

The Human Immunodeficiency Virus

Where did it come from?
Where is it going?

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Canadian Therapeutic Congress, Halifax, May 2007



Canadian HIV Trials Network
Réseau canadien pour les essais VIH

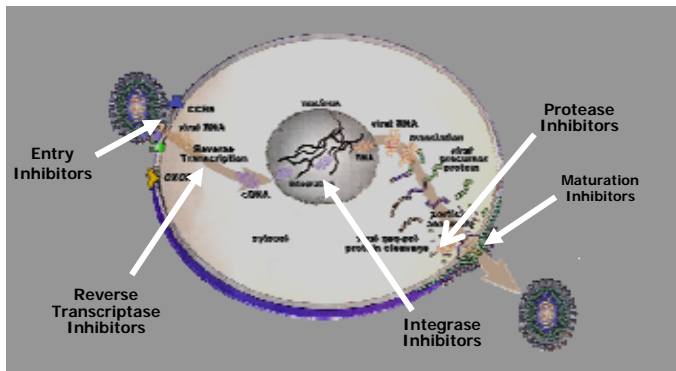
Enrolling toward better treatments, vaccines and cure for HIV/AIDS
Enrollant vers de meilleurs traitements, des vaccins et un traitement pour le VIH/SIDA



What is it?
Where did it come from?
Where is it going?

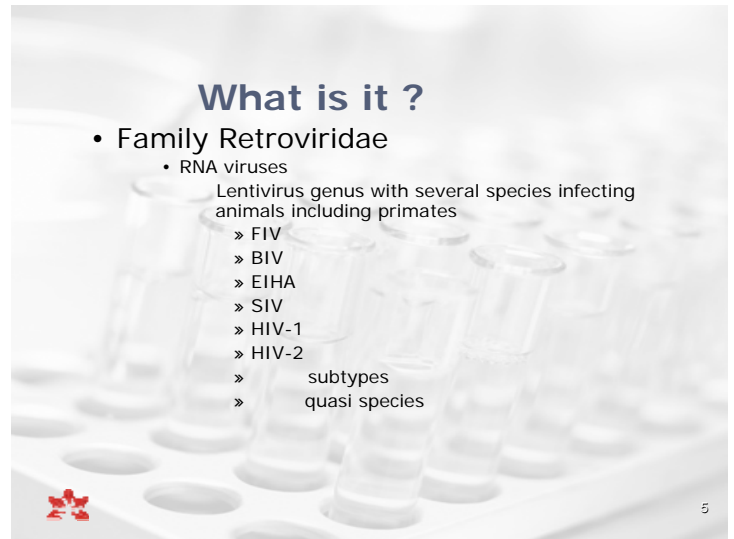


What is it ?



What is it ?

- Family Retroviridae
 - RNA viruses
 - Lentivirus genus with several species infecting animals including primates
 - » FIV
 - » BIV
 - » EIHA
 - » SIV
 - » HIV-1
 - » HIV-2
 - » subtypes
 - » quasi species



Clinical Course

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Where did it Come from?

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Where did it come from ?

- HIV-1
 - Three distinct virus groups M,N,O
 - Group M commonest worldwide
 - 11 subtypes A through K
- HIV-2
 - Six subtypes
 - A through F

Phylogenetic studies support cross species transmission from non-human primates to humans in West Africa

Beatrice H. Hahn et al, Science 28 January 2000

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•HIV-1 Where did it come from?

- Chimpanzee subspecies in West equatorial Africa
- Infected with SIVcpz closely related to HIV-1 group M
- Hunted for food "bush meat"
- HIV-1 group M in human stored blood samples in west Africa by 1959
- Introduction into humans 1930(1910-1950)

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HIV-2 Where did it come from?

- Coastal west Africa
- Sooty mangabeys
- Phylogenetic relationship of SIVsm to HIV-2
- Identical genome structure
- Species is commonly infected with SIVsm
- Hunted for food , kept as pets

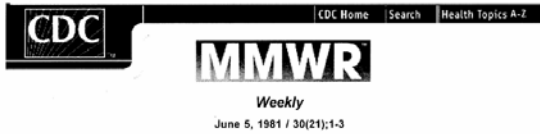
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Where is it Going ?

Mileposts and Challenges

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The first report in North America



Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

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AIDS In North America

- MMWR Weekly Report, June 5, 1981
5 cases PCP in previously healthy young gay men in Los Angeles
- MMWR report one month later of 26 cases Kaposi Sarcoma in gay men from New York and San Francisco
- 1982 " Acquired Immunodeficiency Syndrome" (AIDS) case definition
- 1983 1000 cases reported in total by end of February
Second 1000 by August
Third 1000 by year end
- 1984 HIV-1 isolated

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Survival After Initial AIDS Diagnosis

| Population | Time Period | Median Survival |
|--|---------------|-----------------|
| Surveillance cases USA, Australia, UK | 1980-1985 | 11.5 months |
| Surveillance cases USA | 1986 and 1987 | 13.9 months |
| Patients treated with AZT in USA, Italy, UK | | 22 months |

Adapted from The AIDS Knowledge Base, Little, Brown and Company, 1994

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First placebo controlled trial of AZT in AIDS

The New England Journal of Medicine

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Volume 317

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Number 4

THE EFFICACY OF AZIDOTHYIMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J. D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERG, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEBOW, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D. PHIL., DANNIE KING, PH.D., AND THE AZT COLLABORATIVE WORKING GROUP

Abstract We conducted a double-blind, placebo-controlled trial of the efficacy of oral azidothymidine (AZT) in 282 patients with the acquired immunodeficiency syndrome (AIDS) manifested by *Pneumocystis carinii* pneumonia in 45 subjects receiving placebo, as compared with 24 receiving AZT. The base-line Karnofsky performance score and weight increased significantly among AZT recipients ($P < 0.001$). A statistically significant increase in

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First placebo controlled randomized trial of AZT in AIDS 1987 NEJM

- 282 patients with AIDS or advanced AIDS related complex
- 250 mg AZT q 4 h or placebo
- Study terminated prematurely
- 1 death in 145 AZT subjects
- 19 deaths in 137 placebo subjects ($p < 0.001$)

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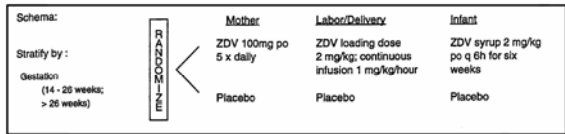
Where is it going?

- 1989 - only one drug: AZT
- The Canadian Multicentre AZT Trial 1987-1990 MCAT Montaner, Schechter, Wainberg, Ruedy et al.
- Canadian HIV Trials Network 1991
- More drugs in development
- 1990-1996 additional RTI's, new classes: NNRTIs and Protease Inhibitors

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ACTG 076 A Phase III Randomized, Placebo-Controlled Trial to Evaluate the Efficacy, Safety and Tolerance of Oral Zidovudine (ZDV) for the Prevention of Maternal-Fetal HIV Transmission

| | | | |
|--|------------------------------------|----------------------|--|
| Activated / Status: | 4-11-91/published and in follow-up | Protocol Co-Chair: | Edward Connor, M.D. David Spiegel, M.D. |
| Fig. Accrual: | 514 women as of 2-18-94/748 | Biostatisticians: | Richard Gelber, Ph.D. David Shapiro, Ph.D. |
| Change to Accrual/Projected Closure to FD: | 2-18-94/1-15-96 | SDAC Data Manager: | Bethann Cunningham, M.S. |
| Latest Protocol: | Version 2.0, 9-1-92 | Medical Monitor: | James Baileys, M.D., Ph.D. Mary Cavanaugh, M.S., C.R.N.P. John Moye, M.D. Patricia Stratten, M.D. |
| Committee / Phase: | Prenatal / III | Protocol Specialist: | Elizabeth Hawkins, A.A. |
| Number of Sites / Data Center: | 59 ACTUs / SDAC | | |



1994 67.5% relative reduction in transmission risk
8.3% in AZT group versus 25.5% in placebo group

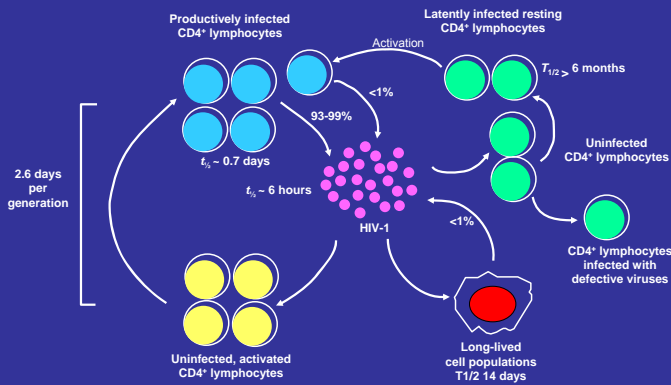


HAART as initial therapy

- Three or more drugs
- RTIs 7 approved
- NNRTIs 3 approved
- PIs 9 approved

Persistence of Infected Cells

The Dynamics of HIV-1 Infection in Vivo



Perelson A, et al. Science 1996;271:1582-6; Ho D. Vaccine 2002;20(Suppl 15):1933;Di Mascio M, et al. J Virology 2003;77:2271-5.

Mutations Conferring Resistance

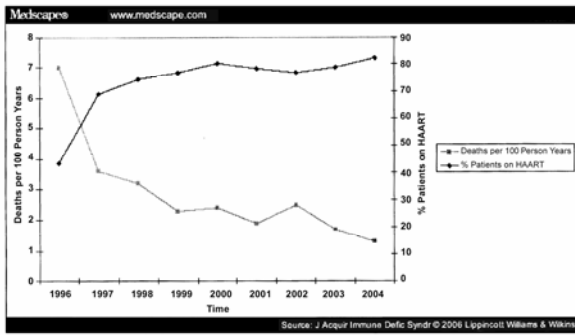
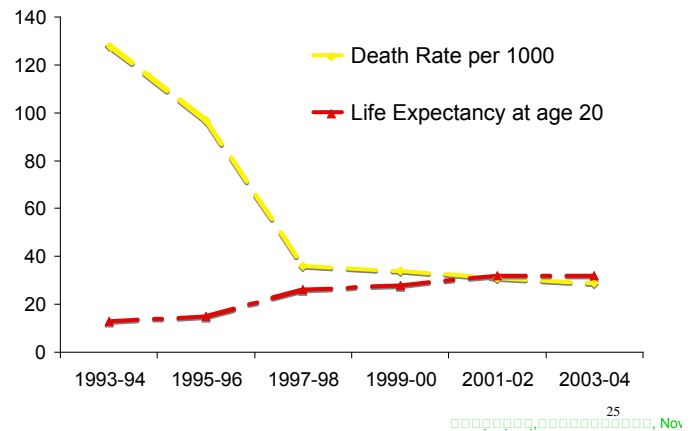


Figure 1.
Mortality and HAART use over time.

Impact of HAART in BC-CfE



What does the future hold?



Global HIV/AIDS estimates, end of 2006

- persons living with HIV/AIDS 39.5 million
 - sub-saharan Africa 24.7 million
- persons newly infected 4.3 million
 - about 12,000 per day
- AIDS deaths 2.9 million
 - about 7900 per day

UNAIDS Report on the Global AIDS Epidemic 2006

New Approaches to HIV Prevention

- Global HIV Prevention Working Group
- Bill and Melinda Gates Foundation & the Henry J. Kaiser Family Foundation
- Focus on prevention research
 - Women and HIV
 - Cervical Barriers to prevent HIV/STD transmission
 - Topically Applied Microbicides: 5 vaginal microbicides in trials

Global HIV/AIDS estimates, end of 2006

- Deaths since 1981 25 million
- Women account for 48 % of adults with HIV
 - In sub-saharan Africa 59%

UNAIDS Report on the Global AIDS Epidemic 2006

New Approaches to HIV Prevention

- Focus on prevention research
 - Male Circumcision 60% reduction in female to male transmission
 - Pre-exposure Prophylaxis with Antiretroviral Drugs in uninfected persons
 - Herpes Suppression
 - HIV Vaccines: IAVI estimates that a 50% effective vaccine given to one third of the population could cut new infections by one half in 15 years
- Expand treatment to prevent transmission

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