

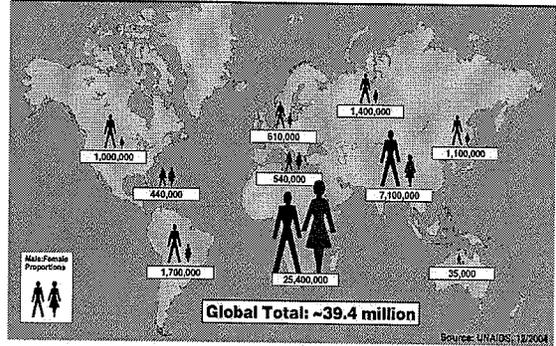
Presentation to PACHA on HIVNET 012



Anthony S. Fauci, M.D.
National Institute of Allergy and Infectious
Diseases
National Institutes of Health
Bethesda, Maryland, USA
February 7, 2005



Estimated Number of Persons Living with HIV/AIDS, December, 2004

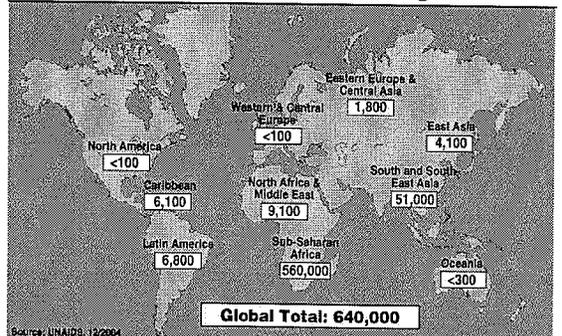


HIV/AIDS in Children: The Global Burden

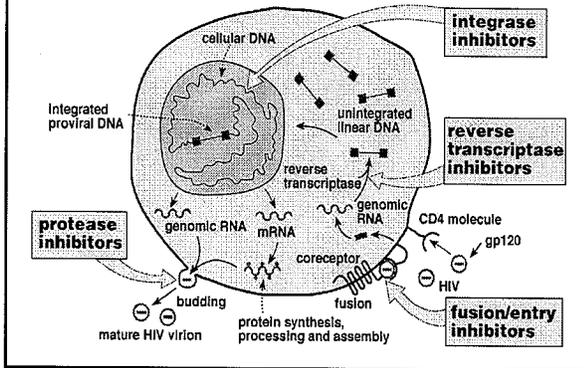
- Appx. 2.2 million children living with HIV/AIDS.
- In 2004, appx. 640,000 new HIV infections in children, vast majority during mother's pregnancy, labor and delivery, or via breastfeeding.
- In 2004, appx. 510,000 child deaths due to HIV/AIDS.

Source: UNAIDS

Estimated Number of Children (<15 years) Newly Infected with HIV During 2004



Targets for Antiretroviral Drugs



FDA-Approved Antiretroviral Medications

NRTI

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Zidovudine
- Zalcitabine
- Tenofovir

NNRTI

- Delavirdine
- Efavirenz
- Nevirapine

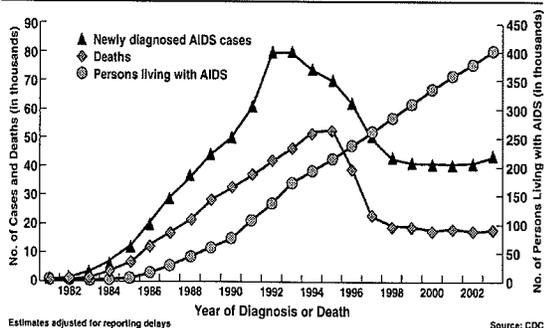
PI

- Amprenavir
- Atazanavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- soft gel
- hard gel

Fusion Inhibitor

- Enfuvirtide (T-20)

AIDS Cases, Deaths, and Persons Living with AIDS, United States, 1981-2003



Estimated Number of People Receiving Antiretroviral Therapy in Developing and Transitional Countries, December 2004

	Number of People on Treatment	Estimated Need	Coverage
Sub-Saharan Africa	310,000	4,000,000	8%
Latin America/Caribbean	275,000	425,000	65%
East, South, and South-East Asia	100,000	1,200,000	8%
Europe and Central Asia	15,000	150,000	10%
North Africa and Middle East	4,000	55,000	7%
All Regions	700,000	5,800,000	12%

Source: WHO/UNAIDS, 12/2005

Strategies to Prevent Mother-to-Child Transmission (MTCT) of HIV

- Decrease fetal exposure to virus before birth by treating mother with antiretroviral therapy during most of pregnancy
- Decrease infant exposure to HIV at delivery by treating mother and infant, and by Caesarian section if feasible
- Decrease postnatal infant HIV infection through breastfeeding by treating mother and/or infant

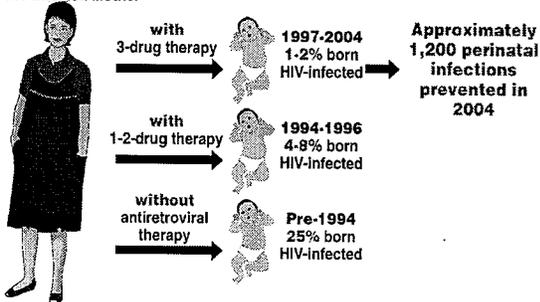
****Most effective strategy will be availability of potent, combination antiretroviral therapy in the entire HIV-infected population****

The New England Journal of Medicine
Established in 1811 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
 VOLUME 31 November 3, 1994 NUMBER 16

Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group
 Edward M. Conner, et al.

Antiretroviral Therapy Reduces Rate of Maternal-Fetal Transmission of HIV in the United States

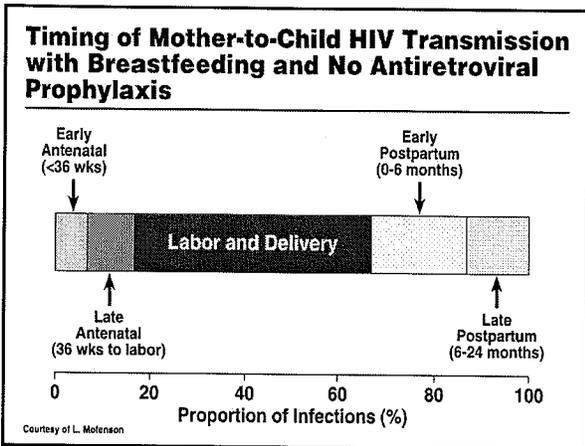
HIV-infected mother



The New York Times
 January 30, 2005

U.S. Is Close to Eliminating AIDS in Infants, Officials Say

...In 1990, as many as 2,000 babies were born infected with H.I.V., the virus that causes AIDS; now, that number has been reduced to a bit more than 200 a year, according to health officials. In New York City, the center of the epidemic, there were 321 newborns infected with H.I.V. in 1990, the year the virus peaked among newborns in the city. In 2003, five babies were born with the virus.



FDA U.S. Food and Drug Administration

FDA News

June 24, 1996

FDA Approves Nevirapine to Treat HIV

FDA today granted accelerated approval for nevirapine, the first in a new class of drugs – non-nucleoside reverse transcriptase inhibitors – cleared by the agency for treating HIV infection.

■ Pediatric approval granted September, 1998

THE LANCET

Volume 354 4 September 1999

Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: HIVNET 012 Randomised trial

Laura A. Guay et al.

Baby Girl (30 Minutes Old) Being Administered Nevirapine Suspension

Source: Boehringer Ingelheim

HIVNET 012 (Uganda): Nevirapine Markedly Reduces Maternal-Fetal HIV Transmission

Total Cost \$4.00

Nevirapine

Mother: 1 dose at onset of labor
Infant: 1 dose within 72 hours

13.1% Infected at 14-16 weeks

Potential to prevent 400,000 HIV infections in infants annually

AZT

Mother: 1 dose at onset of labor, additional doses every 3 hours during labor
Infant: 1 dose twice daily for 1 week

25.1% infected at 14-16 weeks

HIV-Infected Mother

Reference: Guay, et al. *Lancet* 354:785,1999.

THE LANCET

Number 9374 • Founded 1823 • Published weekly

Volume 362 September 13, 2003

Intrapartum and Neonatal Single-Dose Nevirapine Compared with Zidovudine for Prevention of Mother-to-Child Transmission of HIV-1 in Kampala, Uganda: 18-Month Follow-Up of the HIVNET 012 Randomised Trial

J Brooks Jackson et al.

XIII INTERNATIONAL AIDS CONFERENCE ABSTRACTS

XIII International AIDS Conference Abstracts
July, 2000
Durban South Africa

[LbOr2]

The SAINT Trial: Nevirapine (NVP) versus Zidovudine(ZDV)+Lamivudine (3TC) in Prevention of Peripartum HIV Transmission

University of Natal Medical School, Congella, South Africa

Conclusions: Both regimens were effective, with results comparable to those observed with NVP in HIVNET 012 and with ZDV/3TC in PETRA Arm B....

March 1, 2003

The Journal of Infectious Diseases

A Multicenter Randomized Controlled Trial of Nevirapine Versus a Combination of Zidovudine and Lamivudine to Reduce Intrapartum and Early Postpartum Mother-to-Child Transmission of Human Immunodeficiency Virus Type 1

D Moodley et al. for the South African Intrapartum Nevirapine Trial (SAINT) Investigators

No drug-related maternal or pediatric serious adverse events.

"This study further confirms the efficacy and safety of short-course ARV regimens in reducing MTCT rates in developing countries."

The
New England
Journal of Medicine

ESTABLISHED IN 1812 AS THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 351 JULY 15, 2004 NUMBER 3

Single-Dose Perinatal Nevirapine Plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand

M Lallemand et al. for the Perinatal HIV Prevention Trial (Thailand) Investigators

A single dose of NVP to the mother, with or without a dose of NVP to the infant, added to oral AZT prophylaxis starting at 28 weeks' gestation, is highly effective in reducing MTCT of HIV.

No serious adverse effects were associated with NVP therapy.

The
New England
Journal of Medicine

ESTABLISHED IN 1812 AS THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 351 JULY 15, 2004 NUMBER 3

Intrapartum Exposure to Nevirapine and Subsequent Maternal Responses to Nevirapine-Based Antiretroviral Therapy

G. Jourdain, et al.

Jourdain et al: Summary of Nevirapine (NVP) Resistance Data

- In observational study in Thailand, immunocompromised women (CD4+ T-cell counts <250/mm³) received either intrapartum NVP (n=221) or no intrapartum NVP (n=48), and then began NVP-containing HAART.
- At day 10, 32% of mothers receiving intrapartum NVP had resistance mutations.
- At six months, mothers on NVP-containing HAART achieved maximal virologic suppression (<50 HIV RNA copies/ml) as follows:

No intrapartum NVP (n=40)	68%
Intrapartum NVP, no NVP resistance mutations (n=119)	52%
Intrapartum NVP, NVP resistance mutations (n=61)	38%
- Groups had similar clinical improvement and equivalent increases in CD4+ T-cell counts.

The
New England
Journal of Medicine

ESTABLISHED IN 1812 AS THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
VOLUME 351 JULY 15, 2004 NUMBER 3

Antiretroviral Agents - How Best to Protect Infants from HIV and Save Their Mothers from AIDS

Hoosen Coovadia, M.D

"...We need to clarify the longer-term clinical significance of these lower rates of maximal viral suppression, especially given the similar clinical improvement (weight gain) and equivalent increases in CD4 cell counts in the two groups. In addition, the success of HAART after single-dose nevirapine may be improved by delaying treatment until resistance mutations have faded; in the study by Jourdain et al., HAART was given to about half the women within six months after delivery.

...as Jourdain et al. themselves recognized, their results are not a reason to abandon single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1. Single-dose nevirapine is a regimen of striking simplicity, efficacy, and affordability (reminiscent of that of oral poliovirus vaccine)."

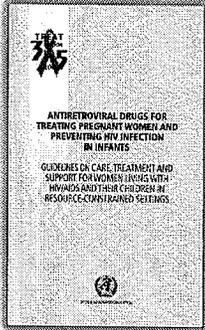

U.S. Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA Public Health Advisory for Nevirapine (Viramune)

January 19, 2005

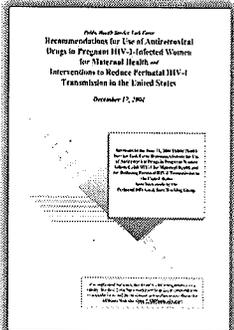
- "Both clinically symptomatic and asymptomatic liver toxicity are observed with **long-term** use of nevirapine in combination with other HIV drugs."
- "Symptomatic liver toxicity has not been reported with the use of single doses of nevirapine to the mother and to the child for prevention of perinatal HIV infection."

WHO and USPHS Guidelines to Prevent Mother-to-Child Transmission of HIV, 2004



ANTIRETROVIRAL DRUGS FOR TREATING PREGNANT WOMEN AND PREVENTING HIV INFECTION IN INFANTS

GUIDELINES ON CARE, TREATMENT AND SUPPORT FOR WOMEN LIVING WITH HIV/AIDS AND THEIR CHILDREN IN RESOURCE-CONSTRAINED SETTINGS



Recommendations for Use of Antiretroviral Drugs to Prevent HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States

December 17, 2004

HIVNET 012 Critical Points

1999

Sep 4 Proof-of-concept study published in *Lancet*, clearly demonstrating safety and efficacy of single dose NVP for the prevention of MTCT of HIV

2000

Jul Corroborating data from SAINT Study presented at XIII International AIDS Conference, Durban, S.A.

2001

Aug Boehringer Ingelheim (BI) filed supplemental NDA with FDA for expansion of NVP indication in US to MTCT

2002

Jan 5-7 BI site visitors report procedural issues to DAIDS
 Jan 28 DAIDS contracted Westat to conduct a site visit
 Feb 18-28 Westat site visit
 Mar 8 Westat report

HIVNET 012 Critical Points

2002 (cont)

Jun 7 DAIDS staff unanimously confirmed that procedural problems identified in early 2002 had no bearing on the proven safety and efficacy of the single-dose nevirapine regimen.

Jun 19 President announced \$500M MTCT initiative for Africa/Caribbean

DAIDS conducted comprehensive Re-monitoring:

- Jun - Advance Team Re-monitoring site visit
- Jul-Sep - Stage 1 Re-monitoring site visit
- Oct-Nov - Stage 2 Re-monitoring site visit

2003

Mar 30 DAIDS published HIVNET 012 Monitoring "Omnibus" Report

2004

Dec 13 Reports of allegations appeared in AP stories

Associated Press

December 13, 2004

U.S. Officials Knew of AIDS Drug Risks

December 14, 2004

AIDS Research Chief Altered Drug Study

December 15, 2004

Woman Died During AIDS Study

“Me Too” Stories/Editorials

Cape Argus (South Africa)
December 27, 2004

US Report Supports Doubt on Nevirapine

Hartford Courant
December 27, 2004

An African “Tuskegee Study”

Palm Beach Post
December 29, 2004

How Not to Fight AIDS

Financial Gazette (Zimbabwe)
January 5, 2005

Shocking Revelations on AIDS Drug

Harsh Criticisms Based on Associated Press Stories

- ***“This was not a thoughtful and reasonable decision, but a crime against humanity.”***
(Rev. Jesse L. Jackson, Dec 16, 2004)
- ***“Dr. Tramont was happy that the peoples of Africa should be used as guinea pigs, given a drug he knew very well should not be prescribed.”***
(ANC Today, Dec 17-23, 2004)

Public Health Implications

- **Activists and Researchers Rally Behind AIDS Drug for Mothers**
(Dec 22, 2004 Erika Check – *Nature*)
- **Allegations Raise Fears of Backlash Against AIDS Prevention Strategy**
(Dec 24, 2004 Jon Cohen – *Science*)
- **Articles criticising nevirapine trial may endanger babies' lives**
(Jan 8, 2005 Bob Roehr – *BMJ*)
- **Nevirapine Misinformation: Will It Kill?**
(Dec 2004 John S. James – *AIDS Treatment News*)



National Institute of Allergy and Infectious Diseases
National Institutes of Health

March 22, 2002

STATEMENT

Review of HIVNET 012

"...An examination of the data to support an extension of the indication for the use of NVP to include prevention of MTCT was recently begun. Although no evidence has been found that the conclusions of HIVNET 012 are invalid or that any trial participants were placed at an increased risk of harm, certain aspects of the collection of the primary data may not conform to FDA regulatory requirements."

Reuters

March 22, 2002

AIDS Drug Defended After U.S. Orders Review

Associated Press

March 24, 2002

**UN Backs AIDS Drug Despite US Govt
Concern Over Trials**

South African Press Association

March 24, 2002

**WHO, UNAIDS to Continue Nevirapine
Support Despite "Irregularities"**

AIDS Treatment News

December 31, 2004

Nevirapine Misinformation: Will it Kill?

"...No new information about nevirapine was released; doctors know that it still has the same risks and benefits after the newspaper stories as before.

But many experts fear that the emotions released by the worldwide misinformation will result in many HIV-positive mothers getting no treatment and unnecessarily infecting their children with HIV."

HIVNET 012

Allegation: NIH officials were warned that research on nevirapine was flawed and may have underreported thousands of severe reactions including deaths.

Fact: This statement is absolutely false. Remonitoring reports of HIVNET 012 found no additional serious adverse reactions related to nevirapine. The original published study and the multiple subsequent reviews of the HIVNET 012 trial found only a very small number of serious adverse reactions that potentially might be due to nevirapine.

HIVNET 012 Serious Adverse Reactions Potentially Attributable to Study Drug

In the six weeks following treatment:

- 309 infants in the AZT arm, 38 had SAEs, 7 events possibly due to AZT
- 320 infants in the NVP arm, 35 had SAEs, only 2 possibly due to NVP
- 302 mothers in the AZT arm, 12 had SAEs, only 1 possibly due to AZT
- 306 mothers in the NVP arm, 16 had SAEs, only 1 possibly due to NVP

HIVNET 012

Allegation: NIH officials chose not to inform the White House in the spring of 2002 about safety issues concerning nevirapine.

Fact: There is no truth to the allegation that NIH officials chose not to inform the White House in the spring of 2002 about safety issues concerning nevirapine.

No direct report to the White House was necessary, because there were no new data that changed the conclusion of the initial HIVNET 012 report, that is, that single-dose nevirapine is a safe and effective regimen for blocking mother-to-infant HIV transmission.

HIVNET 012

Allegation: There has been scientific and administrative misconduct by staff within NIAID's Division of AIDS.

Fact: The allegations of misconduct have been assessed by the NIH Office of the Director and have been found to be completely without merit.

To address the issues of the scientific validity of the study, NIH has contracted with the Institute of Medicine to conduct an additional independent review of HIVNET 012.

HIVNET 012

Allegation: Dr. Edmund Tramont inappropriately "altered" a re-monitoring report related to HIVNET 012.

Fact: These allegations are false. As Director of the NIAID Division of AIDS (DAIDS), Dr. Edmund Tramont had the overall responsibility for generating a re-monitoring report concerning HIVNET 012. He edited several subreports (initially drafted by several DAIDS staff members) to make sure that the final "omnibus" report accurately reflected the *entire* re-monitoring process.

IOM Review of HIVNET 012 Perinatal HIV Prevention Study

Timeline of Activities:

- Review began July 2004
- Meetings:
 - September 30-October 1, 2004 (open meeting September 30)
 - November 4-5, 2004
 - January 4-5, 2005 (open meeting on January 4)
- Anticipated completion date March 2005

Edmund C. Tramont, M.D., F.A.C.P.

- B.S. Rutgers University (1962) / M.D. Boston University (1966)
- Internship / Residency / ID Fellowship: Cornell (Bellevue/Sloan Kettering), Walter Reed
- >145 Research/Scientific Publications
- US Army (1968 – 1991), Colonel (retired), Army Service Medal
 - 1968-69 Walter Reed (assigned to medical team for former President Dwight D. Eisenhower)
 - 1969-83 Chief, Infectious Diseases, Walter Reed (ID surveillance, care & treatment of Viet Nam soldiers)
 - 1974-91 Consultant - Infectious Diseases, Office of the Surgeon General (Developed care & treatment policies for Desert Shield / Desert Storm)
 - 1983-85 Consultant - Medicine, Office of the Surgeon General (Developed Human Subjects Protection Guidelines for the US Army)
 - 1985-91 Director, DoD HIV/AIDS program, Associate Director WRAIR (Established U.S. Military HIV Research Program)

Edmund C. Tramont, M.D., F.A.C.P.

- Clinical Trial Execution/Oversight Experience (domestic and international)
 - Approx. 20 trials for vaccines (USA, Chile, Korea, Thailand, Egypt, and Israel)
 - Approx. 10 trials for antimicrobials (USA, Viet Nam, Kenya, and Thailand)
- University of Maryland (1991 - 2001)
 - Director (Dean) Medical Biotechnology Center (Estab. Institute of Human Virology)
 - Co-founder NovaVax, Inc
- Director, DAIDS/NIAID/NIH (2001 - present)

