HIV: FROM DISCOVERY TO CURE

Michael S. Gottlieb, M.D.

Associate Clinical Professor of Medicine UCLA

From Discovery to Cure
An Epic in Three Parts

Part One: Discovery, OI's to the first ARV's

Part Two: HAART to STR's

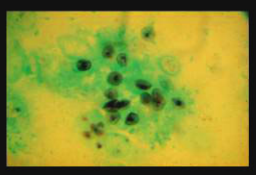
Part Two: Part Three: Cure?

January 1981

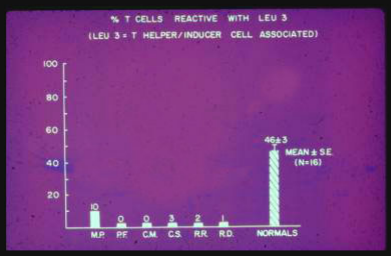
- Inflation and unemployment
- Hostages in Iran
- Reagan inaugurated

January,1981, UCLA Medical Center

Pneumocystis pneumonia



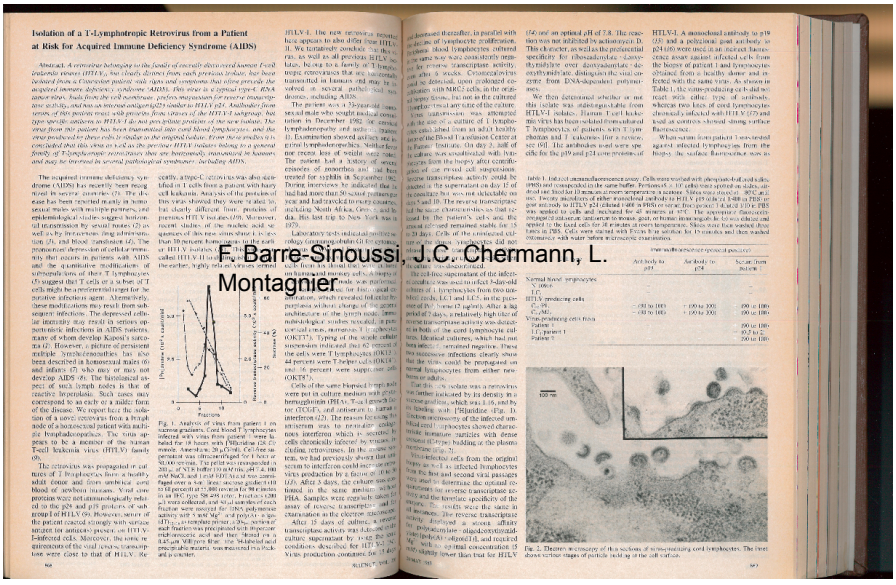
Pneumocystis on smear



T cells of first 6 patients

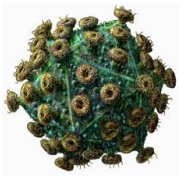
MMWR 6/5/81 NEJM 12/10/81

1981-1984: Rampant Speculation About Etiology



Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

F. Barre-Sinoussi, J.C. Chermann, L. Montagnier



Critical Milestones in the '80's

1981: Discovery of the syndrome, the CD-4 deficiency, STI

1982: Additional means of transmission

1983: Discovery of HIV-1 (LAV; HTLV-3, ARV)

1985: FDA approval of first HIV antibody test

1987: AZT

1989: TMP-SMX Prophylaxis of PcP

1987
First drug to treat HIV infection

The New England
Journal of Medicine

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Volume 317 JULY 23, 1987 Number 4

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

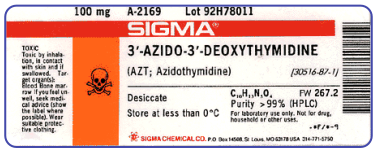
A Double-Blind, Placebo-Controlled Trial

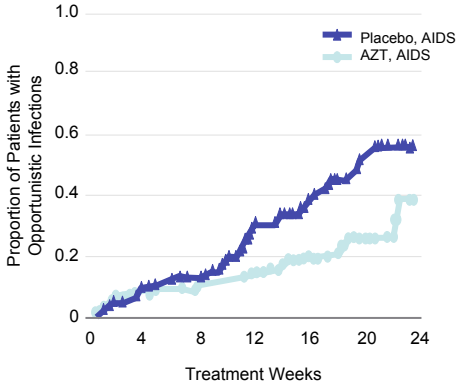
MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B.,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

The First Antiretroviral: AZT

The NEW ENGLAND JOURNAL of MEDICINE

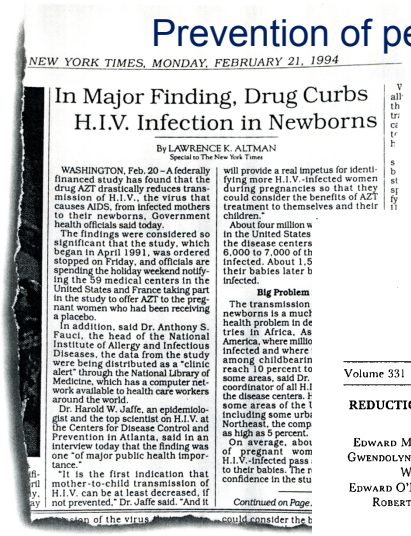
"…AZT administration can **decrease mortality and the frequency of opportunistic** infections…"





Fischl MA et al. N Engl J Med 1987;317:185–91

1994
Prevention of perinatal HIV (PMTCT)



NEW YORK TIMES, MONDAY, FEBRUARY 21, 1994

In Major Finding, Drug Curbs H.I.V. Infection in Newborns

By LAWRENCE K. ALTMAN
Special to The New York Times

WASHINGTON, Feb. 20 – A federally financed study has found that the drug AZT drastically reduces transmission of H.I.V., the virus that causes AIDS, from infected mothers to their newborns, Government health officials said today.

The findings were considered so significant that the study, which began in April 1991, was ordered stopped on Friday, and officials are spending the holiday weekend notifying the 59 medical centers in the United States and France taking part in the study to offer AZT to the pregnant women who had been receiving a placebo.

In addition, said Dr. Anthony S. Fauci, the head of the National Institute of Allergy and Infectious Diseases, the data from the study were being distributed as a "clinic alert" through the National Library of Medicine, which has a computer network available to health care workers around the world.

Dr. Harold W. Jaffe, an epidemiologist and the top scientist on H.I.V. at the Centers for Disease Control and Prevention in Atlanta, said in an interview today that the finding was one "of major public health importance."

"It is the first indication that mother-to-child transmission of H.I.V. can be at least decreased, if not prevented," Dr. Jaffe said. "And it will provide a real impetus for identifying more H.I.V.-infected women during pregnancies so that they could consider the benefits of AZT treatment to themselves and their children."

About four million w in the United States the disease centers 6,000 to 7,000 of th infected. About 1.5 their babies later b infected.

Big Problem

The transmission newborns is a much health problem in de tries in Africa. As America, where millio infected and where among childbearin reach 10 percent to some areas, said Dr. coordinator of all H.I the disease centers. I some areas of the t including some urbi Northeast, the comp as high as 5 percent.

On average, abou of pregnant wom H.I.V.-infected pass to their babies. The r confidence in the stu

Continued on Page

The New England Journal of Medicine

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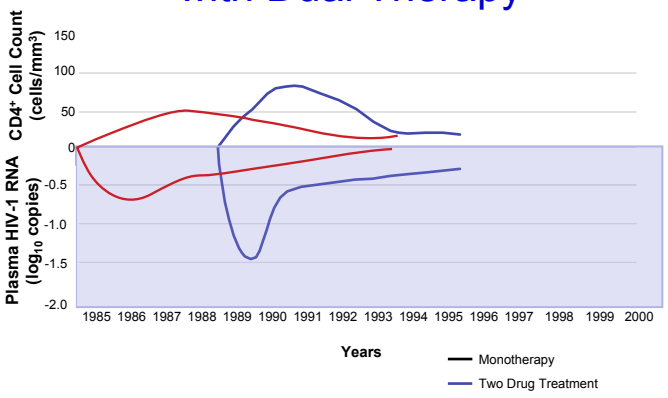
Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., PH.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANÇOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., PH.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., PH.D., FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP*

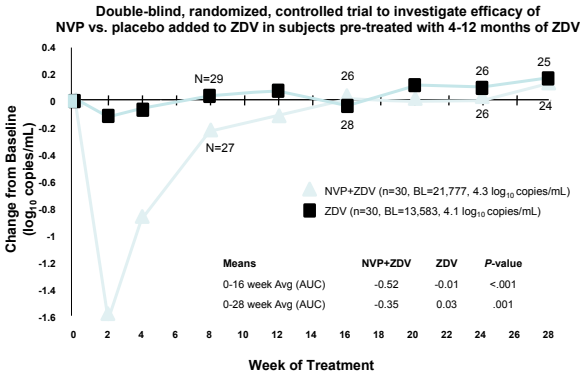
Changes in Surrogate Markers with Dual Therapy



Cohen CJ J Manag Care Pharm. 2006;12(7)(suppl S-b):S6-S11.

BI 1037

Sequential Addition of ARVs Results in Resistance Development

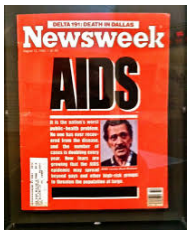


*The clinical significance of changes in serum viral RNA measurements during treatment with Viramune® has not been established.

Adapted from Murphy R. *Exp Opin Invest Drugs* 1996;5(9):1183-1199.

1987-1995

- Interferon
- Isoprinosine
- Compound Q
- AL-721
- Ribavirin
- Curcumin
- Winter melon
- Kombucha broth



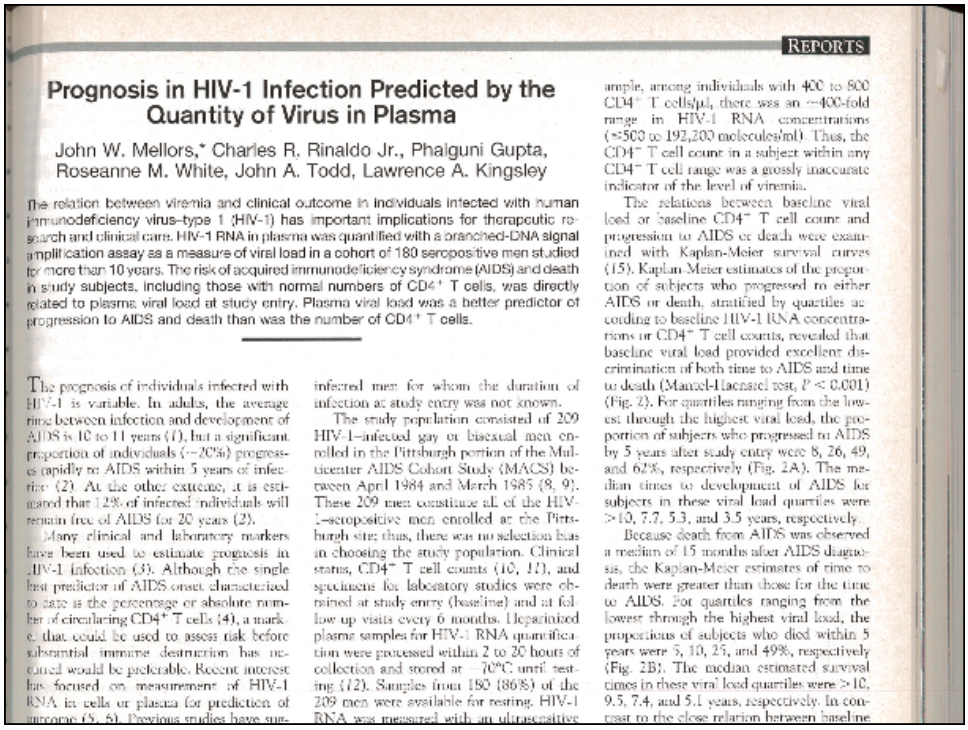
From Discovery to Cure

Part Two: The age of HAART

The Pivotal Year. 1996

11th International Conference on AIDS Vancouver, BC.

- Combination therapy (HAART) leads to a dramatic decline in AIDS-related deaths.
- Mellors reports viral load and CD4 count predict clinical course.
- Montaner, Markowitz, and Gulick report that HAART controls HIV infection and disease progression.
- David Ho advocates for “hit early, hit hard.”
- Sperling reports significant association of viral load and transmission from ACTG 076.



REPORTS

Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma

John W. Mellors,* Charles R. Rinaldo Jr., Phalguni Gupta, Roseanne M. White, John A. Todd, Lawrence A. Kingsley

The relation between viremia and clinical outcome in individuals infected with human immunodeficiency virus–type 1 (HIV-1) has important implications for therapeutic research and clinical care. HIV-1 RNA in plasma was quantified with a branched-DNA signal amplification assay as a measure of viral load in a cohort of 180 seropositive men studied for more than 10 years. The risk of acquired immunodeficiency syndrome (AIDS) and death in study subjects, including those with normal numbers of $CD4^+$ T cells, was directly related to plasma viral load at study entry. Plasma viral load was a better predictor of progression to AIDS and death than was the number of $CD4^+$ T cells.

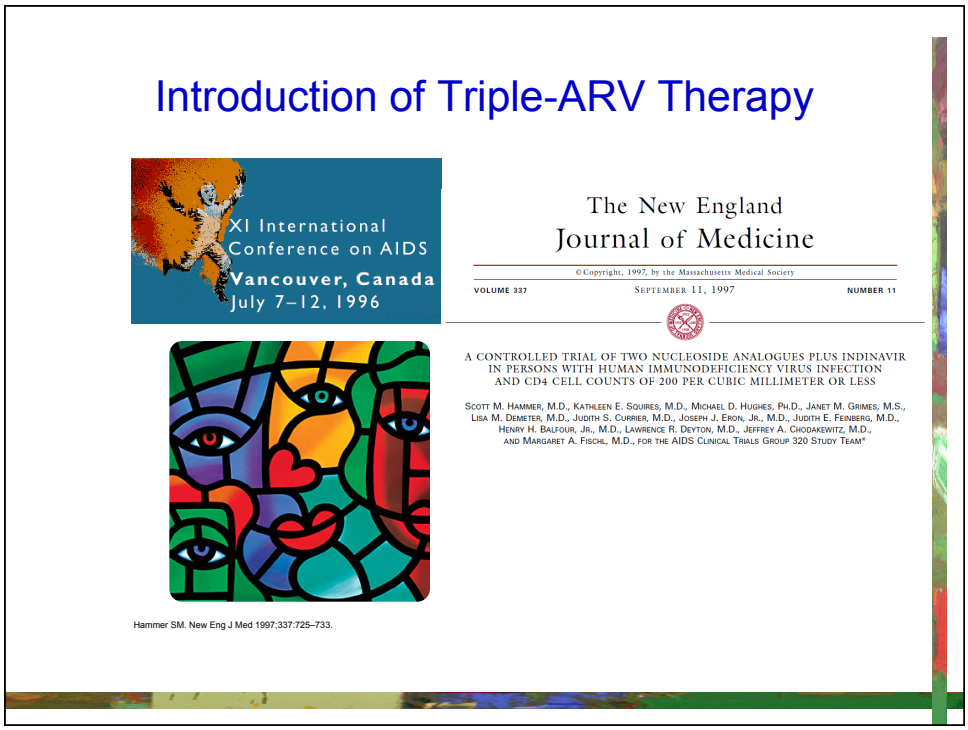
The prognosis of individuals infected with HIV-1 is variable. In adults, the average time between infection and development of AIDS is 10 to 11 years (1), but a significant proportion of individuals (~20%) progresses rapidly to AIDS within 5 years of infection (2). At the other extreme, it is estimated that 12% of infected individuals will remain free of AIDS for 20 years (3).

Many clinical and laboratory markers have been used to estimate prognosis in HIV-1 infection (3). Although the single best predictor of AIDS onset characterized to date is the percentage or absolute number of circulating $CD4^+$ T cells (4), a marker that could be used to assess risk before substantial immune destruction has occurred would be preferable. Recent interest has focused on measurement of HIV-1 RNA in cells or plasma for prediction of outcome (5, 6). Previous studies have surveyed infected men for whom the duration of infection at study entry was not known.

The study population consisted of 209 HIV-1–infected gay or bisexual men enrolled in the Pittsburgh portion of the Multicenter AIDS Cohort Study (MACS) between April 1984 and March 1985 (8, 9). These 209 men constitute all of the HIV-1–seropositive men enrolled at the Pittsburgh site; thus, there was no selection bias in choosing the study population. Clinical status, $CD4^+$ T cell counts (10, 11), and specimens for laboratory studies were obtained at study entry (baseline) and at follow up visits every 6 months. Heparinized plasma samples for HIV-1 RNA quantification were processed within 2 to 20 hours of collection and stored at −70°C until testing (12). Samples from 180 (86%) of the 209 men were available for testing. HIV-1 RNA was measured with an ultrasensitive assay, among individuals with 400 to 800 $CD4^+$ T cells/μl, there was an ~400-fold range in HIV-1 RNA concentrations (~500 to 192,200 molecules/ml). Thus, the $CD4^+$ T cell count in a subject within any $CD4^+$ T cell range was a grossly inaccurate indicator of the level of viremia.

The relations between baseline viral load or baseline $CD4^+$ T cell count and progression to AIDS or death were examined with Kaplan-Meier survival curves (15). Kaplan-Meier estimates of the proportion of subjects who progressed to either AIDS or death, stratified by quartiles according to baseline HIV-1 RNA concentrations or $CD4^+$ T cell counts, revealed that baseline viral load provided excellent discrimination of both time to AIDS and time to death (Mantel-Haenszel test, $P < 0.001$) (Fig. 2). For quartiles ranging from the lowest through the highest viral load, the proportion of subjects who progressed to AIDS by 5 years after study entry were 8, 26, 49, and 62%, respectively (Fig. 2A). The median times to development of AIDS for subjects in these viral load quartiles were >10, 7.7, 5.3, and 3.5 years, respectively.

Because death from AIDS was observed a median of 15 months after AIDS diagnosis, the Kaplan-Meier estimates of time to death were greater than those for the time to AIDS. For quartiles ranging from the lowest through the highest viral load, the proportions of subjects who died within 5 years were 5, 10, 25, and 49%, respectively (Fig. 2B). The median estimated survival times in these viral load quartiles were >10, 9.5, 7.4, and 5.1 years, respectively. In contrast to the close relation between baseline



Introduction of Triple-ARV Therapy

The New England Journal of Medicine

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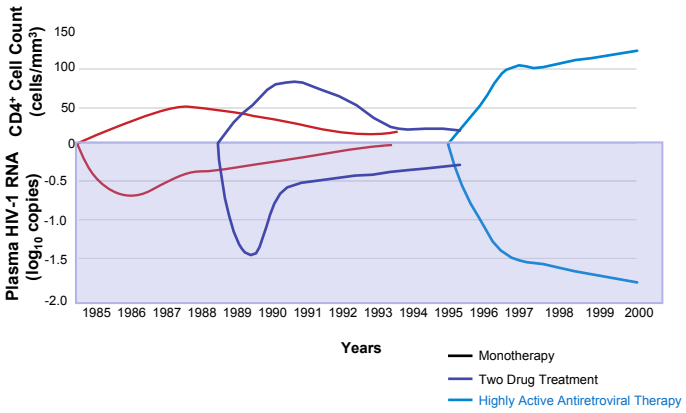
VOLUME 337 SEPTEMBER 11, 1997 NUMBER 11

A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

SCOTT M. HAMMER, M.D., KATHLEEN E. SQUIRES, M.D., MICHAEL D. HUGHES, PH.D., JANET M. GRIMES, M.S., LISA M. DEMETER, M.D., JUDITH S. CURRIER, M.D., JOSEPH J. ERON, JR., M.D., JUDITH E. FEINBERG, M.D., HENRY H. BALFOUR, JR., M.D., LAWRENCE R. DEYTON, M.D., JEFFREY A. CHODAKEWITZ, M.D., AND MARGARET A. FISCHL, M.D., FOR THE AIDS CLINICAL TRIALS GROUP 320 STUDY TEAM*

Hammer SM. New Eng J Med 1997;337:725–733.

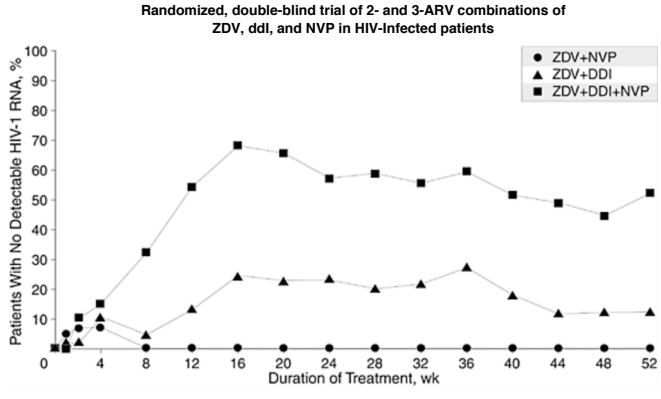
Changes in Surrogate Markers with HAART



Cohen CJ J Manag Care Pharm. 2006;12(7)(suppl S-b):S6-S11.

INCAS Trial: 2-ART vs 3-ART Regimens

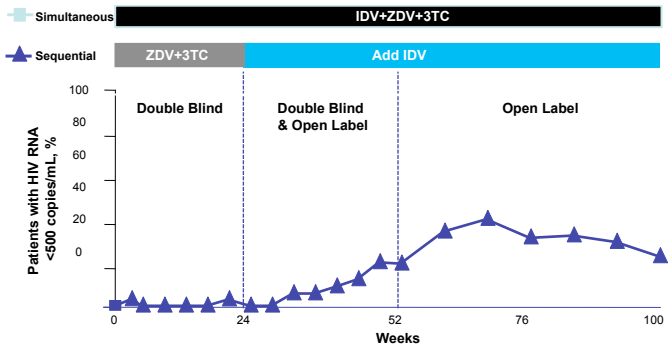
Virologic Suppression (<20 copies/mL) at Week 52



Montaner J, et al. JAMA 1998;279(12):930-937.

Merck 035

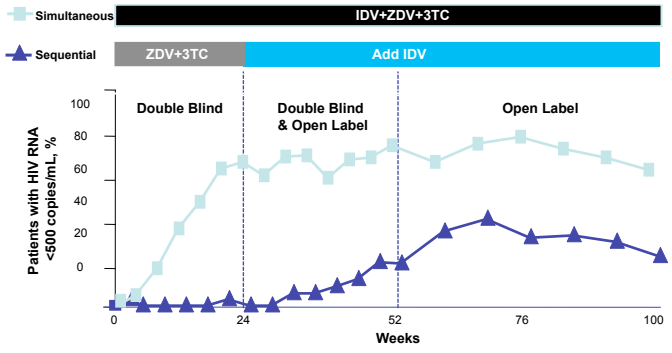
Sequential vs Simultaneous ARVs



Adapted from Gulick RM, *et al. JAMA* 1998;280:35.

Merck 035

Sequential vs Simultaneous ARVs



Simultaneous 3-ARV therapy results in 2 years of durable suppression, which is much longer than sequential therapy with the same ARVs

Adapted from Gulick RM, *et al. JAMA* 1998;280:35.

Lessons Learned

- 3 ARVs lead to durable suppression
  - Prevent viral resistance
- Start 3 active drugs simultaneously
- Recent development: the right two ARV's can do it

Lessons Learned

- 3 ARVs lead to durable suppression
  - Prevent viral resistance
- Start 3 active drugs simultaneously

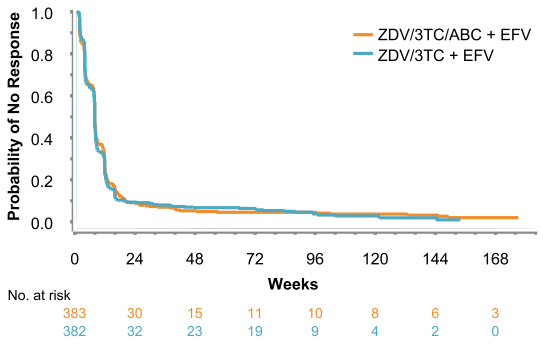
If 3 are good, are 4 better?
ZDV/3TC/EFV vs ZDV/3TC/ABC/EFV

Conceptual slide – based on expert opinion of the presenter.

ACTG 5095: (2 NRTIs vs. 3 NRTIs) with EFV

Time to Virologic Response*

Phase III, double–blind, placebo–controlled study of ART-naïve patients (n=765) randomized 1:1 to ZDV/3TC + EFV or ZDV/3TC/ABC + EFV



No. at risk

383	30	15	11	10	8	6	3
382	32	23	19	9	4	2	0

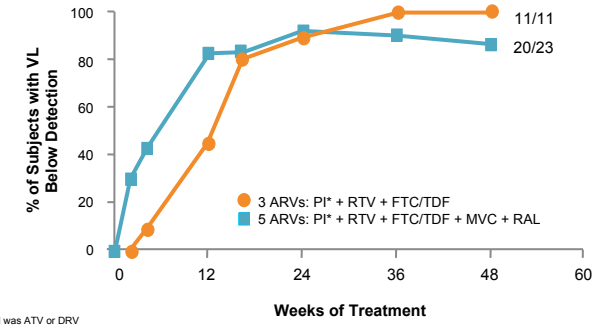
*Confirmed HIV-1 RNA <200 copies/mL

Adapted from Gulick R, et al. 45th ICAAC; December 16–19, 2005; Washington, D.C., Abstract H-416a.
Gulick RM, et al. JAMA 2006;296:769-81.

ADARC 2007-01: 3-Drug Therapy vs. 5-Drug Therapy

Virologic Outcomes

Phase II, open-label study of acutely infected HIV-1 subjects randomized 1:2 to PI* + RTV + FTC/TDF or PI* + RTV + FTC/TDF + MVC + RAL



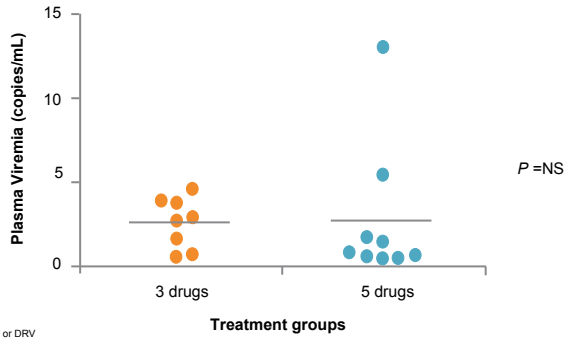
* PI was ATV or DRV

Adapted from Markowitz M *et al. 18th CROI*; Boston MA; Feb 27-Mar 2 2011. Abst 148LB.
Markowitz M, et al. JAIDS 2014;66:140-147.

ADARC 2007-01: 3-Drug Therapy vs. 5-Drug Therapy

Single-Copy Assay Results at Week 48

Phase II, open-label study of acutely infected HIV-1 subjects randomized 1:2 to PI* + RTV + FTC/TDF or PI* + RTV + FTC/TDF + MVC + RAL



* PI was ATV or DRV

Adapted from Markowitz M et al. 18th CROI; Boston MA; Feb 27-Mar 2 2011. Abst 148LB
Markowitz M, et al. JAIDS 2014;66:140-147.

Important Drug Warning: High Rate of Virologic Failure in Patients With HIV Infection Treated With a Once-Daily Triple NRTI Regimen Containing Didanosine, Lamivudine, and Tenofovir

Dear Healthcare Provider Letter From Gilead Sciences, Inc.

October 14, 2003

Dear Health Care Professional,

Gilead Sciences, Inc. (Gilead) is writing to inform you of a **high rate of early virologic failure and emergence of NRTI resistance-associated mutations** observed in a clinical study of HIV-infected treatment-naive patients receiving a once-daily **triple NRTI regimen containing ddI EC, 3TC, and TDF**. These new data are consistent with the high rates of virologic failure observed in several recent clinical studies that have evaluated the use of triple NRTI regimens. Based on these results [in 24-wk, single-site, pilot study (N=24)]:

- 91% virologic failure (<2 $\log_{10}$ HIV RNA reduction by Week 12)
- 95% (20/21) had M184I/V and 50% had K65R in addition to M184V

Sub-optimal virologic response has also been reported with the use of the triple NRTI regimen ABC/3TC/ZDV (Gulick 2003 [A5095 PI-sparing n=1147]) and ABC/ddI/d4T (Gerstoft 2003 [Denmark n=180]), and similarly early virologic failure and high rates of resistance mutations have been reported with ABC/3TC/TDF (Farthing 2003, Gallant 2003). Overall, these studies demonstrate a lower response rate in patients on a triple NRTI regimen. Furthermore, they indicate that patients who achieve viral suppression on a triple NRTI regimen have a higher rate of virologic failure.

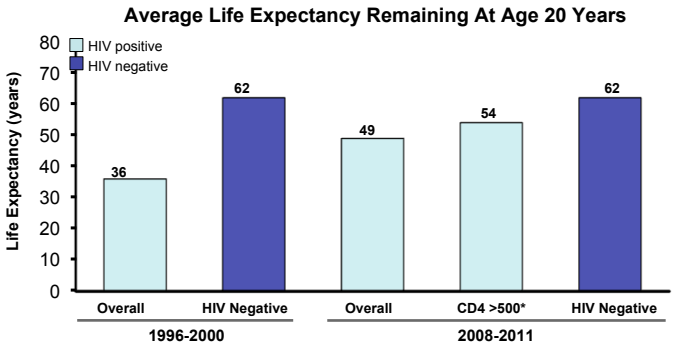
Lessons Learned

- 3 ARVs lead to durable suppression
  - Prevent viral resistance
- Start 3 active drugs simultaneously
  - And three are enough

Lessons Learned

- 3 ARVs lead to durable suppression
  - Prevent viral resistance
- Start 3 active drugs simultaneously
  - And three are enough
- Hit at least two targets

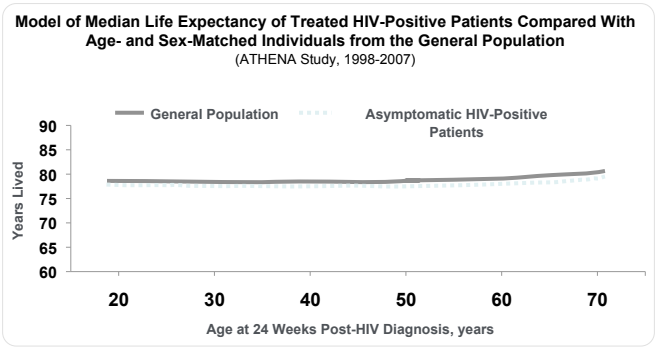
Narrowing the Gap in Life Expectancy Between HIV-Positive and Uninfected Persons



*CD4 (cells/mm^3) at time of starting ART.
Kaiser Permanente Northern California (1996 to 2011):
HIV-positive (n=25,768) and matched non-HIV-infected adults (n=257,600). Males (91%) and MSM (75%).

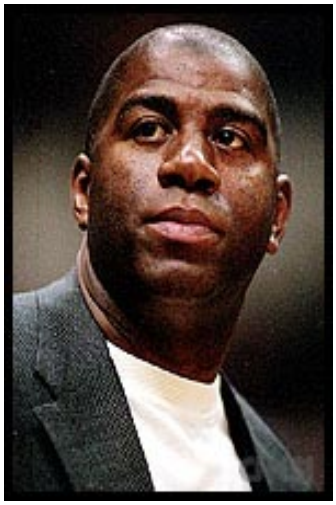
Marcus JL, et al. *JAIDS*. 2016;Mar 29. [Epub ahead of print]..

Current Life Expectancy of HIV-Positive Patients



ATHENA, AIDS Therapy Evaluation Project, Netherlands.
van Sighem AI, et al. *AIDS*. 2010;24:1527-1535.

•1991



From Discovery to Cure
An Epic in Three Parts

Part Two: Part Three: Can HIV be Cured?

The advantages of zero pills vs. one

The Berlin Patient

N Engl J Med. 2009; 360:692-8

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müllig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

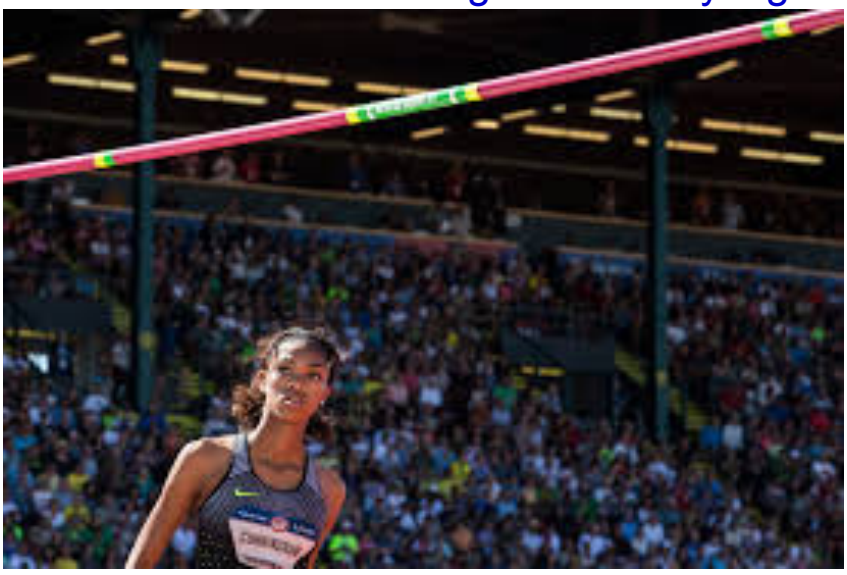
SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

Allers et al. Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation. Blood 2011: 117:2791-9

The 'Berlin Patient,' Timothy Brown, has been cured of HIV since 2007. His story has renewed interest in cure research.

The bar for a sterilizing cure is very high



WHY?

- There are key knowledge gaps re viremia and rebound
- Origin of persistent viremia?
  - Provirus that was latent, now activated?
  - Long-lived productively infected cells?
  - Ongoing replication (pharmacologic sanctuary?)
  - Cell types? Anatomic location?
- Origin of rebound virus after stopping ART
  - One cell, multiple cells?
  - One tissue, multiple tissues?

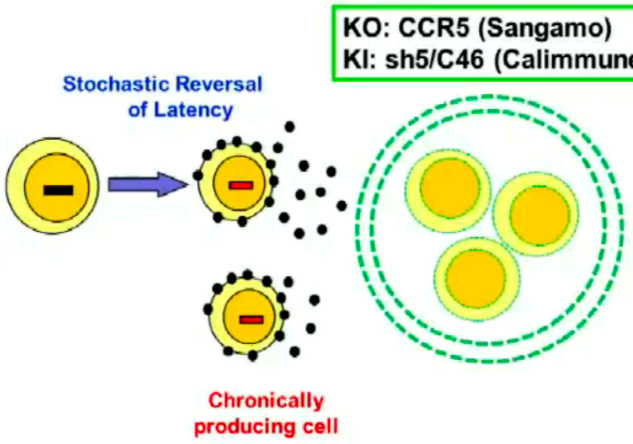
Why a **sterilizing** cure is the holy grail?

- stigma and criminalization of HIV
- economic burden
- access,
- toxicity of ART

Immune Control Approaches

- Antibodies
  - Broadly-neutralizing MoAb (promote ADCC?)
  - Ab drug conjugates
  - Bispecific Ab (anti-HIV/anti-CD3)
  - **Reverse immune exhaustion (anti-PD1/L1)***
- Cellular therapies
  - CD8+T-cells with affinity enhanced TCRs or **CARs (scFv)***
  - Activated NK cells
- Therapeutic Vaccines
  - Multiple approaches
  - Induction of de novo responses to epitope escape variants is key

Host cell modification



Strategies for Eradication of Reservoir

- Limit establishment of reservoir
- CCR5 disruption
- Inactivation of provirus/molecular scissors
- Flush out; shock and kill
- Acitretin, RIG-I inducer
- Immune checkpoint blockers (PD-1, LAG-3, TIGIT)
- AD26/MVA vaccine + TLR7 agonist

A combination of approaches likely necessary

Success Stories

- **Rapid discovery of HIV**
- **AZT in vitro**
- **Activists and political action**
- **PCMTC**
- **PCR**
- **Drug discovery**
- **HAART**
- **STR's**
- **Global access**
- **PrEP and PEP**
- **Injectable ARV's**

Thank
You