatitis B virus

• Over one-third of the world's population has been or is actively infected by the virus, which results in liver inflammation, vomiting, jaundice, and death in the worst cases.

• Hepatitis B is one of a few known non-retroviral viruses which employ reverse transcription as a part of its replication process. Other, unrelated, viruses which use reverse transcription include HIV, the virus which causes AIDS. Hepatitis B's genome is DNA, and reverse transcription is one of the later steps in making new viral particles, whereas HIV has an RNA genome and reverse transcription is one of the first steps in replication.
RNA/DNA reverse-transcribing viruses

Human Immunodeficiency Virus Type 1
HIV/AIDS basics

Where did AIDS come from?

- First identified in US gay males in the early 1980s, severe immunosuppression
- **Pneumocystis carinii** pneumonia
- Other rare opportunistic infections, horrendous suffering and death

Randy Shilts

As a national correspondent for the *San Francisco Chronicle*, Shilts was the first newspaper reporter to cover the AIDS epidemic full time. In his book *And the Band Played On*—AIDS: The First Five Years (1980-1985), he took almost everyone to task on how the first years of the epidemic were handled.
Major killers: HIV/AIDS

- The earliest known case of HIV-1 in a human was from a blood sample collected in 1959 from a man in Kinshasa, Democratic Republic of Congo. (How he became infected is not known.) Genetic analysis of this blood sample suggested that HIV-1 may have stemmed from a single virus in the late 1940s or early 1950s.

- We know that the virus has existed in the United States since at least the mid- to late 1970s. From 1979-1981 rare types of pneumonia, cancer, and other illnesses were being reported by doctors in Los Angeles and New York among a number of male patients who had sex with other men. These were conditions not usually found in people with healthy immune systems.
Early history

- New syndrome recognized by 1981
- Retroviral agent isolated in 1983
- Sexually transmitted, but also via needles, transfusions, birth
- Hit these risk groups hard in the US, but also high prevalence in Haiti, Central Africa
Major killers: HIV/AIDS

- In 1982 public health officials began to use the term "acquired immunodeficiency syndrome," or AIDS, to describe the occurrences of opportunistic infections, Kaposi's sarcoma (a kind of cancer), and *Pneumocystis carinii* pneumonia in previously healthy people. Formal tracking (surveillance) of AIDS cases began that year in the United States.

- In 1983, scientists discovered the virus that causes AIDS. The virus was at first named HTLV-III/LAV (human T-cell lymphotropic virus-type III/lymphadenopathy-associated virus) by an international scientific committee. This name was later changed to HIV (human immunodeficiency virus).

- The discoverer of HIV is Francoise Barre-Sinoussi who worked in the group of Luc Montagnier at Institut Pasteur in Paris.
Viruses are made up of a set of genetic instructions wrapped inside a protective shell.

- HIV is particularly succinct at around 3000 amino acid residues that hijack the cell’s own machinery.
- Genome is in the form of RNA, so it also includes a reverse transcriptase (RNA to DNA enzyme).
- About 20% of your genome is made up of similar “selfish DNA” (more than 10X the amount of your 30,000 protein genes).
1) HIV’s extracellular, or virion stage

2) HIV’s gp120 protein binds to CD4 and coreceptor on host cell

3) HIV’s RNA genome, reverse transcriptase, integrase, and protease enter host cell

4) Reverse transcriptase synthesizes HIV DNA from HIV’s RNA template

5) Integrase splices HIV DNA into host genome. HIV DNA is transcribed to HIV mRNA by the host cell’s RNA polymerase

6) HIV mRNA is translated to HIV precursor proteins by host cell’s ribosomes. Protease cleaves precursors into mature viral proteins

7) New generation of virions assembles inside host cell

8) New virions bud from host cell’s membrane
What is HIV/AIDS?

Figure 1 | Key aspects of the HIV life cycle. Although the human immunodeficiency virus (HIV) is able to infect a variety of cell types, AIDS results from the depletion of CD4⁺ T-HELPER LYMPHOCYTE CELLS, a key component of the human immune system. The env (envelope) gene encodes the proteins of the outer envelope of the virus, the gag (group-specific antigen) gene encode the components of the inner capsid protein, whereas the pol (polymerase) gene codes for the enzymes (such as reverse transcriptase) that are used in viral replication.
HIV/AIDS basics

Evolution in the fast lane:

• About 10 billion virions are generated daily in an infected host (2.5 days per cycle)

• Each has a compact genome made up of about 10,000 nucleotides

• Approximately one mutation is generated for each new genome

• Every possible mutation occurs every day
Global impact of HIV/AIDS

(Source: ref. 28.)
Where did HIV come from?

- Divine retribution
- Doesn’t matter--it doesn’t cause AIDS
- Conspiracy theories - e.g. the CIA did it
- Voodoo rituals
- Ritualistic use of monkey blood
- Contamination of vaccines
- Zoonosis (a disease communicable from animals to humans under natural conditions)

How can we discriminate between these hypotheses?
dsRNA

Human Rotavirus Type A
Major killers: rotavirus (the most important virus you’ve never heard of)

- It used to be thought that gastro-enteritis was usually caused by bacteria.

- It is now realized that about one half of cases of diarrhea cases are due to viral infections.

- Most commonly, rotavirus.
Rotavirus is the most common cause of severe diarrhea among children, resulting in the hospitalization of approximately 55,000 children each year in the United States.

It causes the death of over 600,000 children annually worldwide.

Immunity after infection is incomplete, but repeat infections tend to be less severe than the original infection.
Major killers: rotavirus (the most important virus you’ve never heard of)

• A rotavirus has a characteristic wheel-like appearance when viewed by electron microscopy (the name rotavirus is derived from the Latin rota, meaning "wheel").

• Rotaviruses are nonenveloped, double-shelled viruses.

• The genome is composed of 11 segments of double-stranded RNA, which code for six structural and five nonstructural proteins. The virus is stable in the environment.
Major killers: rotavirus (the most important virus you’ve never heard of)

- In 1998, the U.S. Food and Drug Administration approved a live virus vaccine (Rotashield) for use in children. However, the Advisory Committee on Immunization Practices (ACIP) recommended that Rotashield no longer be recommended for infants in the United States.

- 2 new vaccines now available.

- Vaccines against the common bacterial and viral diarrhea pathogens would save 2-3 million lives per year.

- Then again, so would clean water and sanitation.
ssRNA: negative strand RNA viruses

Influenza A virus

Measles virus

Ebola virus
**Major killers: influenza virus**

- Influenza is caused by a virus that attacks mainly the upper respiratory tract – the nose, throat and bronchi and rarely also the lungs.

- The virus has a single-stranded negative-sense RNA genome in several segments.

- The infection usually lasts for about a week. It is characterized by sudden onset of high fever, headache and severe malaise, non-productive cough, sore throat, and rhinitis.

- Most people recover within one to two weeks without requiring any medical treatment.

- In the very young, the elderly and people suffering from medical conditions such as lung diseases, diabetes, cancer, kidney or heart problems, influenza poses a serious risk. In these people, the infection may lead to severe complications of underlying diseases, pneumonia and death.
Major killers: influenza virus

- rapidly spreads around the world in seasonal epidemics and imposes a considerable economic burden in the form of hospital and other health care costs and lost productivity.

- In annual influenza epidemics 5-15% of the population are affected with upper respiratory tract infections (i.e. 100s of millions of cases)

- Hospitalization and deaths mainly occur in high-risk groups (elderly, chronically ill).

- Although difficult to assess, these annual epidemics are thought to result in between three and five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world. Most deaths currently associated with influenza in industrialized countries occur among the elderly over 65 years of age. (about 36,000 in the USA every year)

- Much less is known about the impact of influenza in the developing world.
Major killers: influenza virus

- The currently circulating influenza viruses that cause human disease are divided into two groups: A and B.

- Influenza A has 2 subtypes which are important for humans: A(H3N2) and A(H1N1), of which the former is currently associated with most deaths.

- Influenza viruses are defined by 2 different protein components, known as antigens, on the surface of the virus. They are spike-like features called haemagglutinin (H) and neuraminidase (N) components.

- The genetic makeup of influenza viruses allows frequent minor genetic changes, known as **antigenic drift**, and these changes require annual reformulation of influenza vaccines.
Major killers: influenza virus

• Three times in the last century, the influenza A viruses have undergone major genetic changes (antigenic shift), resulting in global pandemics and large tolls in terms of both disease and deaths.

• The most infamous pandemic was “Spanish Flu” which affected large parts of the world population and is thought to have killed at least 40 million people in 1918-1919.

• And maybe up to 100 million, at a time when the population of the Earth was around 1.8 billion.
• More recently, two other influenza A pandemics occurred in 1957 ("Asian influenza") and 1968 ("Hong Kong influenza") and caused significant morbidity and mortality globally.

• In contrast to current influenza epidemics, these pandemics were associated with severe outcomes also among healthy younger persons, albeit not on such a dramatic scale as the "Spanish flu" where the death rate was highest among healthy young adults.

• Most recently, outbreaks of a new influenza subtype A(H5N1) directly transmitted from birds to humans have occurred
Major killers: influenza virus

• Vaccination is the principal measure for preventing influenza and reducing the impact of epidemics.

• Various types of influenza vaccines have been available and used for more than 60 years. They are safe and effective in preventing both mild and severe outcomes of influenza.

• Constant genetic changes in influenza viruses mean that the vaccines' virus composition must be adjusted annually to include the most recent circulating influenza A(H3N2), A(H1N1) and influenza B viruses.

• The WHO's Global Influenza Surveillance Network writes the annual vaccine recipe. The network, a partnership of 112 National Influenza Centres in 83 countries, is responsible for monitoring the influenza viruses circulating in humans and rapidly identifying new strains. Based on information collected by the Network, WHO recommends annually a vaccine that targets the 3 most virulent strains in circulation.
Major killers: influenza virus

• Antiviral drugs for influenza are an important adjunct to influenza vaccine for the treatment and prevention of influenza. However, they are not a substitute for vaccination.

• For several years, four antiviral drugs that act by preventing influenza virus replication have been available. They differ in terms of their pharmacokinetics, side effects, routes of administration, target age groups, dosages, and costs.
ssRNA: negative strand RNA viruses

Influenza A virus

Measles virus

Ebola virus
Major killers: measles virus and other “childhood” diseases

• Measles is an infectious viral disease that occurs most often in the late winter and spring. It begins with a fever that lasts for a couple of days, followed by a cough, runny nose, and conjunctivitis (pink eye). A rash starts on the face and upper neck, spreads down the back and trunk, then extends to the arms and hands, as well as the legs and feet. After about five days, the rash fades the same order it appeared.

• Measles is highly contagious. Infected people are usually contagious from about 4 days before their rash starts to 4 days afterwards. The measles virus resides in the mucus in the nose and throat of infected people. When they sneeze or cough, droplets spray into the air and the droplets remain active and contagious on infected surfaces for up to two hours.
Major killers: measles virus and other “childhood” diseases

• Measles itself is unpleasant, but the complications are dangerous.

• Six to 20 percent of the people who get the disease will get an ear infection, diarrhea, or even pneumonia.

• One out of 1000 people with measles will develop inflammation of the brain, and about one out of 1000 will die.

• Measles kills about 1 million children every year in spite of the availability of a safe and effective vaccine
Measles is a crowd disease that probably could not have maintained itself until recently in human populations.

- Related viruses are found in a range of mammals.
- Most closely related is Rinderpest, from bovids.
- Did we acquire measles after settling down and domesticating cattle?
ssRNA: negative strand RNA viruses

Rabies virus

Mumps virus

Hanta viruses

Human respiratory syncytial virus
Major killers: other respiratory infections

- Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age.

- The majority of children hospitalized for RSV infection are under 6 months of age. RSV also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms.

- However, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems.

- RSV is a single-stranded negative-sense, enveloped RNA virus. The virion is variable in shape and size (average diameter of between 120 and 300 nm), is unstable in the environment (surviving only a few hours on environmental surfaces), and is readily inactivated with soap and water and disinfectants.
RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious material contacts mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough.

In temperate climates, RSV infections usually occur during annual community outbreaks, often lasting 4 to 6 months, during the late fall, winter, or early spring months.

Development of an RSV vaccine is a high research priority, but none is yet available.
Major killers: respiratory infections

- Human parainfluenza viruses (HPIVs) are second to respiratory syncytial virus (RSV) as a common cause of lower respiratory tract disease in young children.

- Similar to RSV, HPIVs can cause repeated infections throughout life, usually manifested by an upper respiratory tract illness (e.g., a cold and/or sore throat).

- HPIVs can also cause serious lower respiratory tract disease with repeat infection (e.g., pneumonia, bronchitis, and bronchiolitis), especially among the elderly, and among patients with compromised immune systems.
HPIVs are negative-sense, single-stranded RNA viruses that possess fusion and hemagglutinin-neuraminidase glycoprotein "spikes" on their surface. There are four serotypes types of HPIV (1 through 4) and two subtypes (4a and 4b).

unstable in the environment (surviving a few hours on environmental surfaces), and readily inactivated with soap and water.

No vaccine is currently available to protect against infection caused by any of the HPIVs
<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
<td>Bacterium</td>
<td>Common cause of pneumonia</td>
</tr>
<tr>
<td>Haemophilus</td>
<td></td>
<td>Common cause of pneumonia</td>
</tr>
<tr>
<td>Whooping cough</td>
<td></td>
<td>May spread to other organs</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td>Laryngitis</td>
</tr>
<tr>
<td>Diphtheria</td>
<td></td>
<td>More usually via skin</td>
</tr>
<tr>
<td>Anthrax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plague (‘pneumonic’)</td>
<td></td>
<td>Also via skin (‘bubonic’)</td>
</tr>
<tr>
<td>Common cold</td>
<td>Viruses</td>
<td>Usually self-limited</td>
</tr>
<tr>
<td>Influenza</td>
<td>Virus</td>
<td>May spread to lung (pneumonia)</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td>Also skin rash</td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
<td>Also salivary glands</td>
</tr>
<tr>
<td>Chickenpox</td>
<td></td>
<td>Rash; may recur as shingles</td>
</tr>
<tr>
<td>Rubella</td>
<td></td>
<td>May affect fetus</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>Fungus</td>
<td>May cause allergy</td>
</tr>
<tr>
<td>Histoplasma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ssRNA: positive strand RNA viruses

Poliovirus (poliomyelitis)

Rhinovirus (common cold)

Hepatitis A virus

Dengue virus

West Nile virus

Hepatitis C virus

Foot-and-mouth disease virus

SARS
ssRNA: positive strand RNA viruses

• Hepatitis C infects an estimated 170 million people worldwide and 4 million in the United States.

• There are about 35,000 to 185,000 new cases a year in the United States. Co-infection with HIV is common and rates among HIV positive populations are higher.

• 10,000-20,000 deaths a year in the United States are from HCV; expectations are that this will increase, as those who were infected by transfusion before HCV testing are expected to become apparent.

• A survey conducted in California showed prevalence of up to 34% among prison inmates;[10] 82% of subjects diagnosed with hepatitis C have previously been in jail,[11] and transmission while in prison is well described.[12]

• Egypt has the highest seroprevalence for HCV, up to 20% in some areas. This was linked, in 2000, to a mass-treatment campaign for schistosomiasis, which is endemic in that country.
**other important diarrhea viruses**

- Noroviruses are a group of viruses that cause the “stomach flu,” or gastroenteritis in people.

- Enveloped, single-stranded positive-sense RNA virus

- The term norovirus was recently approved as the official name for this group of viruses. Several other names have been used for noroviruses, including:
  - Norwalk-like viruses (NLVs)
  - caliciviruses (because they belong to the virus family *Caliciviridae*)
• The symptoms of norovirus illness usually include nausea, vomiting, diarrhea, and some stomach cramping.

• The illness is usually brief and milder than rotaviral infection, with symptoms lasting only about 1 or 2 days.

• Also known as…
• * stomach flu – this “stomach flu” is not related to the flu (or influenza), which is a respiratory illness caused by influenza virus.
• * viral gastroenteritis – the most common name for illness caused by norovirus. Gastroenteritis refers to an inflammation of the stomach and intestines.
• * food poisoning (although there are other causes of food poisoning)
### Vectored diseases

#### Table 2.4 Some diseases transmitted by insects or other vectors

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Vector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plague</td>
<td>Bacterium</td>
<td>Flea (from rats)</td>
</tr>
<tr>
<td>Tularaemia</td>
<td>&quot;</td>
<td>Flea, tick, louse</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td>&quot;</td>
<td>Louse</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>&quot;</td>
<td>Tick</td>
</tr>
<tr>
<td>Typhus</td>
<td>Rickettsia</td>
<td>Flea, louse</td>
</tr>
<tr>
<td>Dengue</td>
<td>Virus</td>
<td>Mosquito</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan</td>
<td>&quot;</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>&quot;</td>
<td>Sandfly</td>
</tr>
<tr>
<td>Sleeping sickness</td>
<td>&quot;</td>
<td>Tsetse fly</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td>&quot;</td>
<td>Reduviid bug</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Worm</td>
<td>Blackfly</td>
</tr>
<tr>
<td>Filariasis</td>
<td>&quot;</td>
<td>Mosquito</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>&quot;</td>
<td>Snail</td>
</tr>
</tbody>
</table>
# Zoonoses:

### Table 2.5 Major diseases caught from animals (zoonoses)

<table>
<thead>
<tr>
<th>Pathogen/disease</th>
<th>Type of organism</th>
<th>Animal reservoir/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine tuberculosis</td>
<td>Bacterium</td>
<td>Cattle; rare since pasteurization</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>&quot;</td>
<td>Cattle, goat, dog</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>&quot;</td>
<td>Horse, cattle, dog</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>&quot;</td>
<td>Deer</td>
</tr>
<tr>
<td>Plague</td>
<td>&quot;</td>
<td>Rat</td>
</tr>
<tr>
<td>Tularaemia</td>
<td>&quot;</td>
<td>Rat</td>
</tr>
<tr>
<td>Anthrax</td>
<td>&quot;</td>
<td>Farm animals</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>&quot;</td>
<td>Farm and dairy products</td>
</tr>
<tr>
<td>Psittacosis</td>
<td>Chlamydia</td>
<td>Birds</td>
</tr>
<tr>
<td>Rabies</td>
<td>Virus</td>
<td>Bat, dog, fox, racoon</td>
</tr>
<tr>
<td>Influenza</td>
<td>&quot;</td>
<td>Birds, pig</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>&quot;</td>
<td>Rodents</td>
</tr>
<tr>
<td>Ebola, Marburg</td>
<td>&quot;</td>
<td>Monkeys</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>&quot;</td>
<td>Chimpanzees; monkeys (originally, now human (\rightarrow) human)</td>
</tr>
<tr>
<td><em>Cryptococcus</em></td>
<td>Fungus</td>
<td>Birds</td>
</tr>
<tr>
<td><em>Toxoplasma</em></td>
<td>Protozoan</td>
<td>Cat</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>&quot;</td>
<td>Birds, mammals</td>
</tr>
<tr>
<td><em>Echinococcus</em></td>
<td>Worm</td>
<td>Dog</td>
</tr>
<tr>
<td>Tapeworms(s)</td>
<td>&quot;</td>
<td>Pig, cattle</td>
</tr>
<tr>
<td><em>Toxocara</em></td>
<td>&quot;</td>
<td>Dog</td>
</tr>
</tbody>
</table>