Research on non-human primate models of HIV

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GEORGIA
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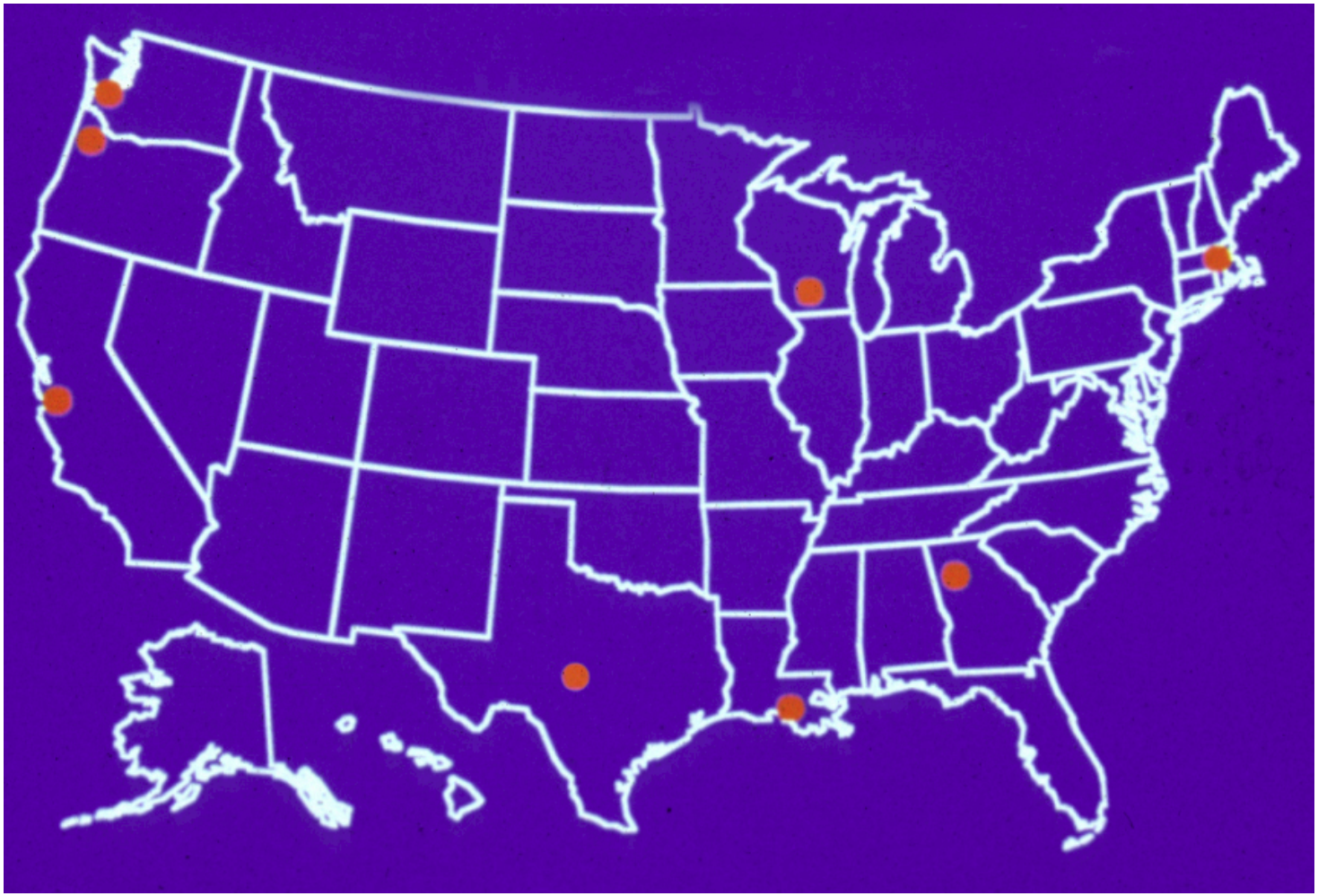
Animal rights activism: a personal survey

Since 1990 I have asked >100 dentists (for a total of >2,000 years of clinical practice) a simple, basic question…..

US Primate Research Centers:
a network of seven national primate research centers (NPRC) funded by the National Institutes of Health.



Primate Centers: Rules & Regulations

- **All US Primate Centers are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) with full re-evaluation every 3 years (Yerkes accredited since 1985).**

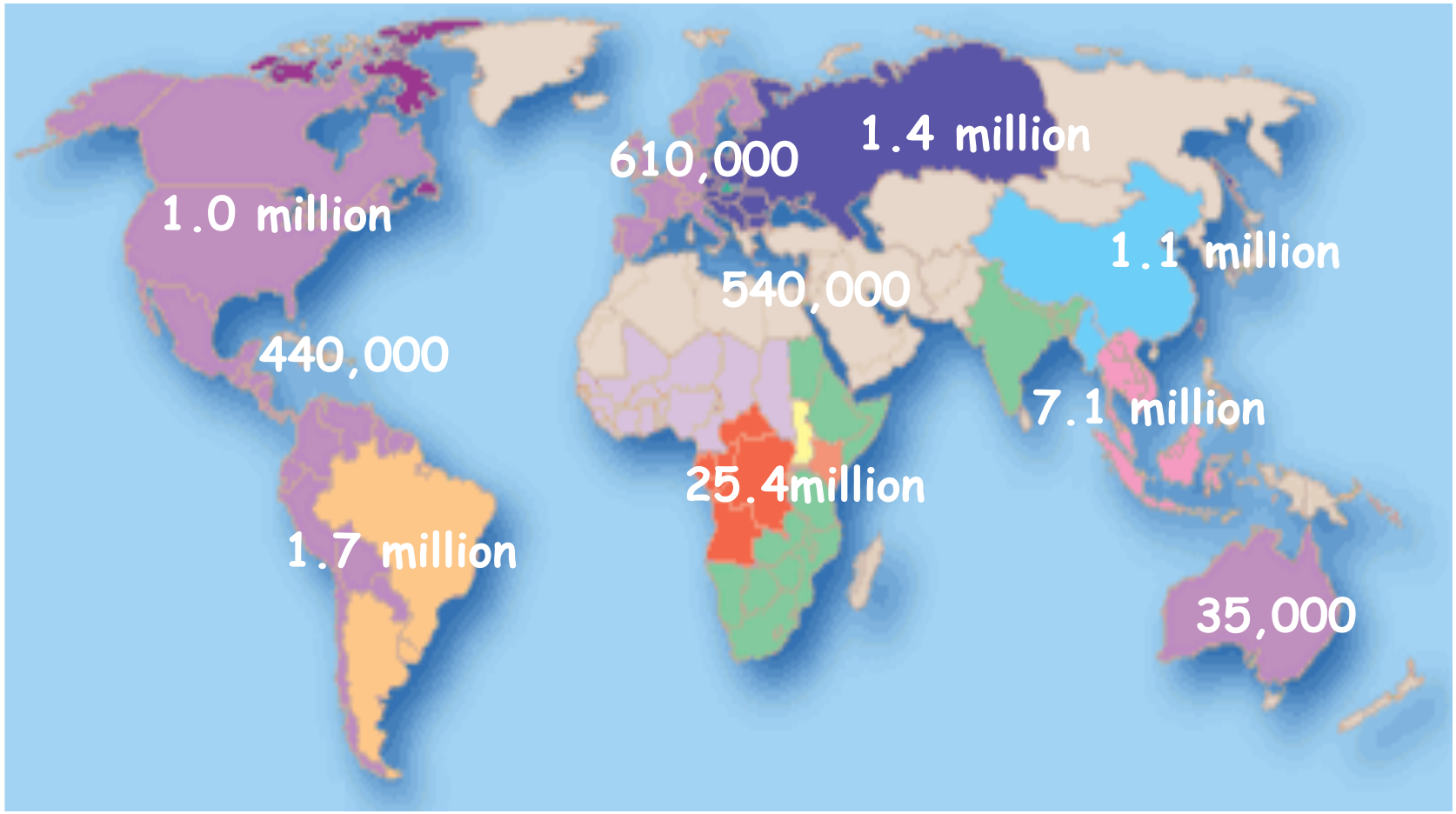
- **The AAALAC evaluation represents the "Gold Standard" for animal care and use programs.**

- **All NHP studies are reviewed by the Institutional Animal Care and Usage Committee (IACUC), and approved protocols are subject to annual re-approval.**

- **All employees involved in NHP research receive specific training with re-assessment every three years.**

- **All NIH-funded grants include a Vertebrate Animal Section**

Current state of the HIV/AIDS Epidemic



1981-2015: Thirty-four years of AIDS

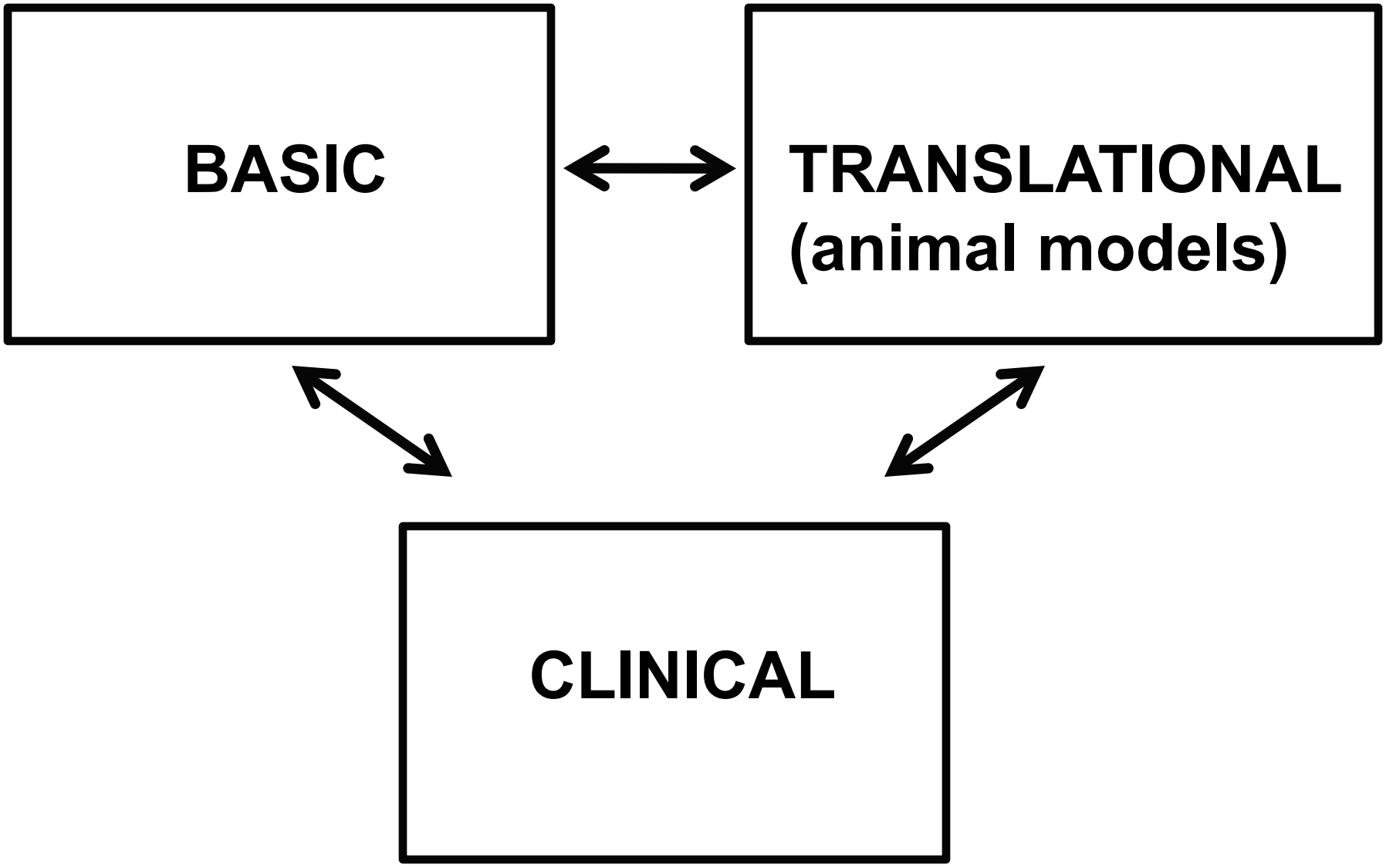
The glass half-full:

1. Discovery and characterization of the etiologic agent.
2. Development of lab tests to monitor and prevent the infection.
3. Definition of the origin of the epidemics.
4. Development of a large array of potent anti-HIV drugs, with consequent major reduction in mortality and MTCT.

The glass half-empty:

1. Absence of a vaccine or a long lasting microbicide.
2. Absence of a treatment that can eradicate infection.
3. Incomplete understanding of the pathogenesis of infection.

Contemporary HIV/AIDS Research: an Integrated Approach

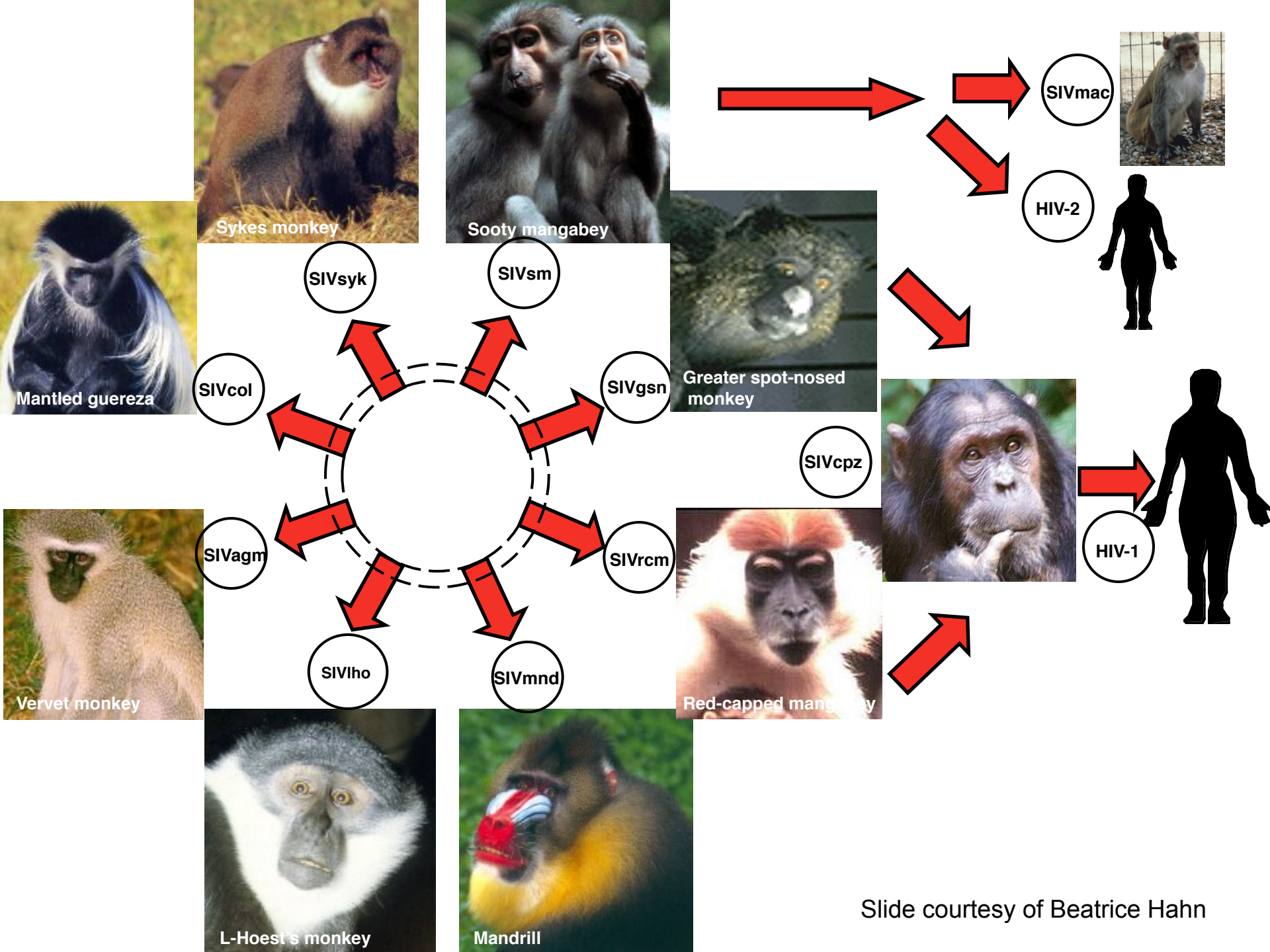


Animal Models for AIDS Research:

1. Chimpanzees

2. Monkeys:
   - -African Monkeys (natural and non-natural hosts)
   - -Asian Monkeys (non-natural hosts)
   - -New World Monkeys (non-hosts)

3. Rodents:
   - -Transgenic rodents expressing HIV proteins
   - -”Humanized rodents”



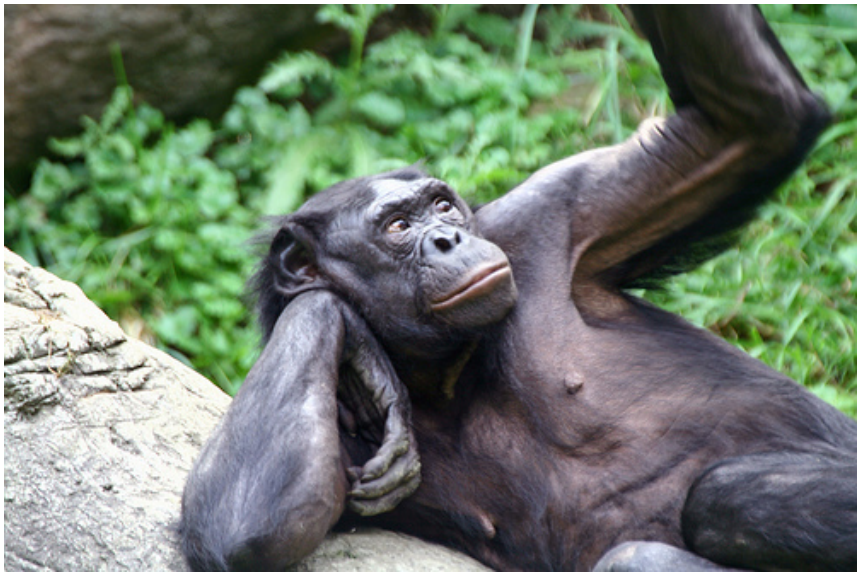
Slide courtesy of Beatrice Hahn

Chimpanzees:

Two species: Common chimpanzee and Bonobos

Four sub-species of common chimpanzees: Pan troglodytes troglodytes; verus; vellerosus, and schweinfurthii.

P.t. troglodytes and p.t. schweinfurthii are “natural” SIV hosts.



Chimpanzees:

Infectable with HIV-1 and SIVcpz

HIV-1- infection is non pathogenic; SIVcpz is moderately pathogenic

Major regulatory issues:
-2011: report of the US Institute of Medicine

-2012: retirement of the NIH-owned chimpanzees

-2013: US Congress passes the "The Chimpanzee Health Improvement, Maintenance and Protection Act"

-2015: US Fish & Wildlife lists all captive chimpanzees as "endangered"

Monkey models:

Monkey models:

African monkeys include >40 species of "natural SIV hosts. These infections are common, evolutionary "ancient", and by-and-large non-pathogenic.

Some African monkey species (i.e., baboons, patas) do not seem to be SIV hosts.

Asian monkeys (i.e., macaques) are experimental hosts for SIV (and SHIV) infection. The infection can be pathogenic and represents the most widely used animal model for AIDS research.

New world monkeys are resistant to SIV infection.

SIV Infection of Asian Macaques

Asian macaques infected with SIV or SHIV experience a disease similar to HIV infection in humans

SIV infection of macaques is a well studied, robust model for research on HIV transmission, pathogenesis, therapy, and prevention (including vaccines). In fact, it may be the best animal model ever developed for a human disease

Similarities between HIV & pathogenic SIV infection of macaques

1. Chronic progressive infection associated with opportunistic infections and CNS involvement (simian AIDS).
2. Presence of a minority of "benign" cases (LTNP, EC) associated with low viremia and specific MHC Class-I alleles.
3. Kinetics of viremia characterized by acute peak and post-peak decline.
4. Presence of vigorous but ultimately ineffective innate and adaptive immune responses to the virus.
5. Key pathogenic events include chronic immune activation, mucosal immune dysfunction, microbial translocation, and high levels of infection of central-memory CD4+ T cells.
6. Virus replication can be suppressed by ART with persisting reservoirs of latently infected cells.

Perhaps the best animal model available for any human disease?

Historical Results

1. Studies of the early events of virus transmission and dissemination.
2. Accurate immunological and virological analyses of the acute phase of infection.
3. Detailed characterization of the pathology in tissues.
4. Characterization of the in vivo role of specific viral proteins (i.e. delta Nef viruses etc)
5. Definition of the role of the host immune response in controlling virus replication by using “depletion” techniques.
6. Studies of pathogenesis using “invasive” techniques (i.e., repeated tissue sampling, cell labeling techniques, etc).
7. Pre-clinical testing of candidate AIDS vaccines, microbicides, and antiretroviral strategies.

The model is vastly under-utilized for studies of HIV eradication

Opportunities provided by NHP models in studies of HIV cure/eradication

1. Identity, dose, and route of virus challenge known.
2. Control for various clinical parameters that are virtually impossible to control in humans (time of infection, duration of ART etc).
3. Comprehensive cellular and anatomic characterization of *both* active and persistent reservoirs (including elective necropsy).
4. Pilot trials of in vivo eradication conducted in a timely and controlled fashion; treatment interruption is possible.
5. Testing of “risky” interventions (i.e., combination therapy, cell depletion studies, stem cell-based interventions etc)

Thank you very much for your attention