The Eras of the HIV Epidemic

1930-1980

1981-1986

1987-1995

Early

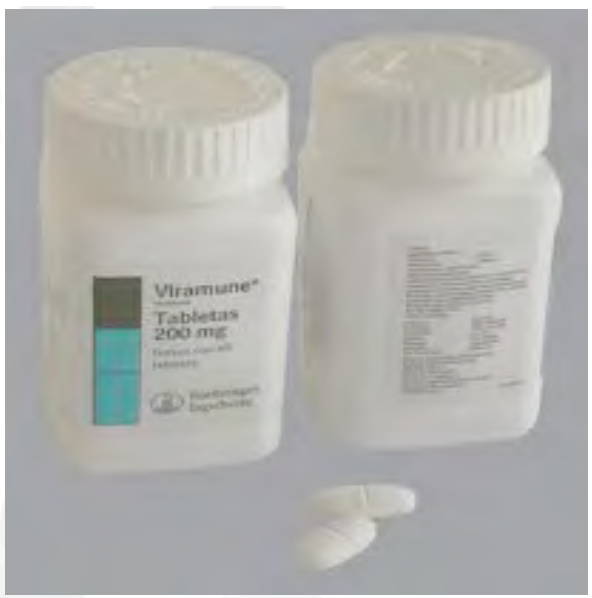
HAART

1996-20

05

The Early-HAART Era: 1996-2005

1996: 1st NNRTI
Nevirapine



2nd PI
Indinavir

3rd PI
Ritonavir

The Early-HAART Era: 1996-2005

1996: Establishment of Japanese Regional AIDS Care Core Hospitals and AIDS training collaboration with the US

Japanese physicians receive AIDS training at LAC+USC

Bathed in lights from a Japanese television crew, a trio of government physicians from Tokyo visited the Pacific AIDS Education Center for a glimpse of how their American counterparts care for patients with HIV.

Later, after completing tours of AIDS clinics and hospices, viewing actual patient examinations and participating in training seminars, the doctors, Makoto Aoki, Tadao Okano and Yoshihisa Akimoto, said they were pleased with all they had learned.

"We're very impressed with the thoroughness of the examination and the precision of the diagnosis by the doctors," Aoki said, noting that in Japan, doctors labor under such heavy work loads that they rarely spend more than five minutes with each patient.

"We're also impressed that you have so many volunteers at hospices and in the community who are well-motivated, well-trained and professional," he said.

For two weeks, the Japanese doctors participated in an intensive clinical care program here to learn what approaches work best in battling AIDS.

Such training is crucial because in Japan there is such heavy stigma attached to patients with AIDS and HIV that most hospitals and doctors simply refuse to treat them.

As a result, the government has had to require designated hospitals to begin treating HIV-positive patients.

"This kind of stigma only makes the situation worse," Aoki said.

Jerry Gates, director of the AIDS Education and Training Center, said the Japanese wanted to enter the program because the level of training it provides cannot be matched in their own country where there are comparatively few AIDS cases—which officially number about 4,000.

"We have a national reputation as a premier place to do clinical training. We offer an intensive program where, in a very short period of time, one can learn and practice those kinds of skills that are necessary to do the initial care for patients with HIV disease and see all the kinds of opportunistic infections one would expect to see in practice," Gates added.

Aoki agreed, adding "In this country, you have lots of experience with the disease. If you have a patient with this level of blood cells, you start this treatment. If the level of cells falls below another level, you start a different treatment. That's the kind of standardized care we don't have."

Ann Khalsa, assistant professor of clinical family medicine, prasied her visitors as caring and attentive to patients, and appreciative of the training they received.

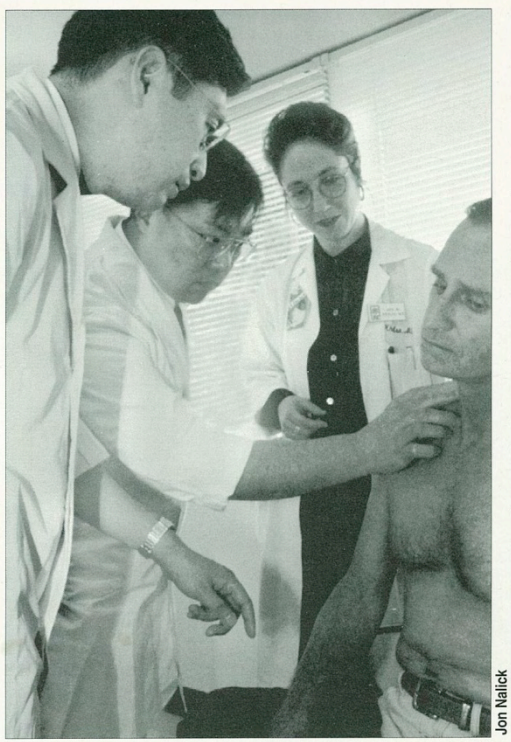
Khalsa, chief clinical trainer for the Aids Education and Training Program, had them particiapte in patient exams and interviews at the Rand Schrader Clinic for their training.

"We also sent them to APLA and Being Alive so they could start to prepare a community response to AIDS in Japan. It's exciting to realize the impact that the program can have and I can have. It's an honor and I just love doing it," she said.

Akimoto praised the program and its instructors, saying that they offered valuable experience and expertise that would help serve patients in his country.

"Overall, this was a wonderful experience."

—Jon Nalick



Jon Nalick

Japanese physicians Makoto Aoki (left) and Yoshihisa Akimoto examine Jay Fields, 47, of West Hollywood as part of training they received from Ann Khalsa of the Pacific AIDS Education and Training Program.

University of Southern California HSC Weekly April 5, 1996

The Early-HAART Era: 1996-2005

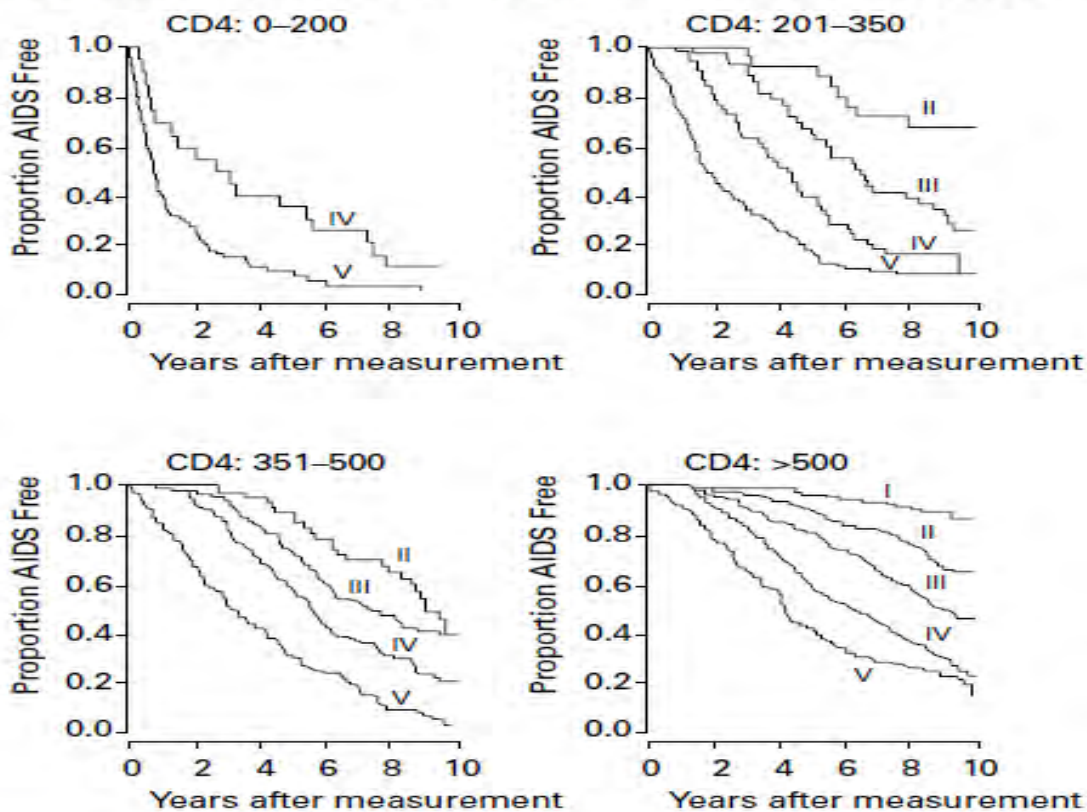
1996: 11th International AIDS Conference: "One World, One Hope"

Era of "HAART" cocktail therapy begins

The Early-HAART Era: 1996-2005

1996: Survival associated with baseline CD4 & VL

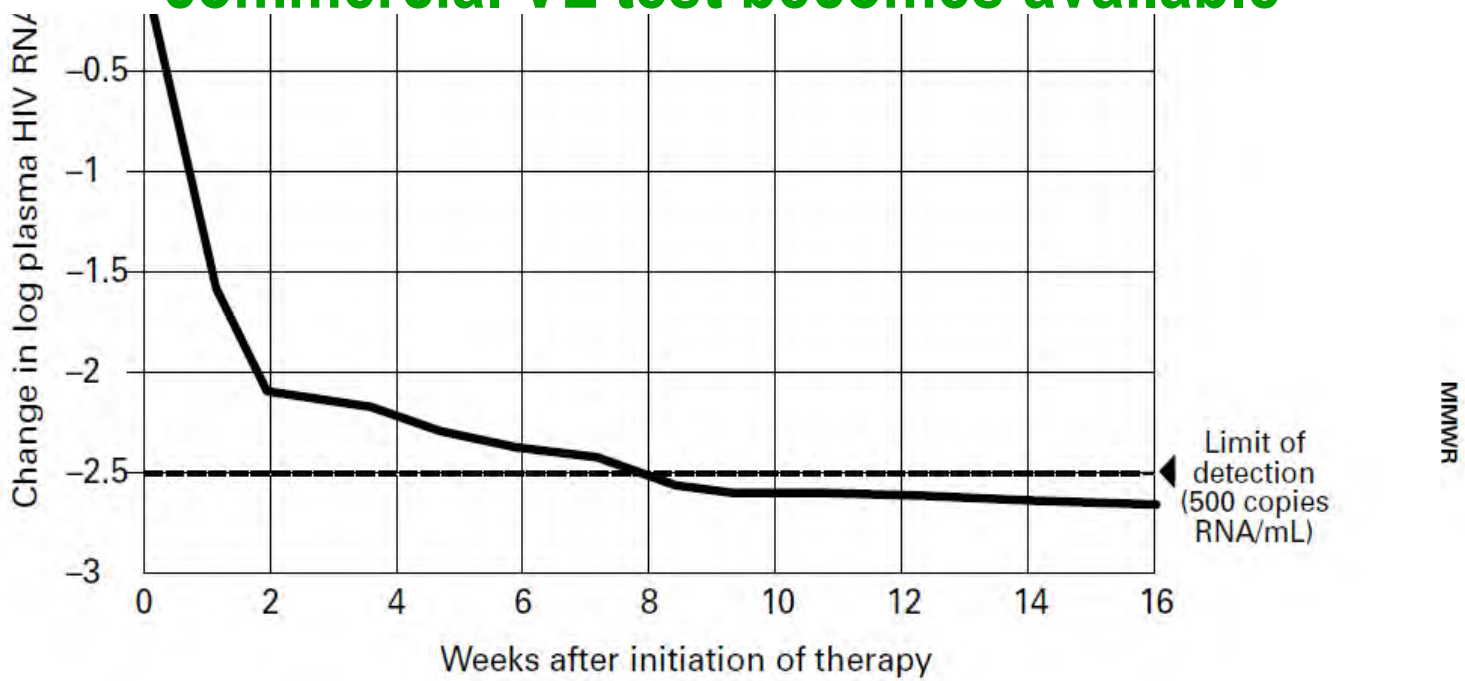
FIGURE 2. AIDS-free survival by baseline plasma HIV RNA and CD4+ T cell levels



Kaplan-Meier curves showing AIDS-free survival by plasma HIV RNA category among groups of persons with different baseline CD4+ T cell counts who participated in the Multicenter AIDS

The Early-HAART Era: 1996-2005

1996: VL suppression is new antiretroviral treatment goal, commercial VL test becomes available



A representative time course of rate of decline in plasma HIV RNA concentration (in $\log_{10}$ copies of RNA/mL) following initiation of a potent regimen of combination antiretroviral therapy (e.g., two nucleoside analog reverse transcriptase inhibitors [such as zidovudine

The Early-HAART Era: 1996-2005

1996: Use of CD4 and VL surrogate markers speed up clinical trials end points

Changes in Plasma HIV-1 RNA and CD4+ Lymphocyte Counts and the Risk of Progression to AIDS

William A. O'Brien, M.S., M.D., Pamela M. Hartigan, Ph.D., David Martin, Pharm.D., James Esinhart, Ph.D., Andrew Hill, Ph.D., Sharon Benoit, M.P.H., Marc Rubin, M.D., Michael S. Simberkoff, M.D., John D. Hamilton, M.D., and the Veterans Affairs Cooperative Study Group on AIDS

N Engl J Med 1996; 334:426-431 | February 15, 1996

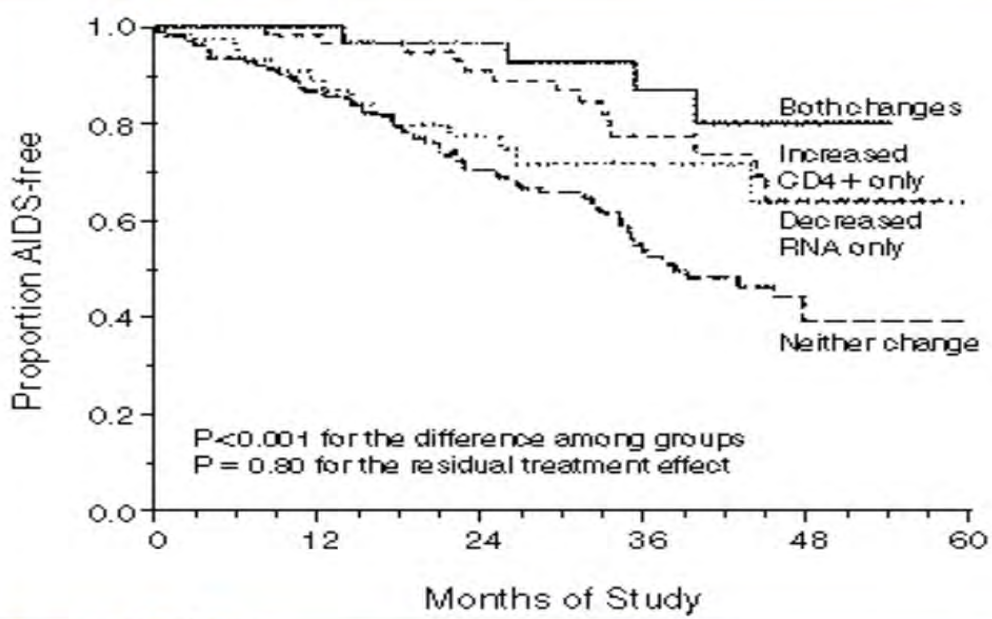


Figure 2. Kaplan–Meier Analysis of the Time to the Progression to AIDS in Patients Found to Have Both a Six-Month Mean Decrease of at Least 75 Percent in Plasma HIV-1 RNA and a Six-Month Mean Increase of at Least 10 Percent in the CD4+ Lymphocyte Count, One of These Changes, or Neither Change.

The Early-HAART Era: 1996-2005

1996: David Ho defines viral dynamics

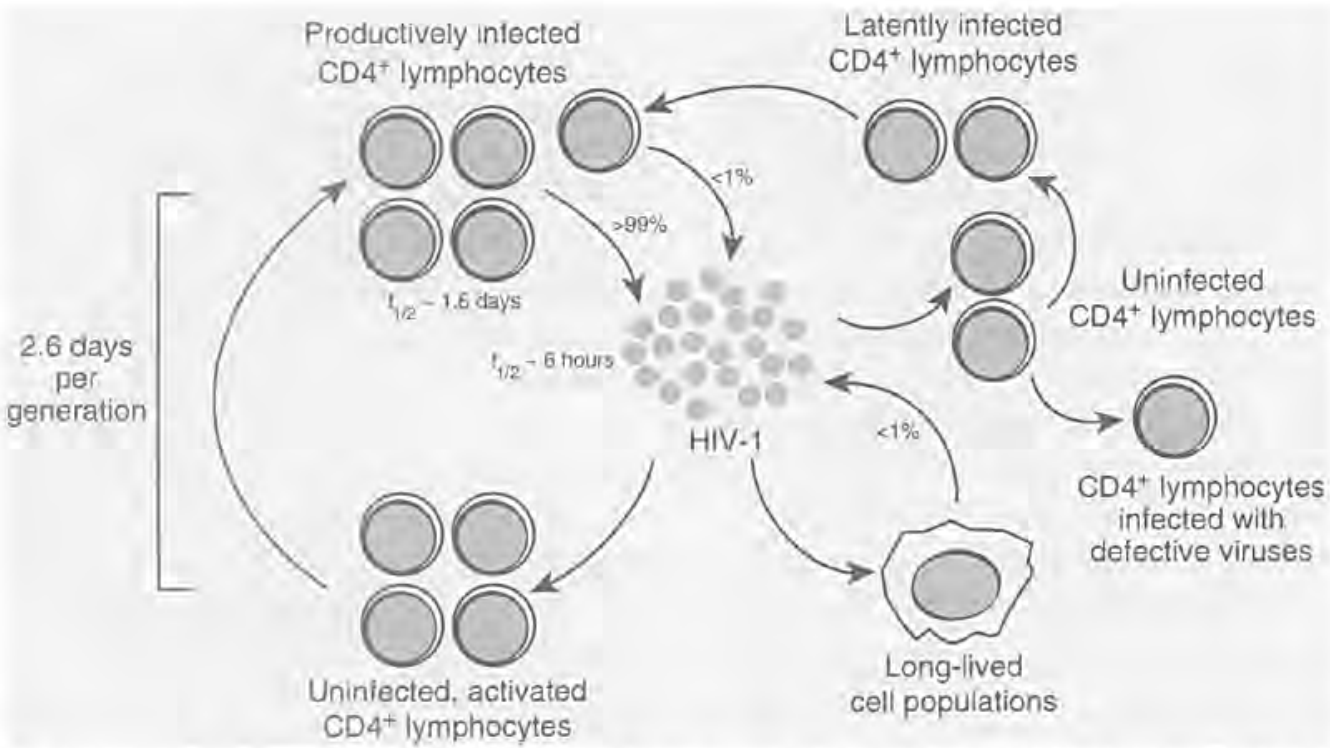


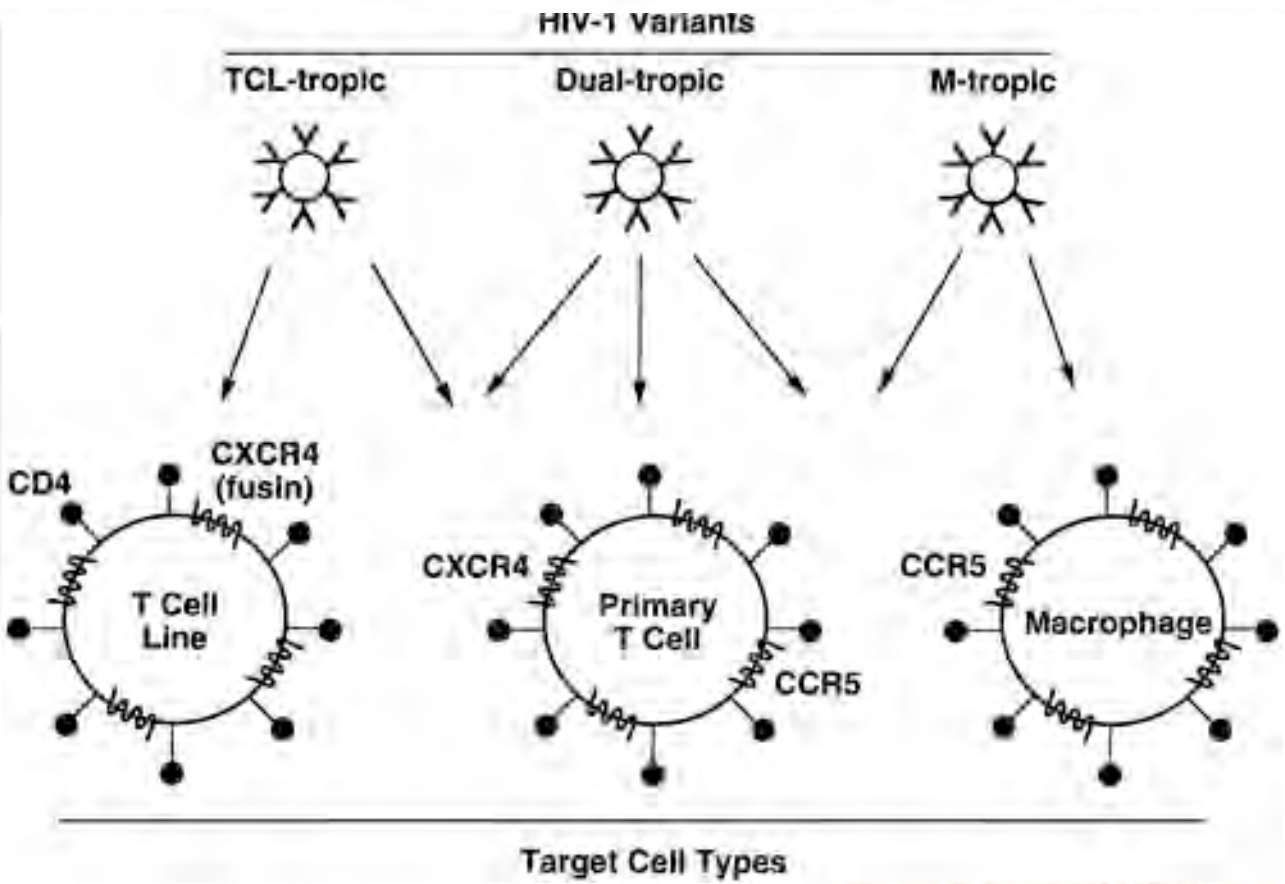
Fig. 2. Schematic summary of the dynamics of HIV-1 infection in vivo. Shown in the center is the cell-free virion population that is sampled when the viral load in plasma is measured.

SCIENCE • VOL. 271 • 15 MARCH 1996

The Early-HAART Era: 1996-2005

1996: Viral tropism discovered

HIV-1 entry into CD4$^+$ cells is mediated by the chemokine receptor CC-CKR-5



Nature **381**, 667 - 673 (20 June 1996);

The Early-HAART Era: 1996-2005

1996: Co-receptor deficiency confers resistance to HIV

Cell, Vol. 86, 367–377, August 9, 1996, Copyright ©1996 by Cell Press

Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection

Discussion

We show here that two individuals who are resistant to HIV-1 infection in spite of repeated exposures are homozygous for a defect in the gene encoding CKR-5, a major coreceptor for macrophage-tropic HIV-1 isolates.

The Early-HAART Era: 1996-2005

1996: Brazil is first developing nation to begin ARV distribution

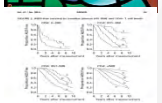
The Early-HAART Era: 1996-2005

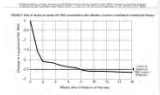
1996: UNAIDS begins

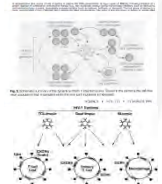
The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

- AIDS Clinical Center at the International Medical Center of Japan
- Regional AIDS Care Core Hospitals
- Japan – US AETC clinical training





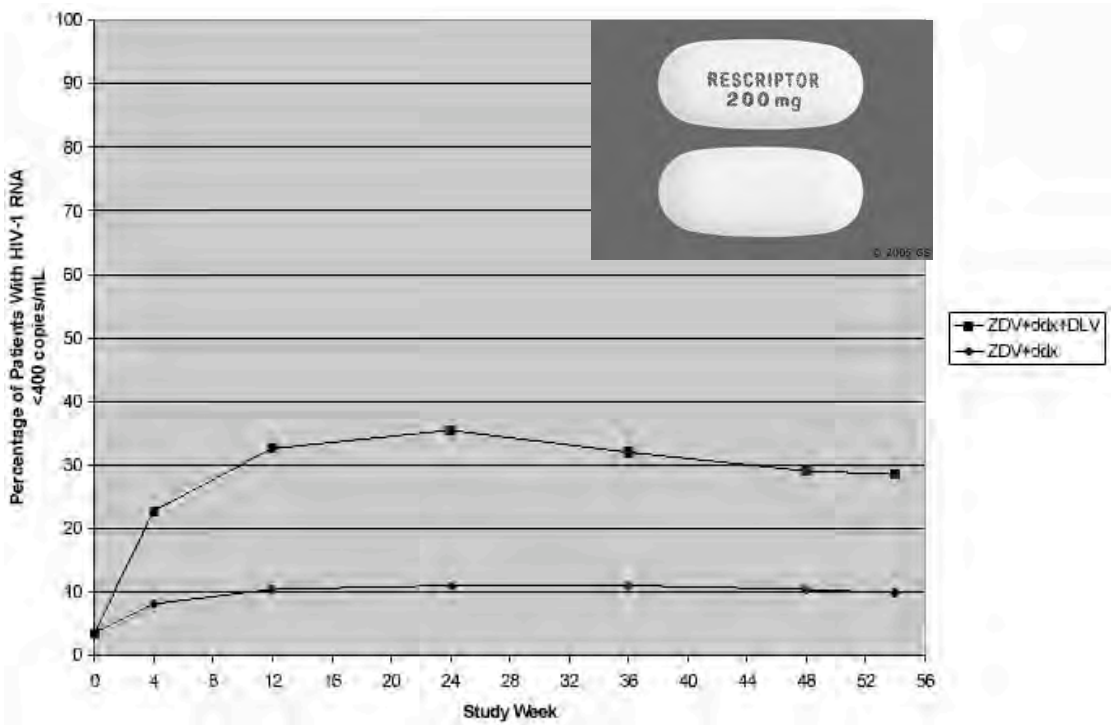


Joint United Nations Programme on HIV/AIDS
UNAIDS
UNICEF • UNDP • UNFPA • UNDCP
UNESCO • WHO • WORLD BANK

The Early-HAART Era: 1996-2005

1997: 1st combination NRTI: Combivir

2nd NNRTI: DLV Delavirdine



The Early-HAART Era: 1996-2005

1997: 4th PI: NFV Nelfinavir

PI Reformulation: Saquinavir soft gel caps

The Early-HAART Era: 1996-2005

1997: Patients struggle with high pill burden

The Early-HAART Era: 1996-2005

1997: HIV reservoir persists on HAART

Science 14 November 1997:
Vol. 278 no. 5341 pp. 1295-1300
DOI: 10.1126/science.278.5341.1295

Identification of a Reservoir for HIV-1 in Patients on Highly Active Antiretroviral Therapy

Diana Finzi, Monika Hermankova, Theodore Pierson, Lucy M. Carruth, Christopher Buck, Richard E. Chaisson, Thomas C. Quinn, Karen Chadwick, Joseph Margolick, Ronald Brookmeyer, Joel Gallant, Martin Markowitz, David D. Ho, Douglas D. Richman and Robert F. Siliciano*

The Early-HAART Era: 1996-2005

1997: Persistent CD4 increases on HAART

Conference Coverage (ICAAC)

T-Cell Gain Slow But Steady After Effective HIV Treatment

Published in **Gene Therapy Weekly**, *November 3rd, 1997*

Slow but steady T-cell increases in people receiving effective anti-HIV therapy may mean that their immune systems eventually will recover.

While it is too soon to know the extent to which competent immune function can be restored to people with HIV disease, available data are promising for those who begin highly active antiretroviral therapy (HAART) while their CD4 T-cell counts are still above 100 cells/(mu)L.

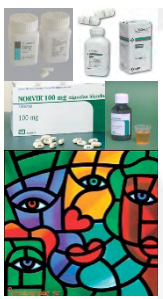
"Data suggest that there can really be repopulation of naive T cells that might have a full expression of the T-cell repertoire and might result in effective immune reconstitution, eventually," said Donald E. Mosier of The Scripps Research...

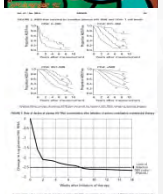
The Early-HAART Era: 1996-2005

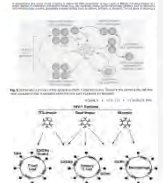
1997: AIDS walks across the USA

The Early-HAART Era: 1996-2005

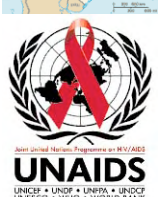
1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

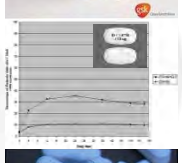


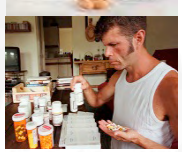




- AIDS Clinical Center at the International Medical Center of Japan
- Regional AIDS Care Core Hospitals
- Japan – US AETC clinical training





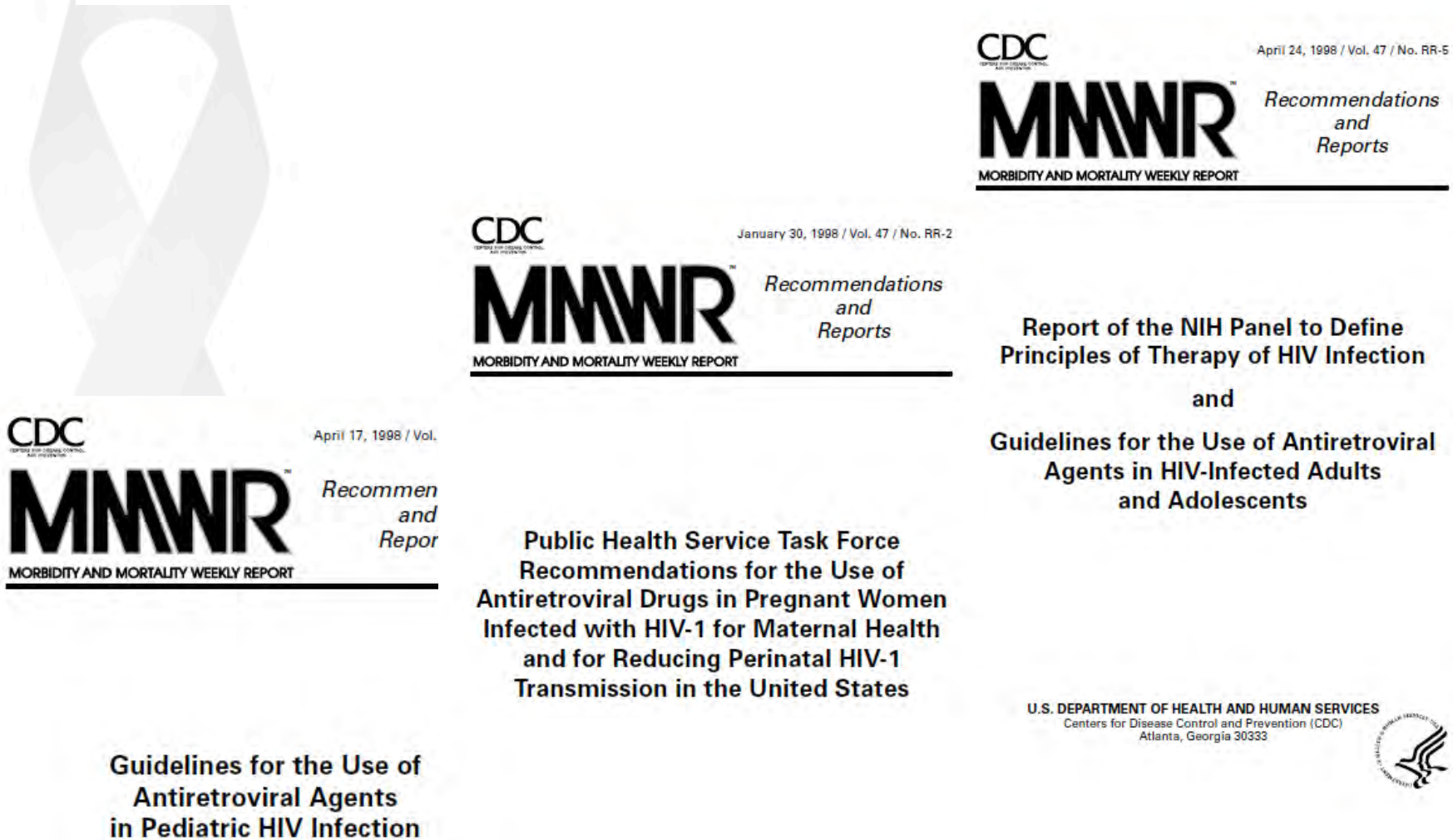


Identification of a Reservoir for HIV-1
Antiretroviral Therapy

Conference Coverage (ICAAC)
T-Cell Gain Slow But Steady
Treatment

The Early-HAART Era: 1996-2005

1998: US DHHS Antiretroviral Guidelines



The Early-HAART Era: 1996-2005

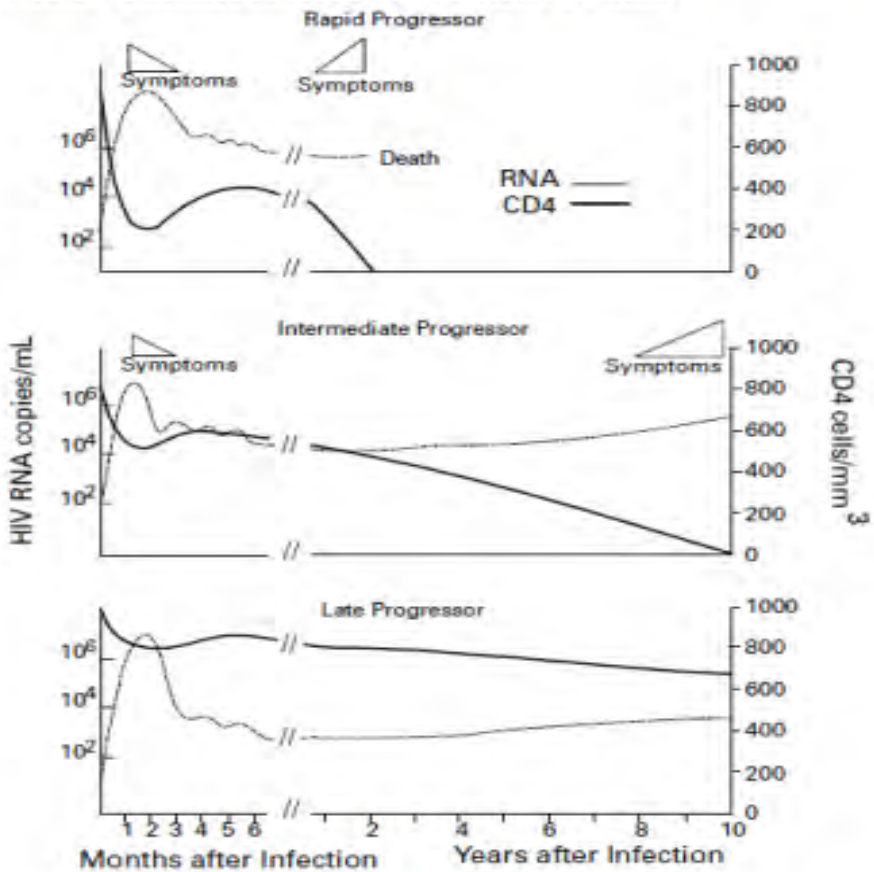
1998: 5th NRTI: Abacavir

3rd NNRTI: Efavirenz

The Early-HAART Era: 1996-2005

1998: Different disease progression patterns

FIGURE 1. Generalized time course of HIV infection and disease



Three different patterns of disease progression: rapid, intermediate, and late progression.

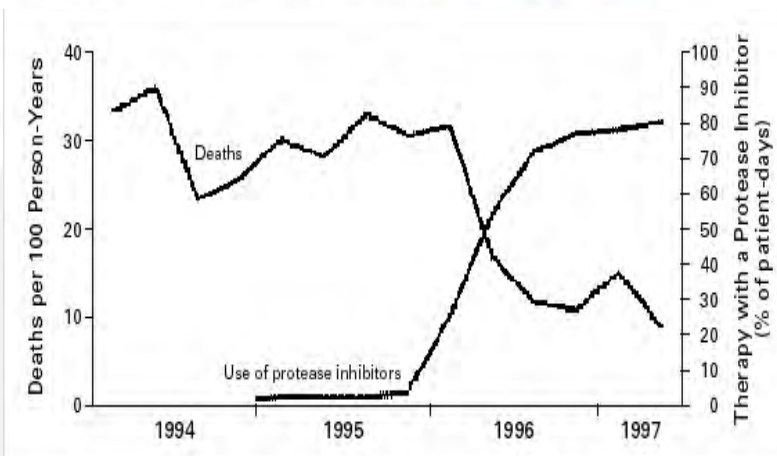
The Early-HAART Era: 1996-2005

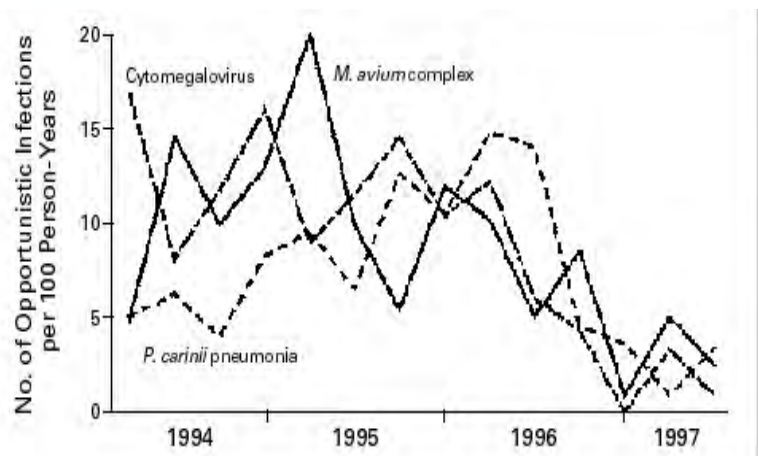
1998: HAART reduces AIDS morbidity and mortality

Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection

Frank J. Palella, Jr., M.D., Kathleen M. Delaney, M.S., Anne C. Moorman, B.S.N., M.P.H., Mark O. Loveless, M.D., Jack Fuhrer, M.D., Glen A. Satten, Ph.D., Diane J. Aschman, R.Ph., M.S., Scott D. Holmberg, M.D., M.P.H., and the HIV Outpatient Study Investigators

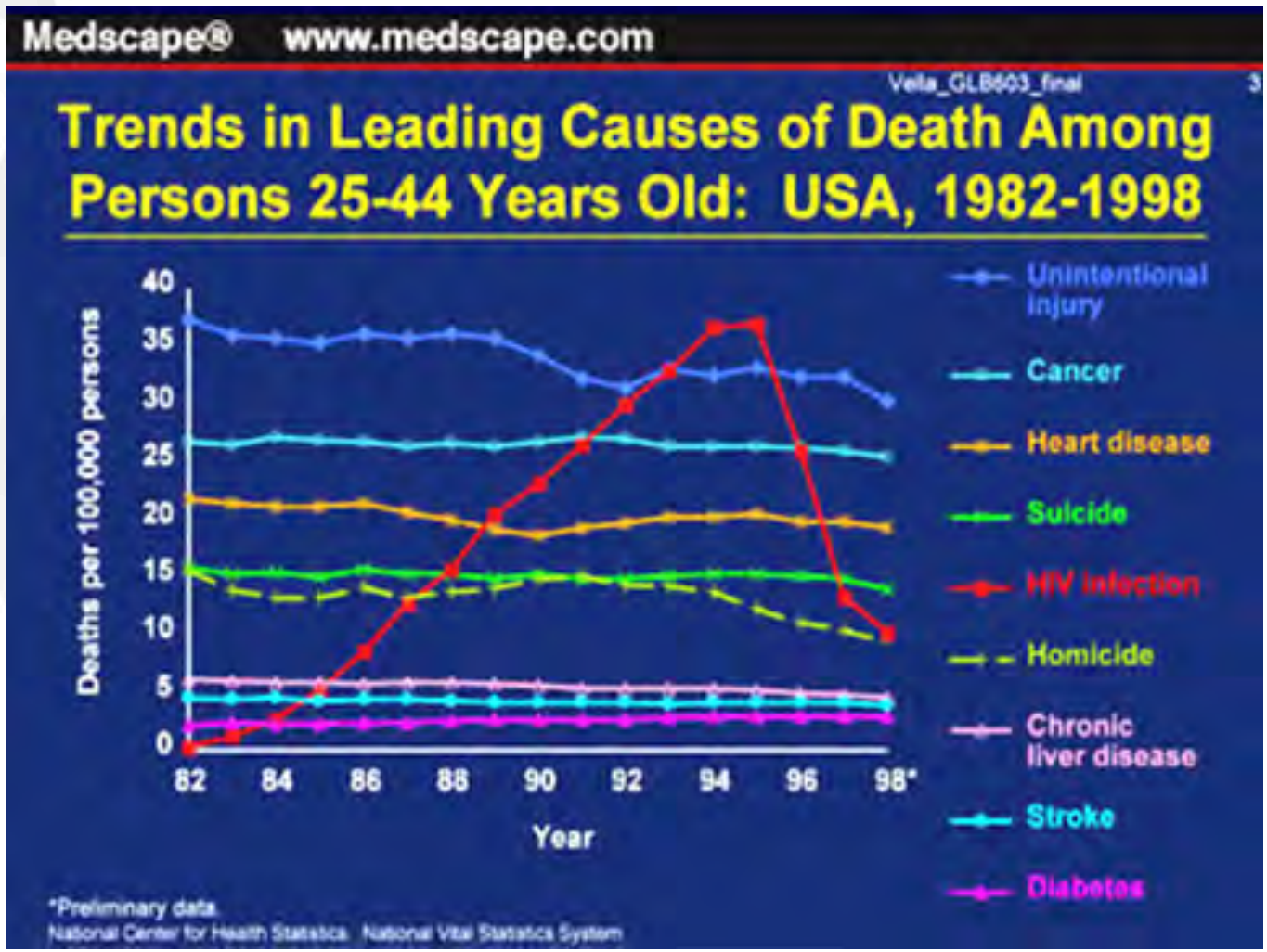
N Engl J Med 1998; 338:853-860 | March 26, 1998





The Early-HAART Era: 1996-2005

1998: AIDS no longer leading cause of death



The Early-HAART Era: 1996-2005

1998: Resistance testing begins in clinical practice

Antiretroviral Drug Resistance Testing in Adults With HIV Infection

Implications for Clinical Management

International AIDS Society-USA Consensus Statement

JAMA. 1998;279(24):1984-1991

The Early-HAART Era: 1996-2005

1998: Latent reservoir during primary infection

PNAS
Proceedings of the National Academy of Sciences of the United States of America

Early establishment of a pool of latently infected, resting $CD4^+$ T cells during primary HIV-1 infection

Tae-Wook Chun*†, Delphine Engel*, M. Michelle Berrey‡, Theresa Shea‡, Lawrence Corey‡, and Anthony S. Fauci*

PNAS July 21, 1998 vol. 95 no. 15 8869-8873

The Early-HAART Era: 1996-2005

1998: Mitochondrial toxicity of NRTIs

Table 3. Adverse events of reverse transcriptase inhibitors.

	Zidovudine	Lamivudine	Stavudine	Zalcitabine	Didanosine
Type Analogue	Nucleoside Thymidine	Nucleoside Cytidine	Nucleoside Thymidine	Nucleoside Cytidine	Nucleoside Adenosine
Neuropathy	–	–	++	++	++
Myopathy	++	–	–	–	–
Cardiomyopathy	+	–	–	+	+
Pancreatitis	–	+/–	+	–	++
Hepatic steatosis/hepatitis	+	+/–	+	–	+
Lactic acidosis	+	–	+	–	+
Nephrologic toxicity	–	–	–	–	–
Bone-marrow toxicity	++	–	–	+	+
Skin toxicity	–	–	–	–	–
References	[2,49,51,52, 64,97,99]	[5,102,			8, 9]

AIDS. 12(14):1735-1744, October 1998

The Early-HAART Era: 1996-2005

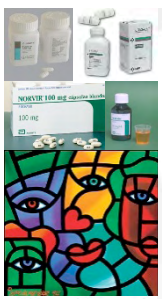
1998: Lipodystrophy cast doubt on long-term ART safety

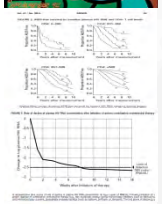
The Early-HAART Era: 1996-2005

1998: First human HIV vaccine trial begins

The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





- AIDS Clinical Center at the International Medical Center of Japan
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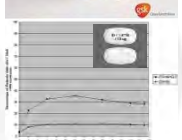
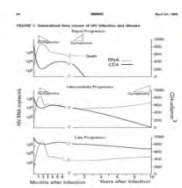


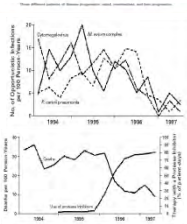
Identification of a Reservoir for HIV-1 Antiretroviral Therapy

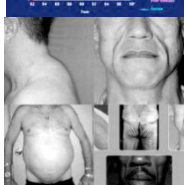
Conference Coverage (ICAAC)

T-Cell Gain Slow But Steady / Treatment

Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States



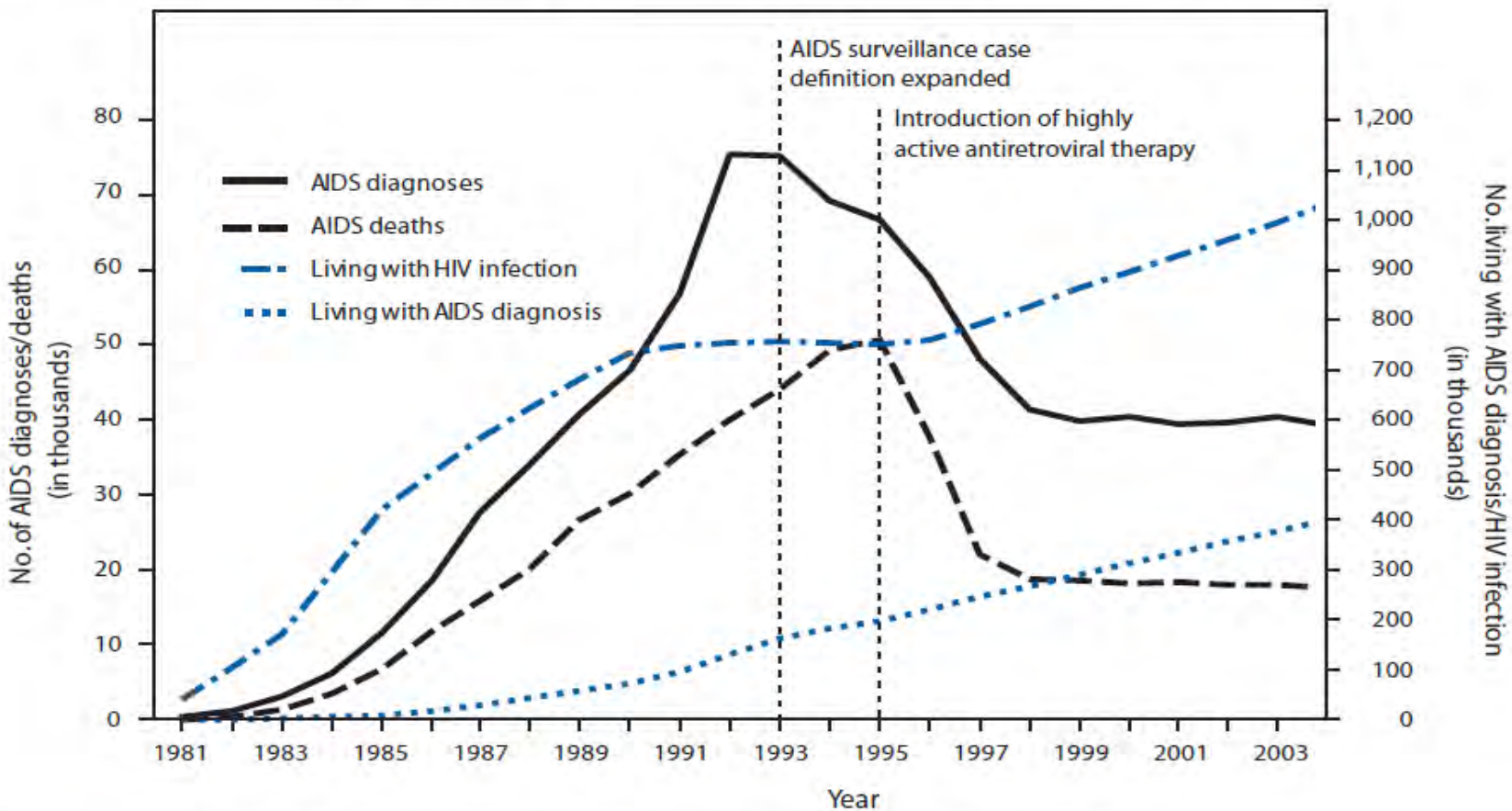




The Early-HAART Era: 1996-2005

1999: AIDS case and death rates "plateau"

FIGURE. Estimated number of AIDS diagnoses and deaths and estimated number of persons living with AIDS diagnosis* and living with diagnosed or undiagnosed HIV infection† among persons aged ≥13 years — United States



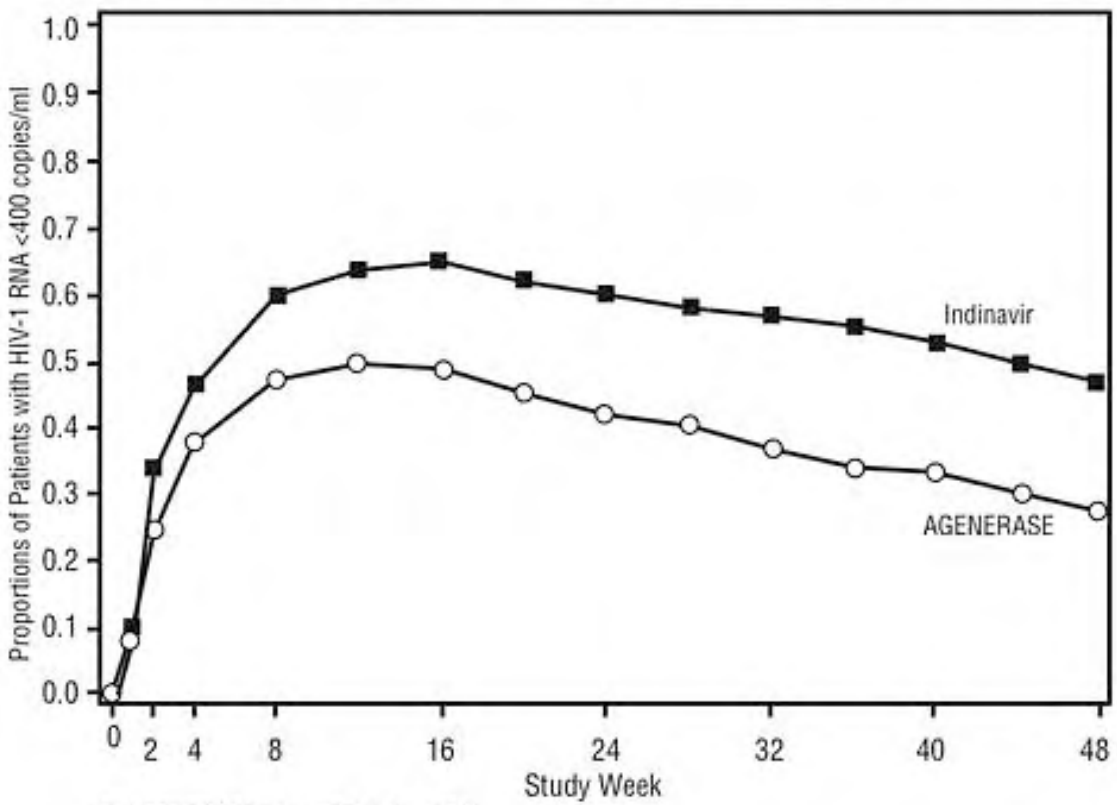
The Early-HAART Era: 1996-2005

1999: 5th PI: Amprenavir

The Early-HAART Era: 1996-2005

1999: HAART regimen success only ~50%

Figure 1: Virologic Response Through Week 48, PROAB30006*,†



○ AGENERASE plus NRT s (n = 254)

■ Indinavir plus NRTIs (N = 250)

*Roche AMPLICOR HIV-1 MONITOR assay.

†Discontinuations and missing data were considered as HIV-1 RNA 400 copies/mL.

The Early-HAART Era: 1996-2005

1999: High pill burden regimen components

DAILY DOSING OF AVAILABLE ANTIRETROVIRAL AGENTS

CLASS/DRUG	USUAL ADULT DAILY DOSING	SPECIAL CONSIDERATIONS
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
VIRAMUNE® (nevirapine)	1 x 200 mg tablet 2 times a day	Lead-in dosing for first 14 days of therapy: 1 x 200 mg tablet once a day.
Sustiva™ (efavirenz)	3 x 200 mg capsules 1 time a day	To improve tolerability of nervous system side effects, bedtime dosing is recommended during the first 2-4 weeks of therapy and in patients who continue to experience these symptoms. High fat meals should be avoided.
Rescriptor® (delavirdine mesylate)	4 x 100 mg tablets 3 times a day	Should be taken at least 1 hour apart from didanosine and from antacids.
NUCLEOSIDE ANALOGUES		
Combivir™ (lamivudine/zidovudine)	1 x 150 mg/300 mg tablet 2 times a day	Should not be prescribed for patients requiring dosage adjustments.
Epivir® (lamivudine-also known as 3TC)	1 x 150 mg tablet 2 times a day	
Zerit® (stavudine-also known as d4T)	1 x 40 mg capsule 2 times a day	
Ziagen™ (abacavir sulfate)	1 x 300 mg tablet 2 times a day	
Hivid® (zalcitabine-also known as ddC)	1 x 0.75 mg tablet 3 times a day	Should not be used concomitantly with didanosine. Do not take simultaneously with magnesium/aluminum containing antacids.
Videx® (didanosine-also known as ddI)	2 x 100 mg tablets 2 times a day	Take on empty stomach. Alcohol may exacerbate toxicity.
Retrovir® (zidovudine-also known as ZDV or AZT)	2 x 100 mg capsules 3 times a day; 1 x 300 mg tablet 2 times a day	
PROTEASE INHIBITORS		
Crixivan® (indinavir)	2 x 400 mg capsules every 8 hours	Take on empty stomach 1 hour before or 2 hours after a meal. Drink at least 1.5 liters of liquid daily.
Invirase® (saquinavir mesylate)	3 x 200 mg hard gelatin capsules 3 times a day	Take within 2 hours after a full meal. Saquinavir taken without food may have less bioavailability.
Viracept® (nelfinavir mesylate)	3 x 250 mg tablets 3 times a day	Take with a meal or light snack.
Norvir™ (ritonavir)	6 x 100 mg capsules 2 times a day	Should be refrigerated. Take with meals. Titrated lead-in dosing: start at no less than 300 mg b.i.d.; increase by 100 mg increments b.i.d. up to 600 mg b.i.d.
Fortovase™ (saquinavir)	6 x 200 mg soft gelatin capsules 3 times a day	Take within 2 hours after a full meal. Saquinavir taken without food may have less bioavailability.

The Early-HAART Era: 1996-2005

1999: High cross-resistance among 1st generation ARVs

Nucleosides and Nucleotides

AZT	41			67	69*	70				151		210	215	219	333	184 restores AZT sensitivity in presence of 41+215 333 resistant to AZT + 3TC
3TC					69*					151	184				333	
ddI			65		69*		74			151	*184*					
ddC			65		69*		74			151	184					Incomplete data
d4T		*50*			69*			*75*		151						Mechanism unclear
ABC			65		69*		74		115	151	184					Multiple mutations required
ADV			65		69*					151						

69* = 69SSS insertion, which leads to cross resistance for the class and is difficult to identify in genotypic testing
151 = leads to cross resistance to NRTI class when present along with ≥3 mutations

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

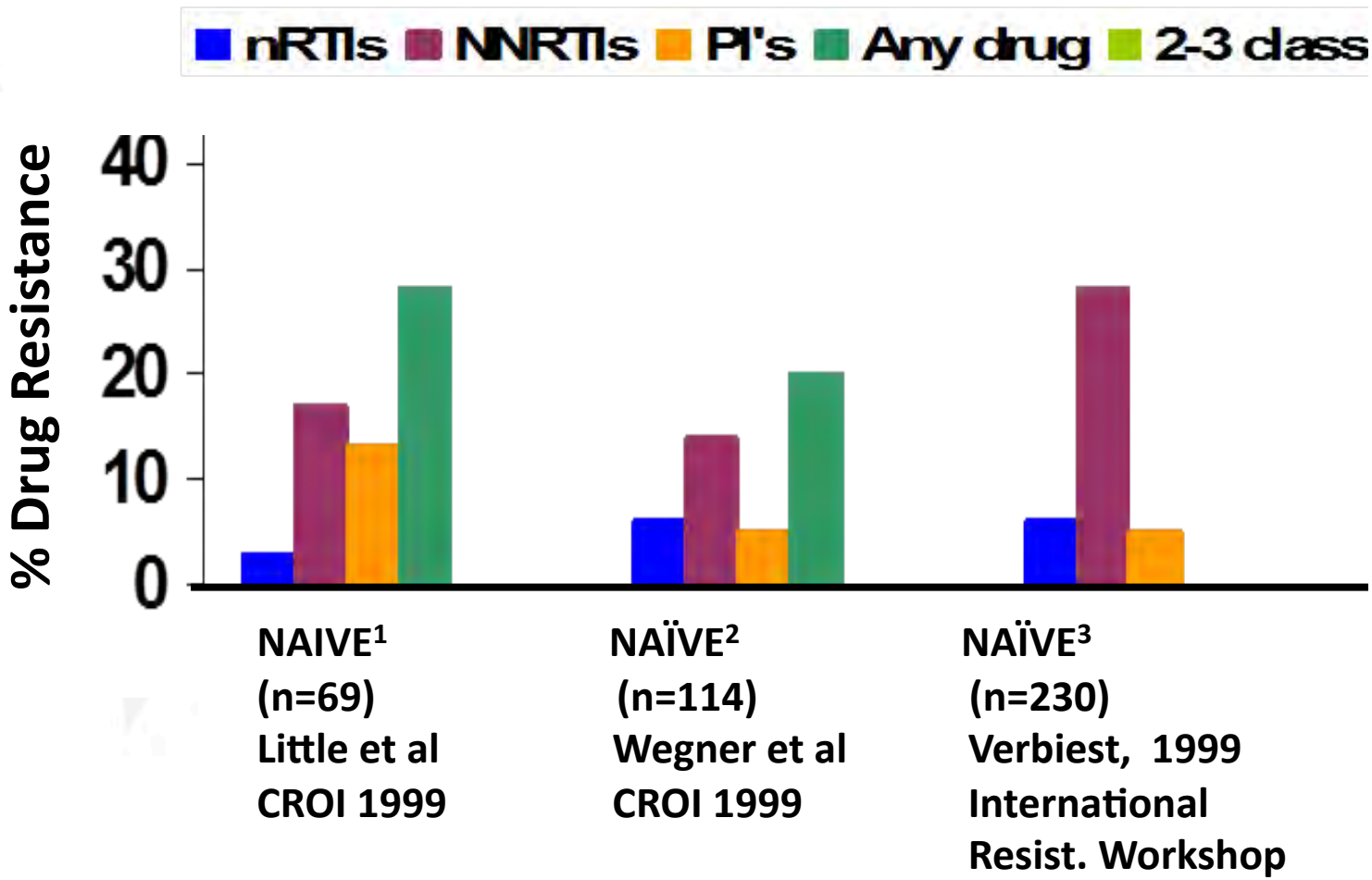
DLV		103				181				236	NNRTI resistance occurs quickly if viral suppression is incomplete K103N and Y181C are the most common mutations and lead to cross-resistance. Y181C alone may not lead to EFV resistance
EFV	100	103		108	179	181	188		225		
NVP	100	103	106	108		181	188	190			

Protease Inhibitors

APV	*10*						*36*	*46*	47		50	54	*63*	*71*			82	84		90	1° mutation: I50V
IDV	*10*	20	24		32		*36*	46		*48*		54	*63*	*71*	73		82	84		90	Requires ≥3 mutations
NFV	*10*			30			*36*	*46*		*48*				*71*		77		84	88	90	1° mutation: D30N
RTV	*10*	20			32	33	*36*	*46*				54	*63*	*71*			82	84		90	Multiple mutns required
SQV	*10*	20	24	30			*36*	*46*		48		54	*63*	*71*	73		82	84		90	1° mutns: G48V & L90M

The Early-HAART Era: 1996-2005

1999: High rates of resistance from sequential medication recycling



The Early-HAART Era: 1996-2005

1999: Focus on ARV adherence and toxicities

Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients

However, HAART has two main drawbacks: toxicity and low compliance. Although the frequency and the effects of toxicity have been assessed in clinical trials [2–4], they have not been thoroughly evaluated in clinical settings. Low compliance, which is often a consequence of persistent side effects, may lead to sub-optimal therapy or to therapy discontinuation and ultimately to treatment failure [8].

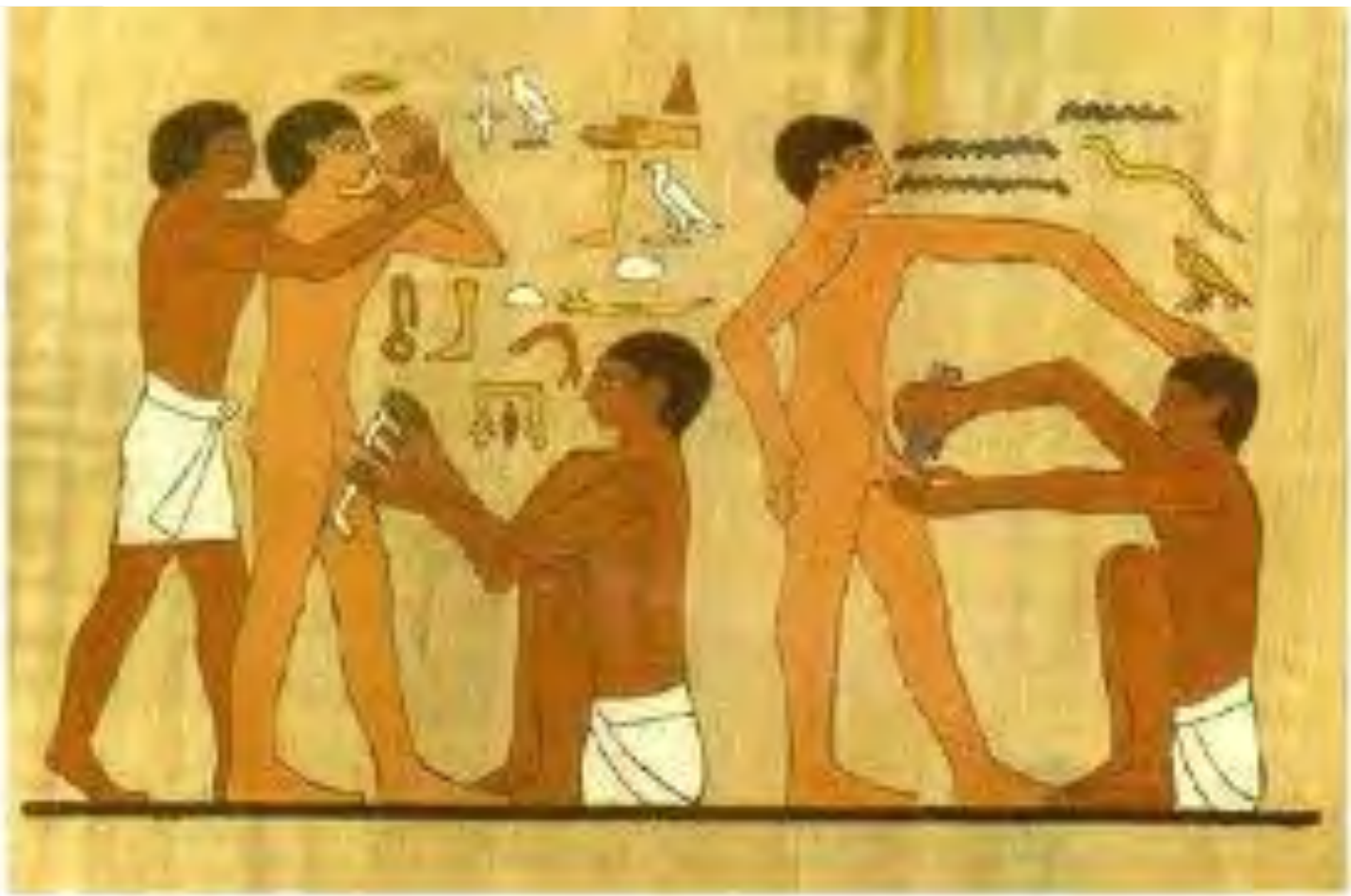
AIDS 2000, Vol 14 No 5

The Early-HAART Era: 1996-2005

1999: West African chimpanzee reported to be source of HIV

The Early-HAART Era: 1996-2005

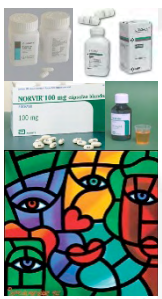
1999: Male circumcision promoted for HIV prevention

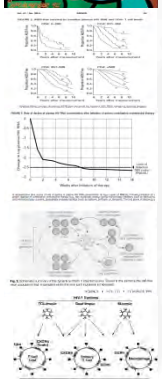


Halperin, Lancet 1999; 1813354:

The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





- AIDS Clinical Center at the International Medical Center of Japan
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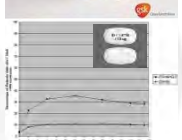
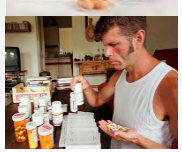
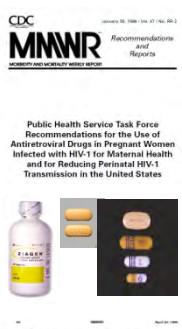


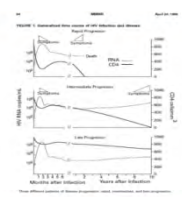
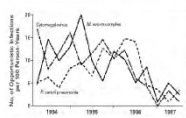
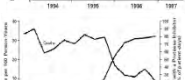



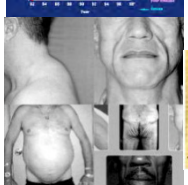
Identification of a Reservoir for HIV-1 Antiretroviral Therapy

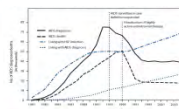
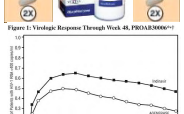
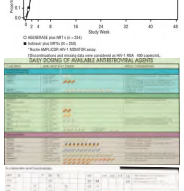
Conference Coverage (ICAAC)
T-Cell Gain Slow But Steady
Treatment

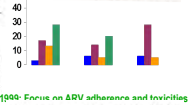
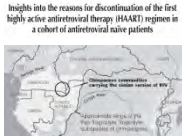
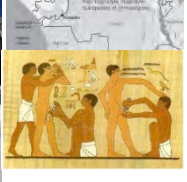


Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States

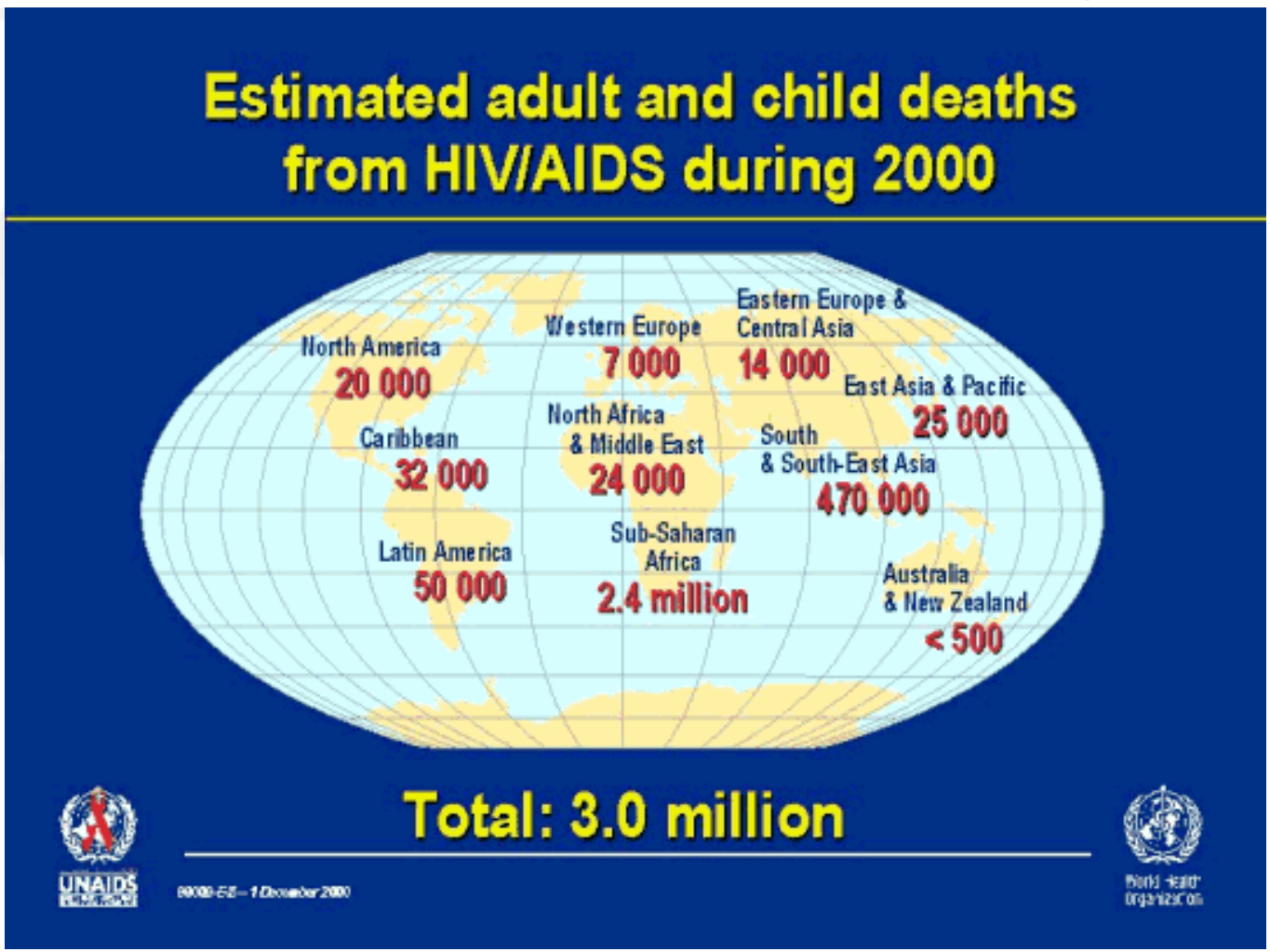



The Early-HAART Era: 1996-2005

2000: AIDS deaths disproportionate In developing countries



The Early-HAART Era: 1996-2005

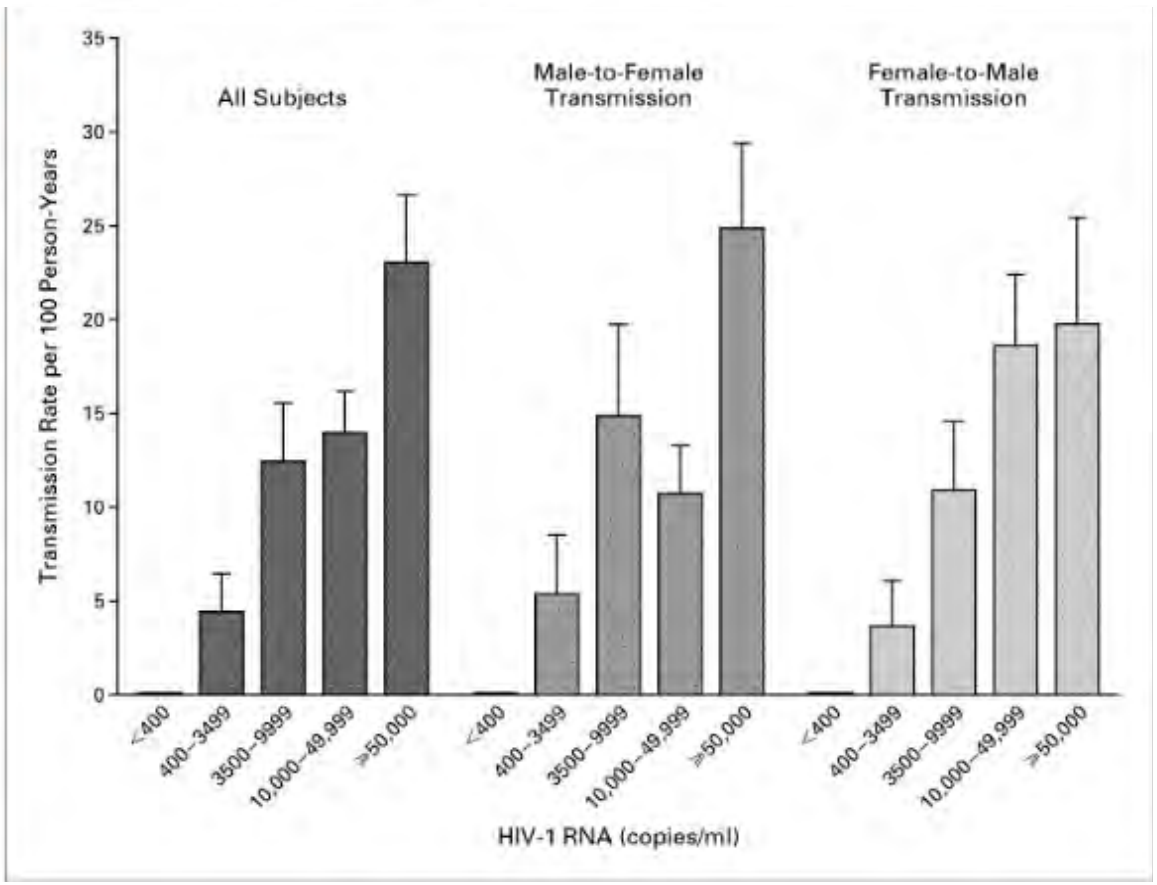
2000: Unmarked “AIDS” graves in Africa

The Early-HAART Era: 1996-2005

2000: HIV transmission reduced at low VL levels

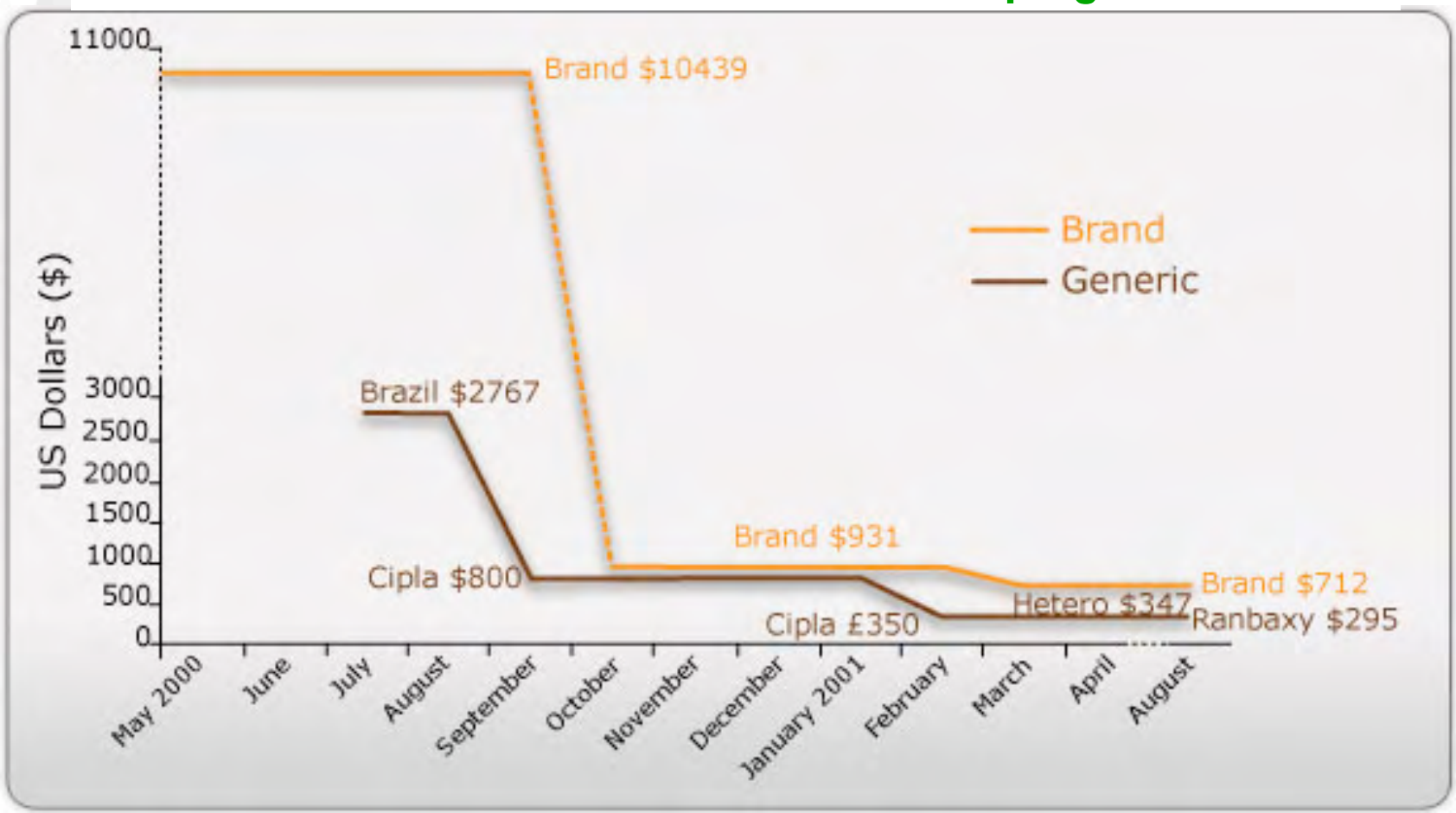
Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1

Rakai Project. NEJM 2000; 342:921



The Early-HAART Era: 1996-2005

2000: ARV become affordable in developing countries



The Early-HAART Era: 1996-2005

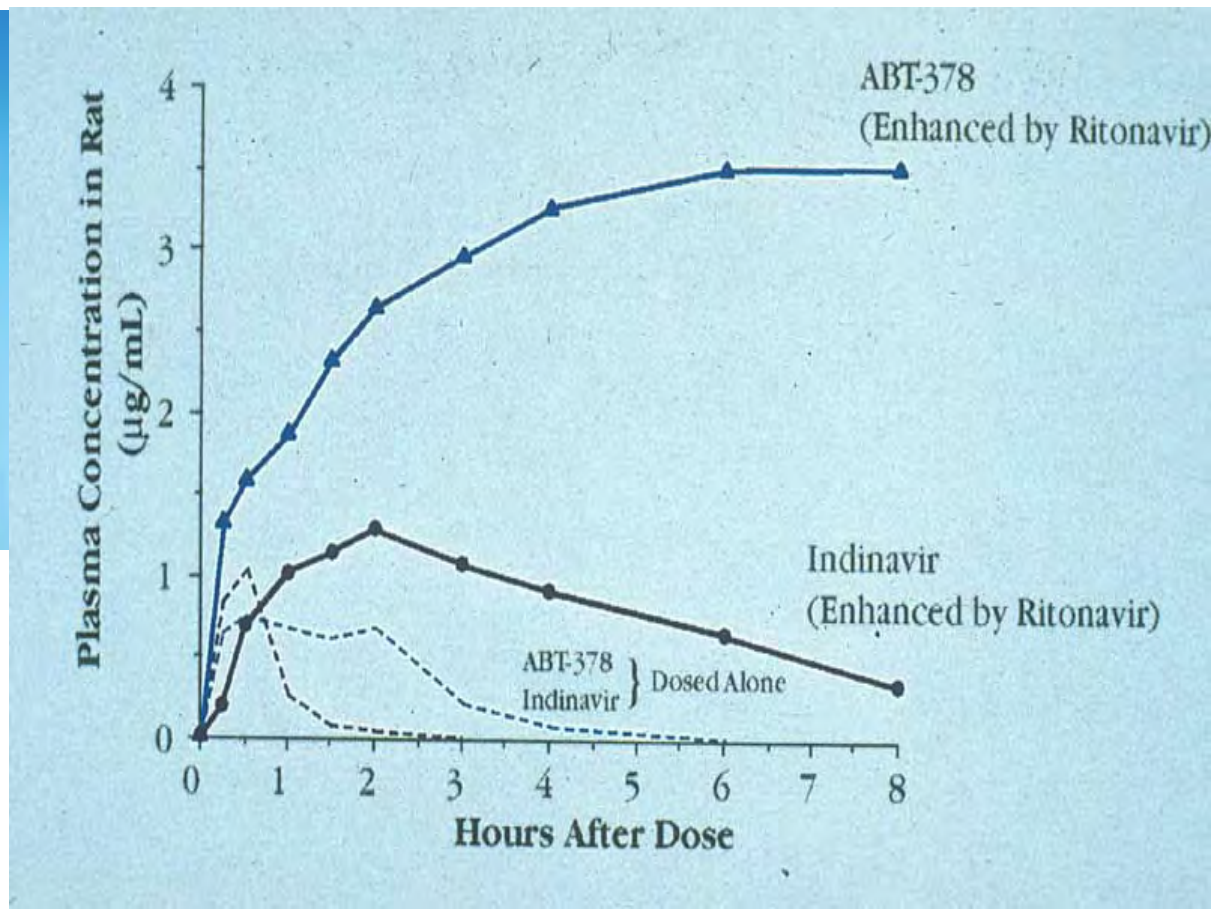
2000: 2nd NRTI combination Trizivir

NRTI Reformulation Videx EC

The Early-HAART Era: 1996-2005

2000: 1st Combined boosted PI: Kaletra

Kaletra SGCs



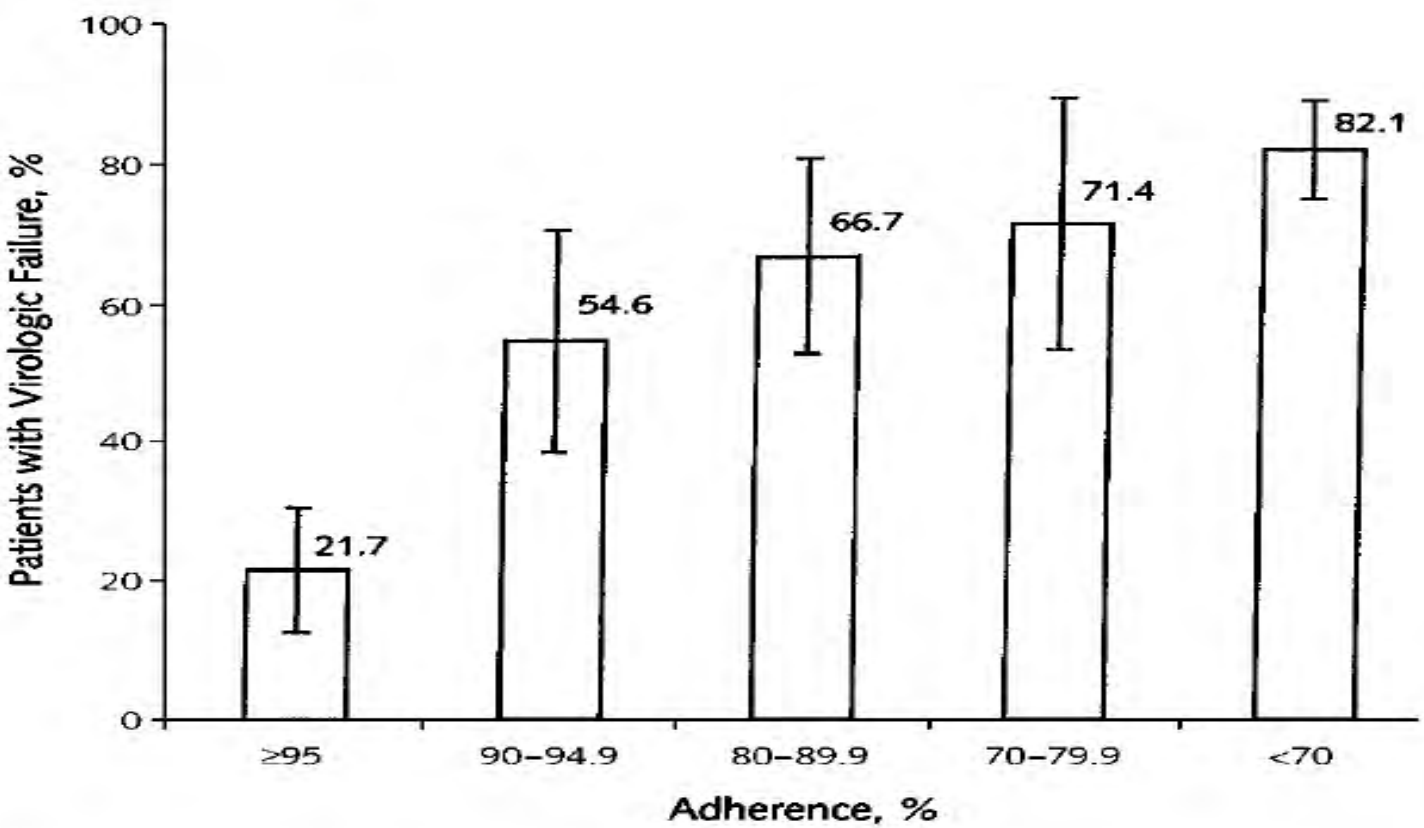
The Early-HAART Era: 1996-2005

2000: High rate viral failure with <95% adherence

Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection

David L. Paterson, MB, BS, FRACP; Susan Swindells, MD; Jeffrey Mohr, MSW; Cheryl Squier, RN; Marilyn M. Wagener, MPH; and Nina Singh, MD

Ann Intern Med. 2000;133:21-30.

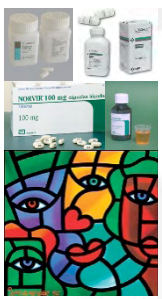


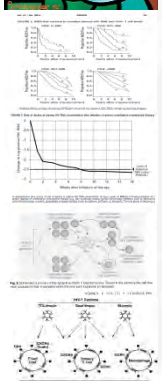
The Early-HAART Era: 1996-2005

2000: International AIDS Conference held in South Africa

The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





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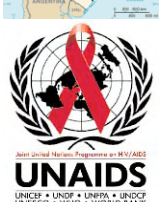

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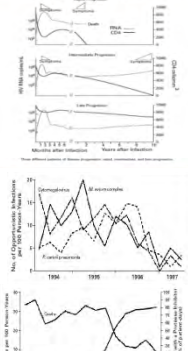
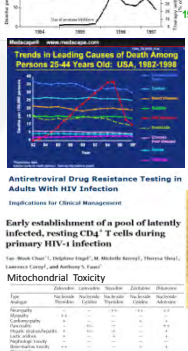


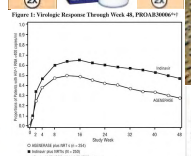


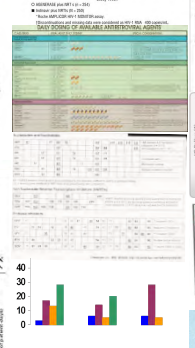
Antiretroviral Drug Resistance Testing in Adults With HIV Infection

Implications for Clinical Management

Early establishment of a pool of latently infected, resting $CD4^+$ T cells during primary HIV-1 infection

Mitochondrial Toxicity





Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients

The Early-HAART Era: 1996-2005

2001: China admits to high HIV-infection rate

The Early-HAART Era: 1996-2005

2001: UN Secretary Kofi Annan announces Global AIDS Fund

The Early-HAART Era: 1996-2005

2001: CDC reports HIV increasing twice as fast among >50yo

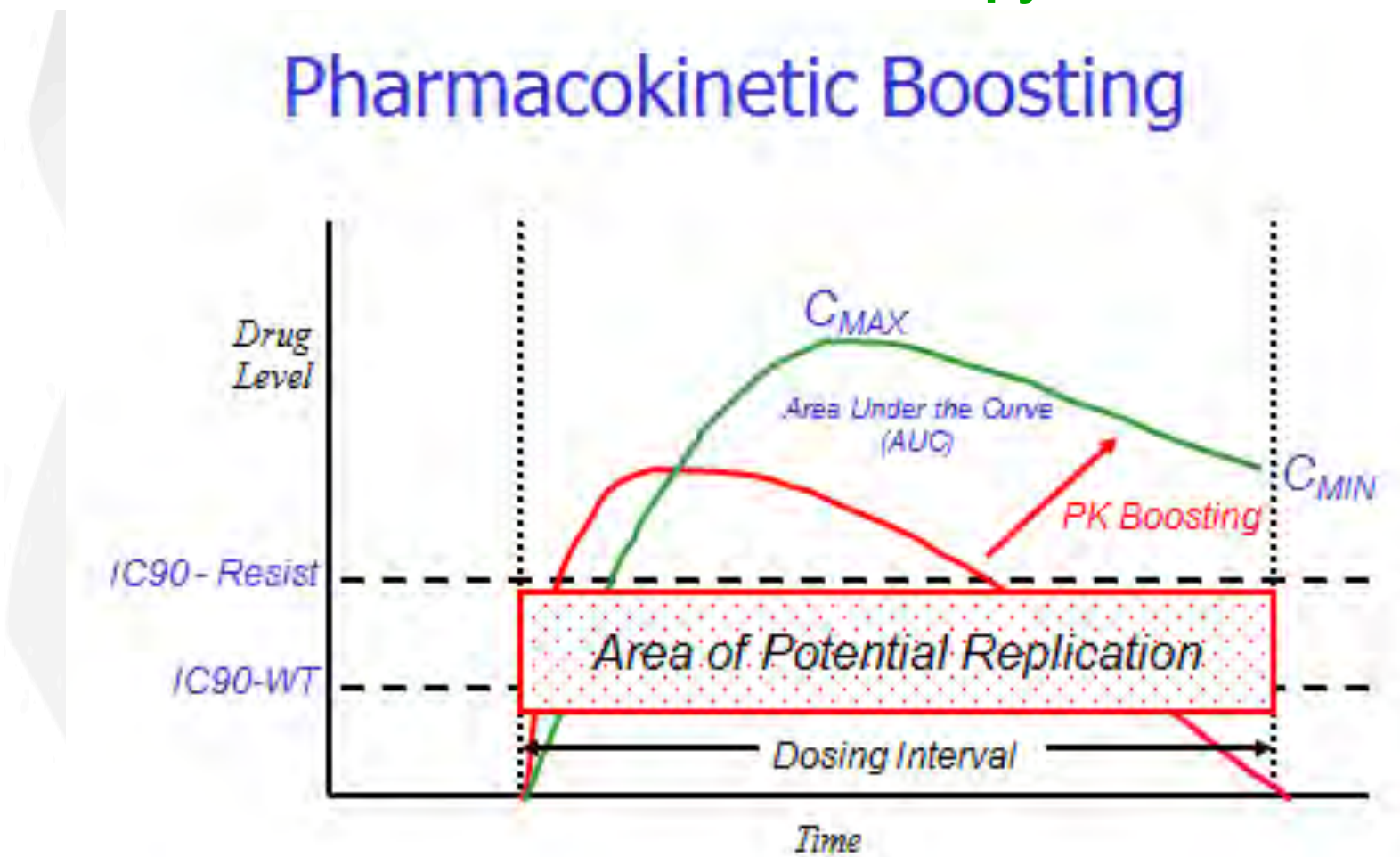
Officials have speculated that a more open society, people entering the dating scene after the monogamy of a marriage and the absence of a fear of pregnancy is causing the alarming rise in sexually transmitted infections.

The Early-HAART Era: 1996-2005

2001: 7th NRTI: Tenofovir

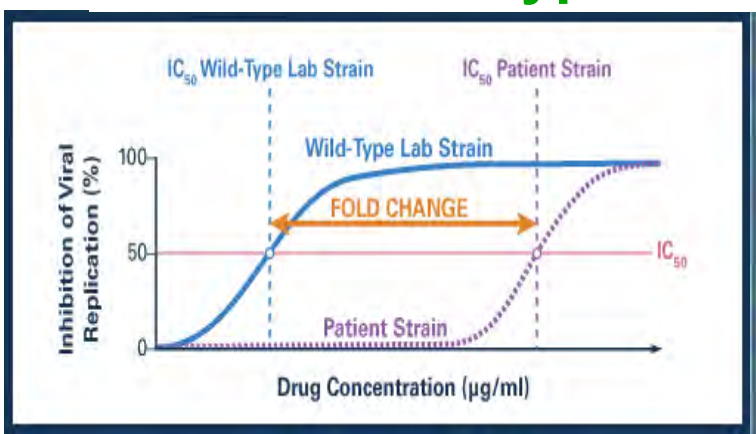
The Early-HAART Era: 1996-2005

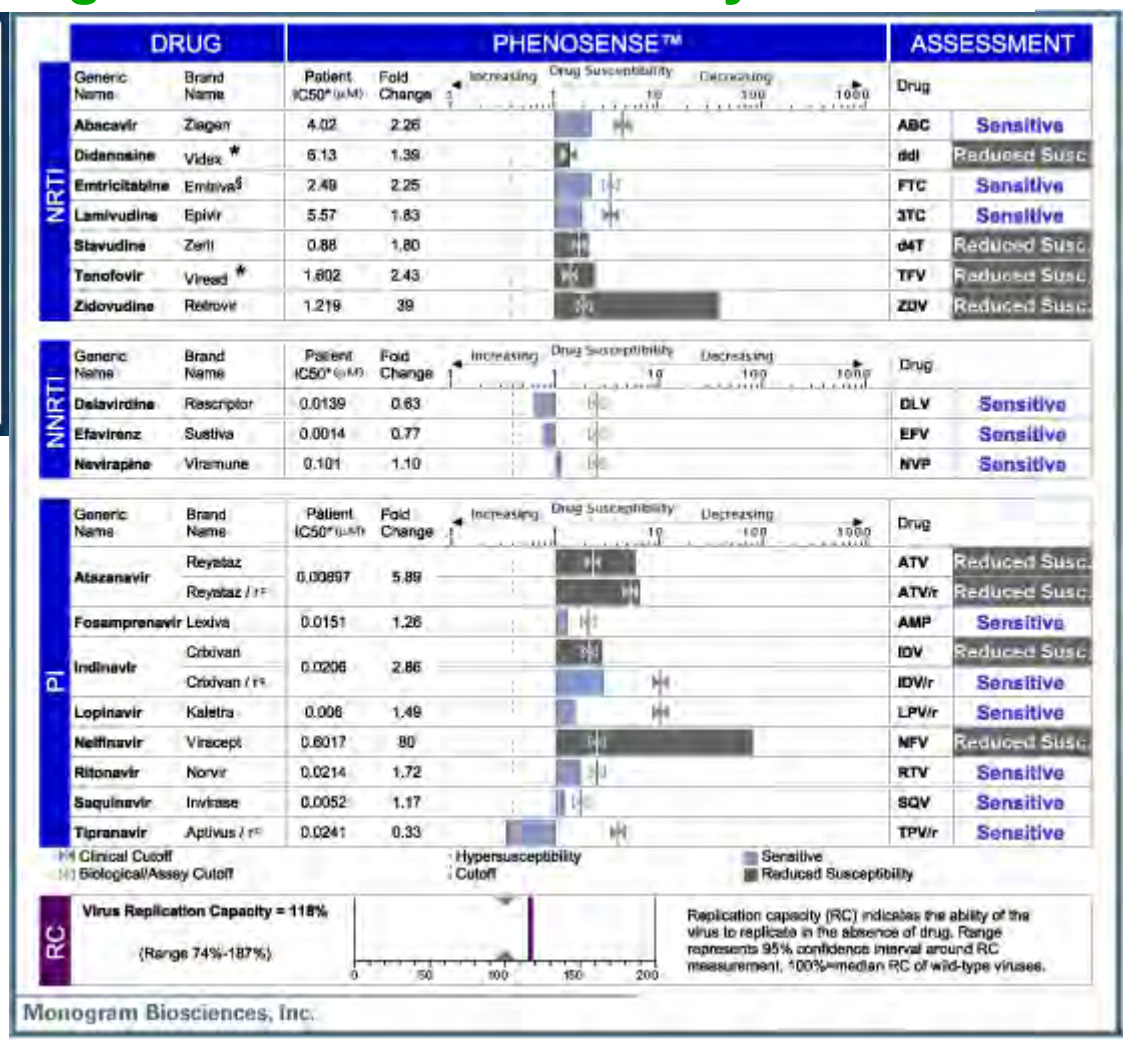
2001: PK Boosting becomes new "norm" for PI-based therapy



The Early-HAART Era: 1996-2005

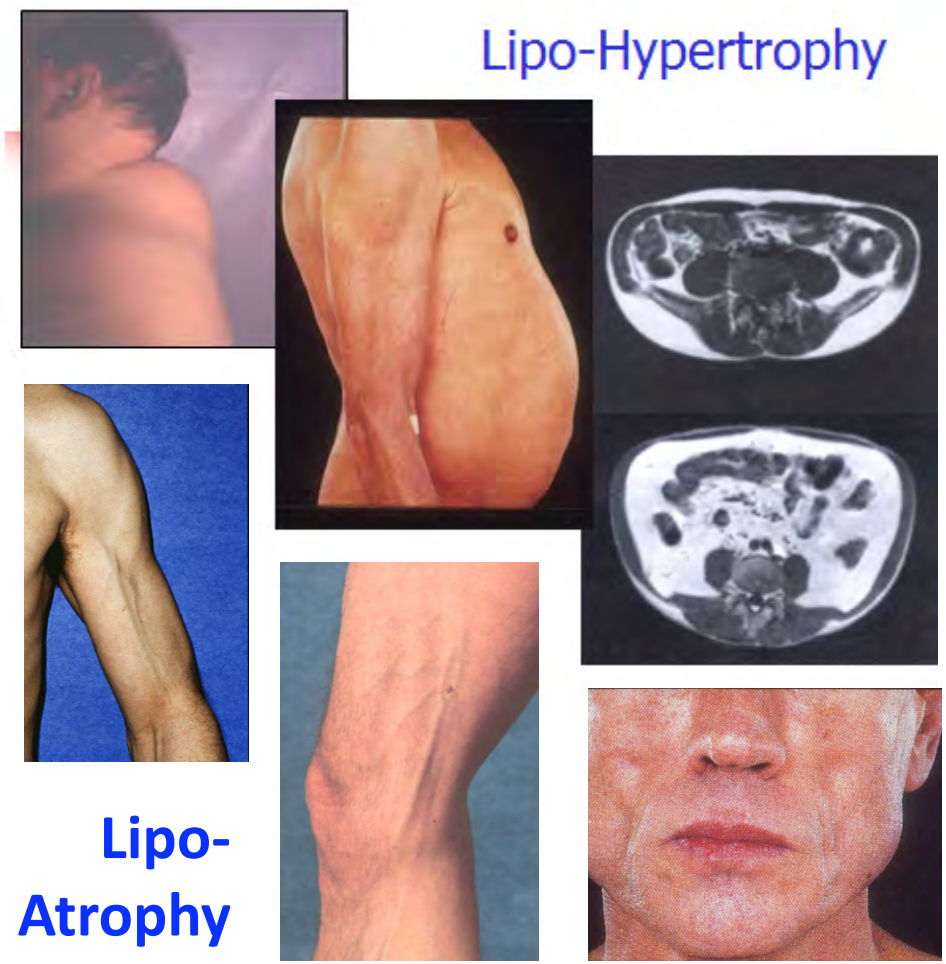
2001: Phenotype testing becomes more widely utilized





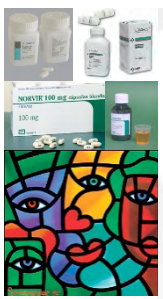
The Early-HAART Era: 1996-2005

2001: Lipodystrophy becomes reason to defer ART

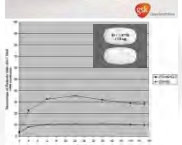


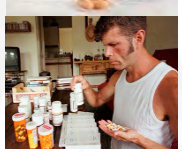
The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



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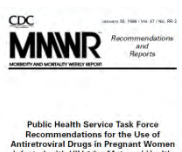

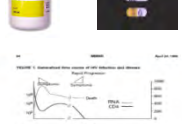

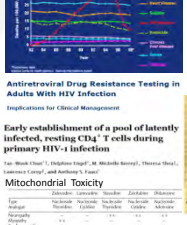

CDC
MMWR
Recommendations and Reports
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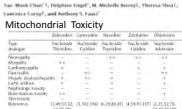
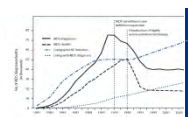
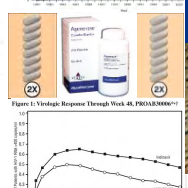
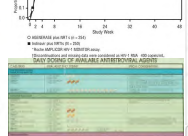
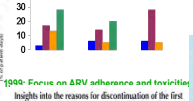
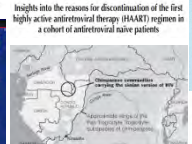
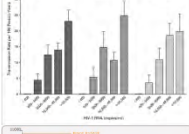
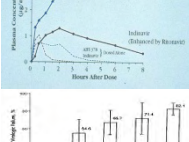





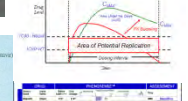
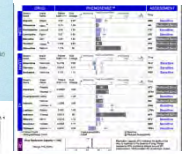
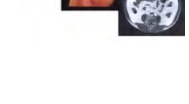






The Early-HAART Era: 1996-2005

2002: Women outnumber men in Sub-Saharan Africa

The Early-HAART Era: 1996-2005

2002: Protesters demand ARVs for resource-poor countries

a n

The Early-HAART Era: 1996-2005

2002: International ART treatment goal announced

SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS:

TREATMENT GUIDELINES FOR A PUBLIC HEALTH APPROACH

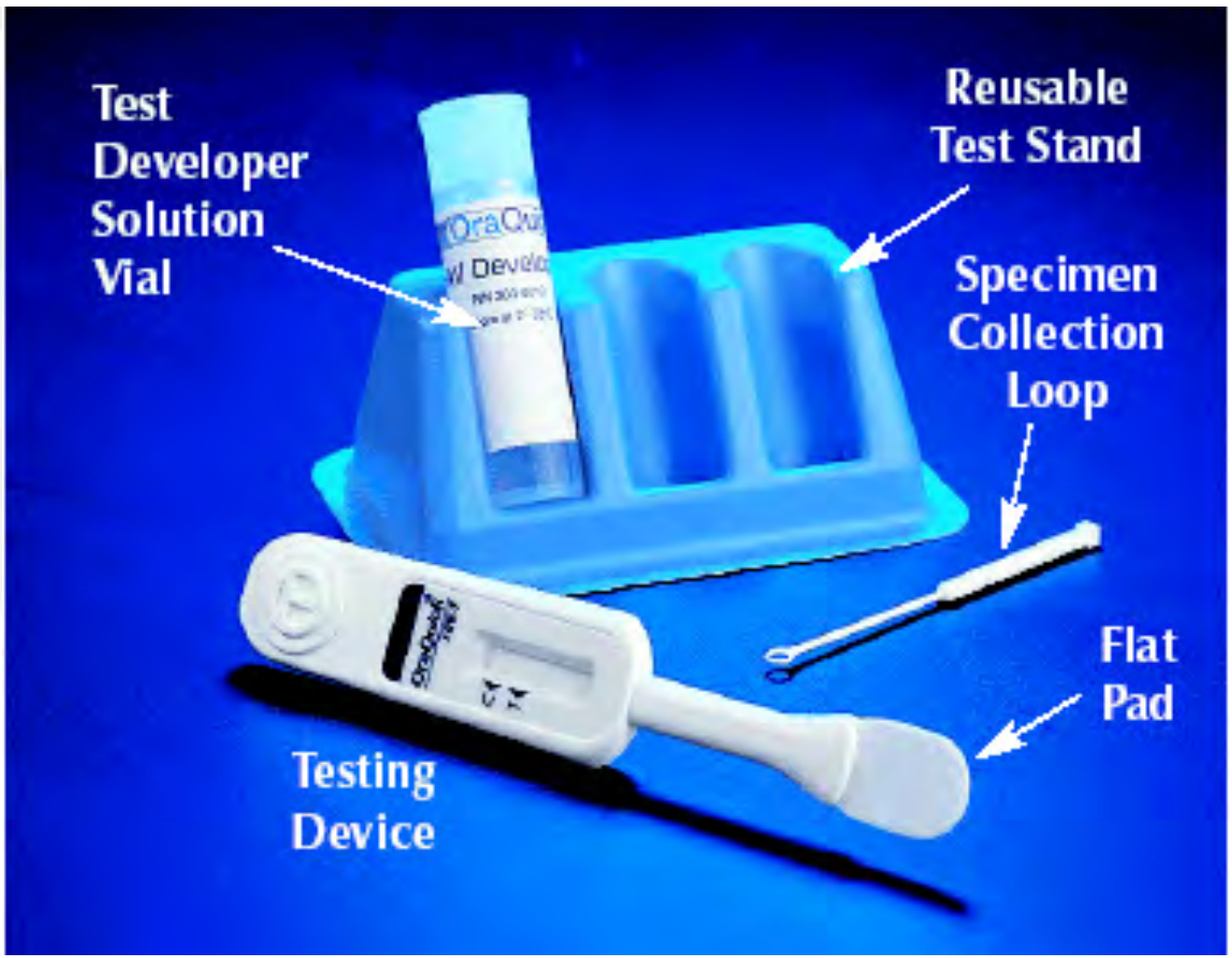
WHO recommends that, in resource-limited settings, HIV-infected adults and adolescents should start ARV therapy when the infection has been confirmed and one of the following conditions is present.

- Clinically advanced HIV disease:
  - WHO Stage IV HIV disease, irrespective of the CD4 cell count;
  - WHO Stage III disease with consideration of using CD4 cell counts <350/mm^3 to assist decision-making.
- WHO Stage I or II HIV disease with CD4 cell counts <200/mm^3 (Table A).

WORLD HEALTH ORGANIZATION
GENEVA
2004

The Early-HAART Era: 1996-2005

2002: FDA approves first 20 minute rapid HIV test



The Early-HAART Era: 1996-2005

2002: HIV testing offered in communities across the US

The Early-HAART Era: 1996-2005

2002: HIV replication highly resistance-prone

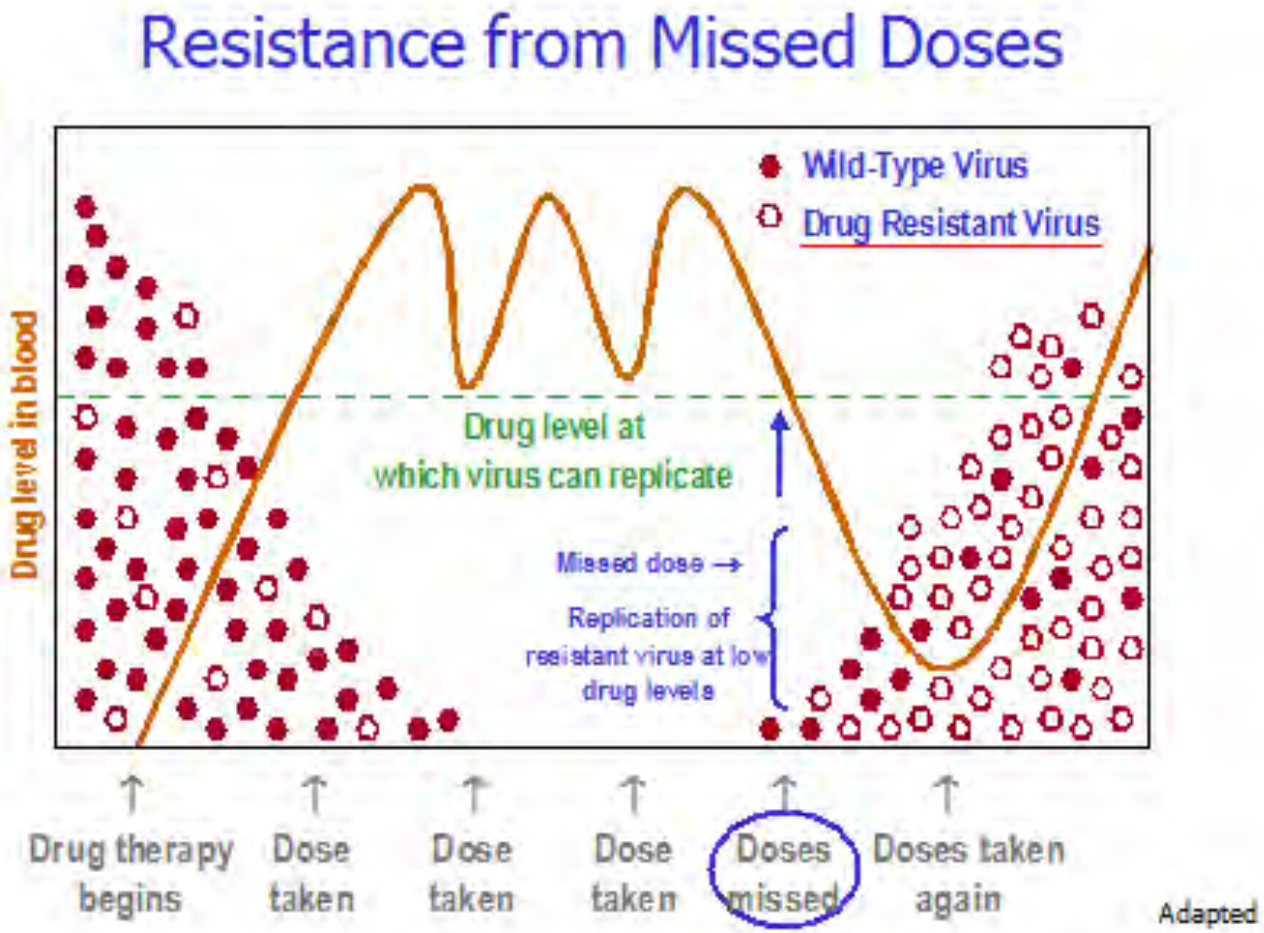
J Biol Chem. 2002 Oct 11;277(41):38053-61. Epub 2002 Jul 31.

Mutational analysis of HIV-1 long terminal repeats to explore the relative contribution of reverse transcriptase and RNA polymerase II to viral mutagenesis.

HIV-1 evolves rapidly, which is thought to result from one or more error-prone steps in the virus life cycle. Because HIV-1 reverse transcriptase (RT) does not possess 3′- to 5′-exonucleolytic proofreading activity and because RT has been shown to be error-prone in cell free systems, it should be an important contributor to the high rate of HIV-1 mutation. However, because RNA

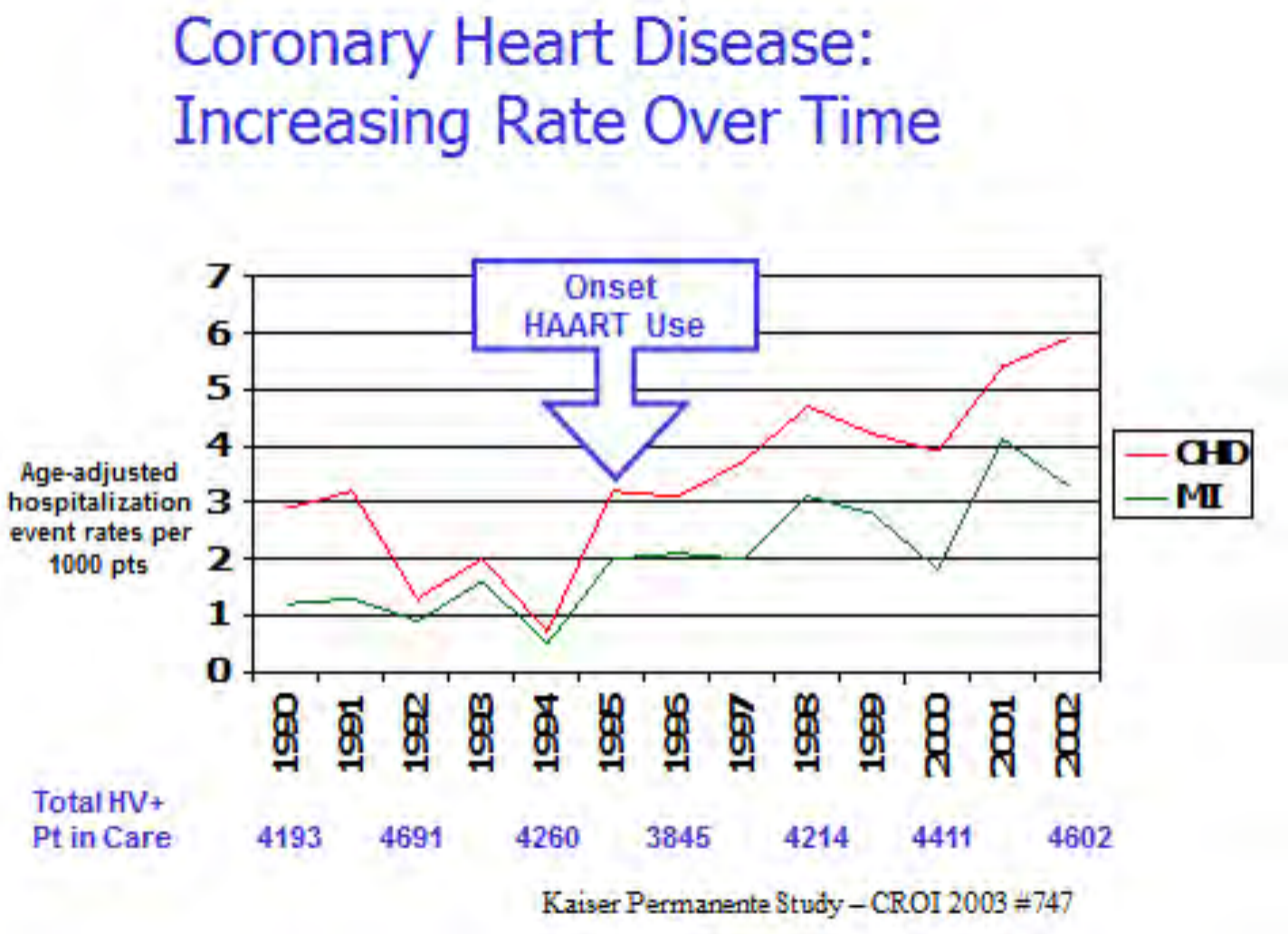
The Early-HAART Era: 1996-2005

2002: Resistance due to selection of pre-existing resistant virus



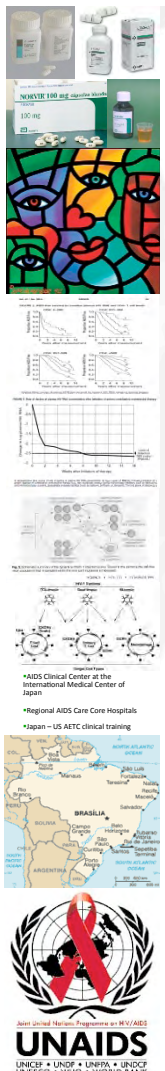
The Early-HAART Era: 1996-2005

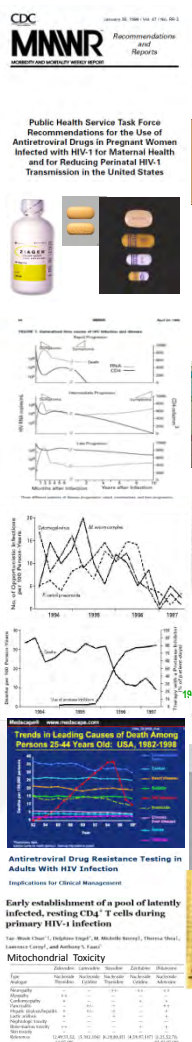
2002: Increasing metabolic and cardiovascular complications

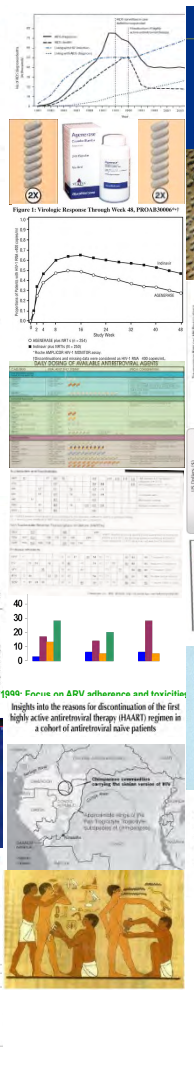


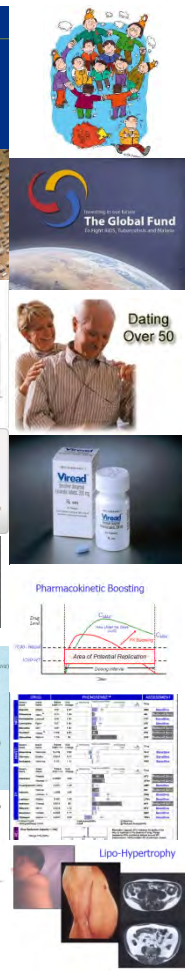
The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



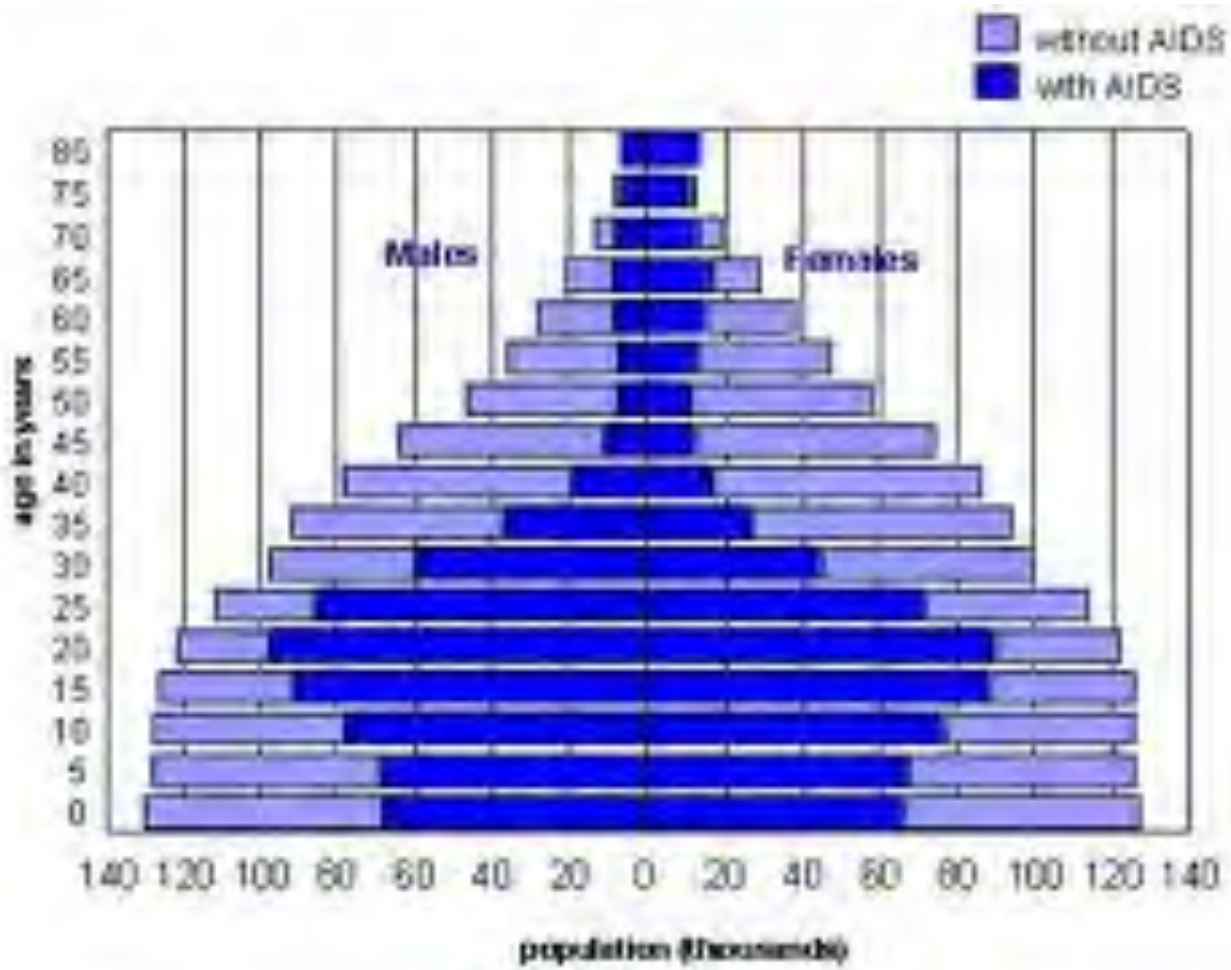






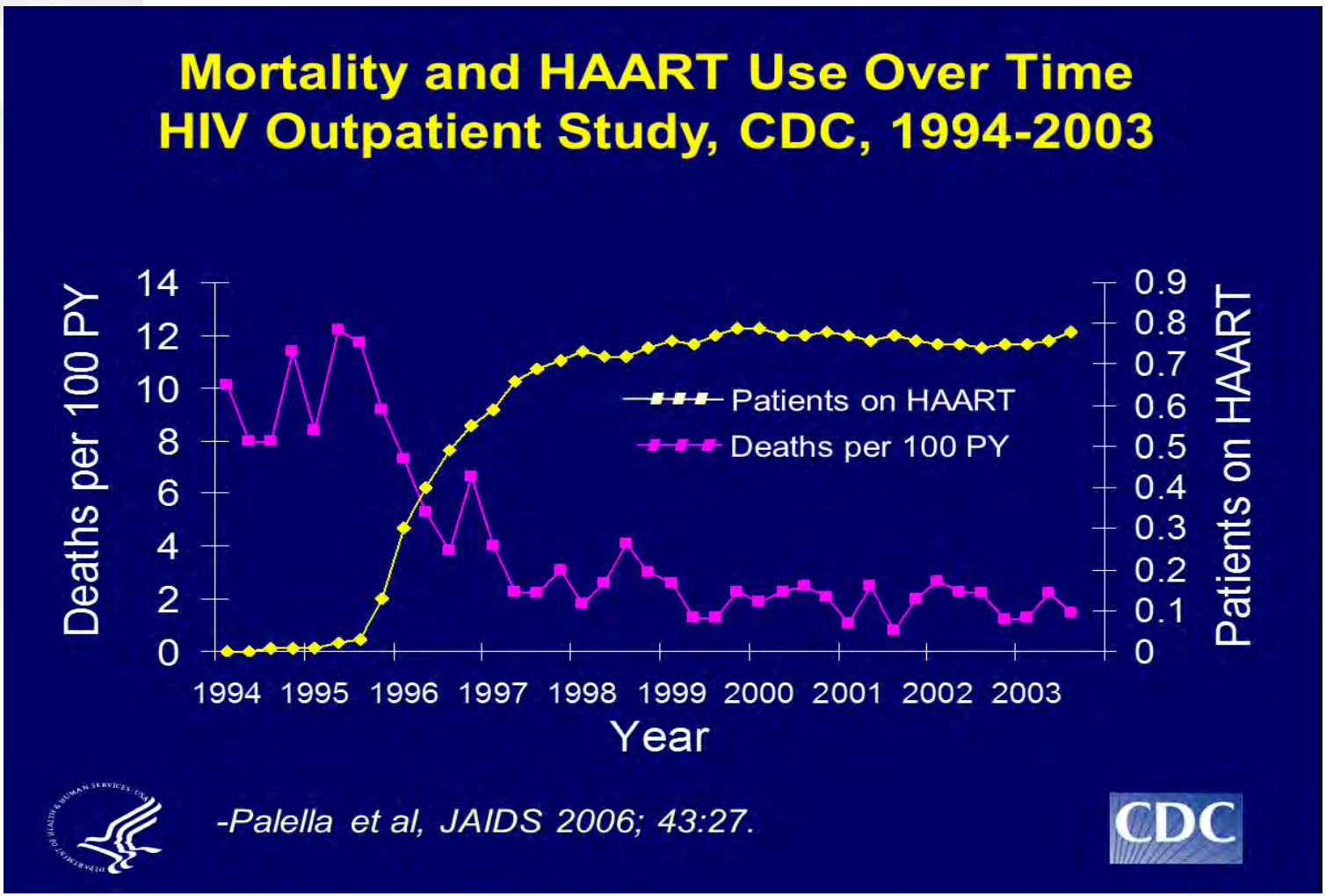
The Early-HAART Era: 1996-2005

2003: Botswana has world's highest HIV prevalence: 38.8%



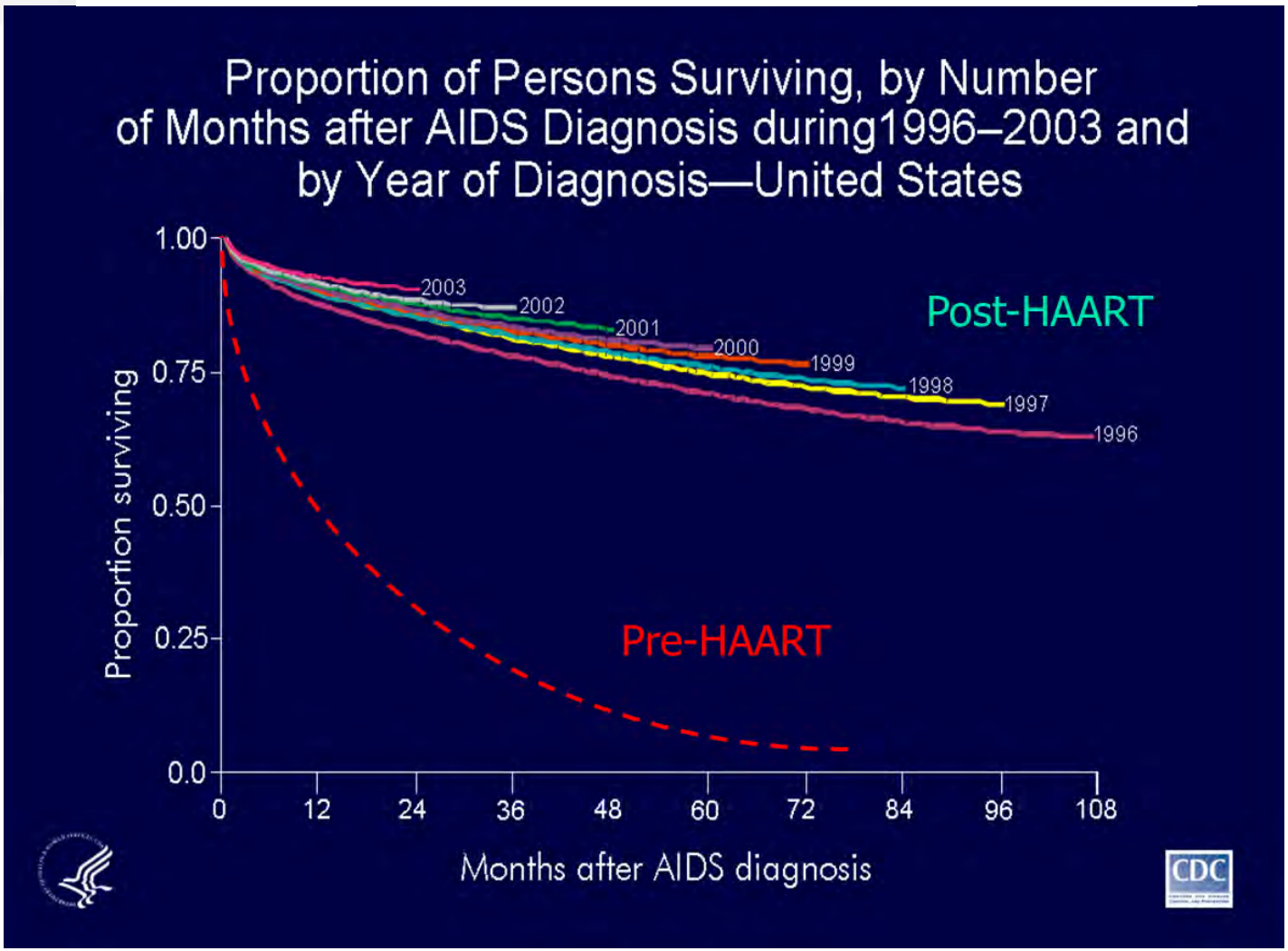
The Early-HAART Era: 1996-2005

2003: Decline in mortality persists with HAART



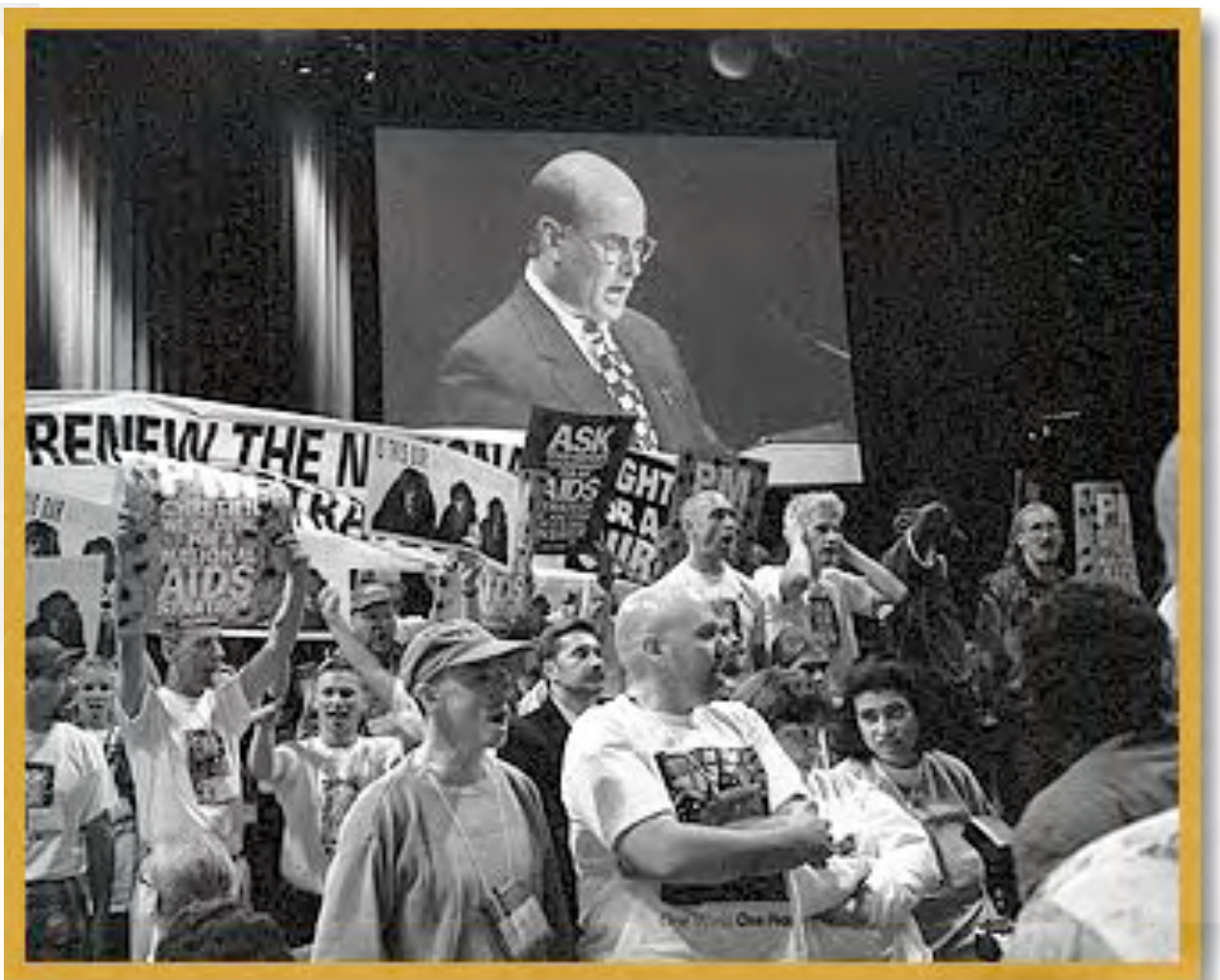
The Early-HAART Era: 1996-2005

2003: AIDS no longer "death sentence"



The Early-HAART Era: 1996-2005

2003: AIDS activists speak up at conferences



The Early-HAART Era: 1996-2005

2003: 1st entry inhibitor
Enfuvirtide (T-20)

8th NRTI
Emtricitabine

The Early-HAART Era: 1996-2005

2003: 8th PI

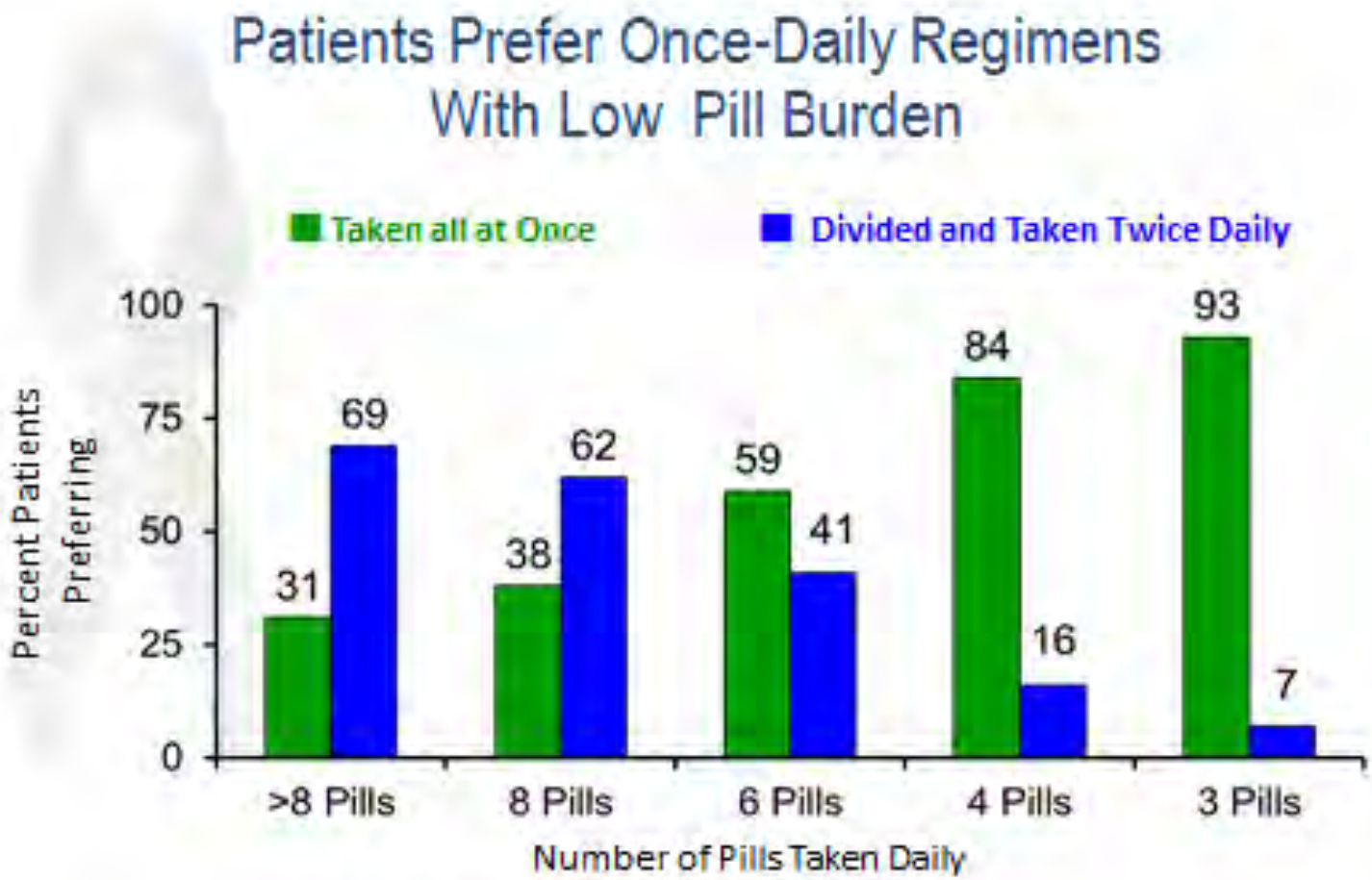
Atazanavir

9thPI

Fosamprenavir

The Early-HAART Era: 1996-2005

2003: Patient preference linked to adherence

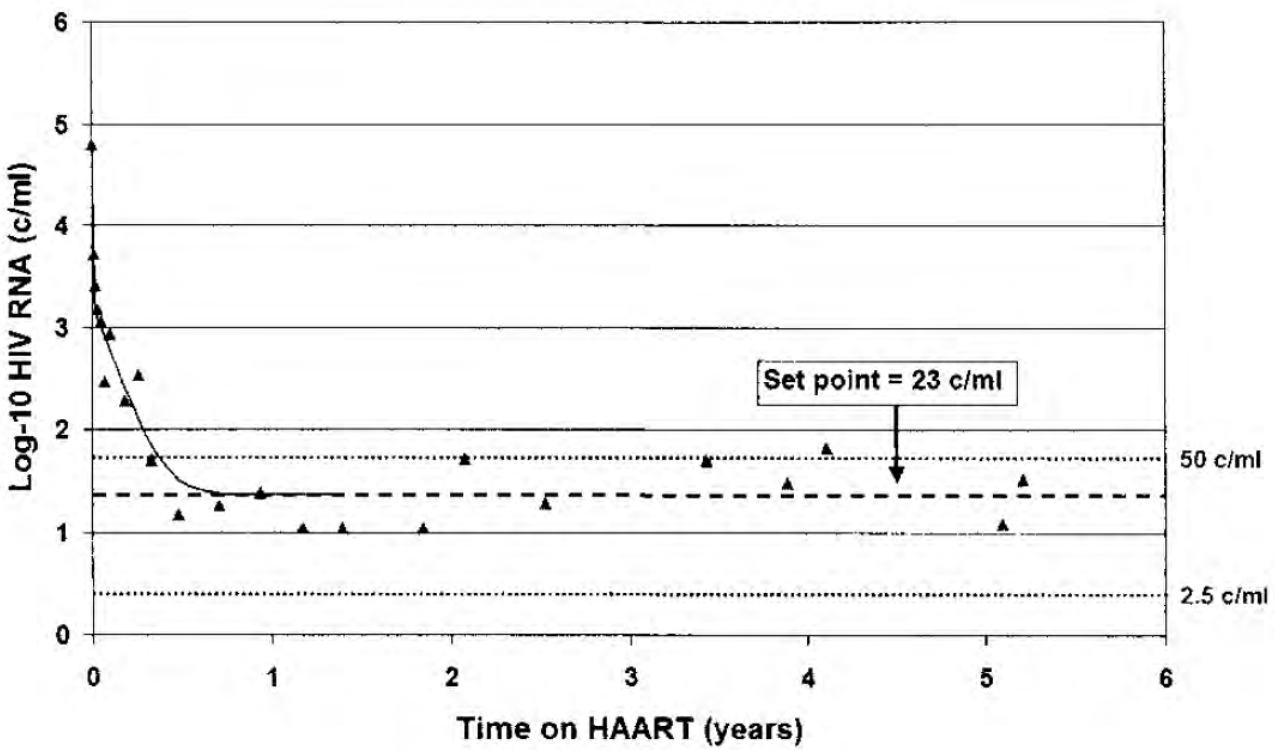


Moyle G. *Int J STD AIDS.* 2003;14: (Suppl 1):34-36.

The Early-HAART Era: 1996-2005

2003: Residual viremia while undetectable on HAART

Productive Infection Maintains a Dynamic Steady State of Residual Viremia in Human Immunodeficiency Virus Type 1-Infected Persons Treated with Suppressive Antiretroviral Therapy for Five Years



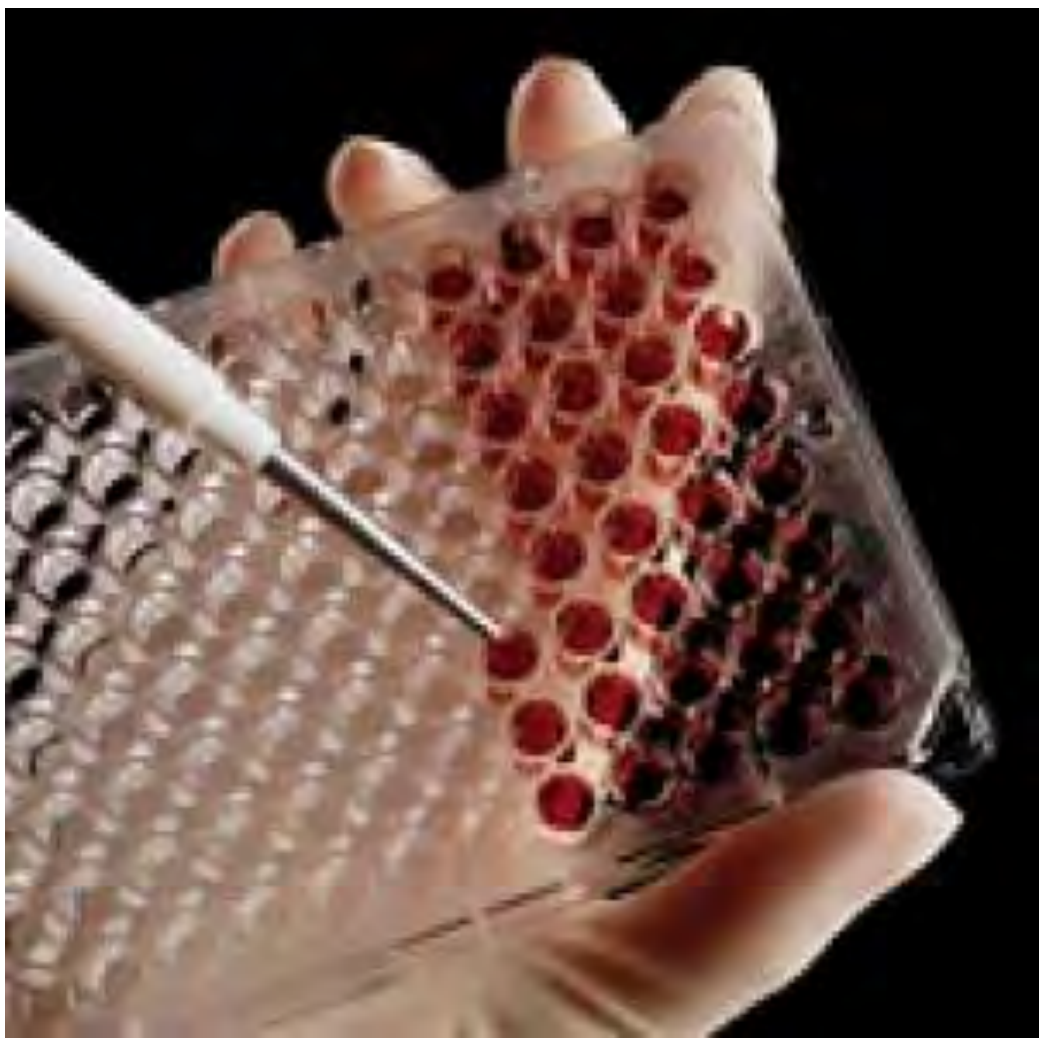
The Early-HAART Era: 1996-2005

2003: Impaired CD4 gain due to CD8 activation

T Cell Activation Is Associated with Lower $CD4^+$ T Cell Gains in Human Immunodeficiency Virus–Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy

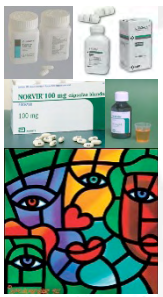
The Early-HAART Era: 1996-2005

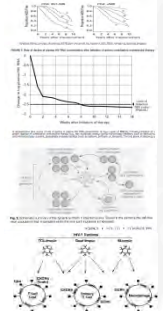
2003: AIDS vaccine trials report lack of immunity

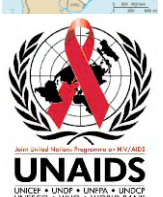


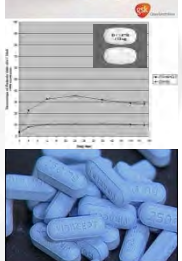
The Early-HAART Era: 1996-2005

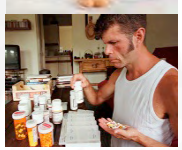
1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

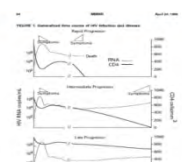
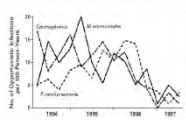


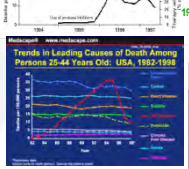


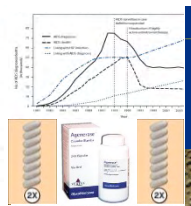
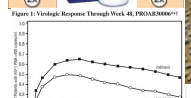
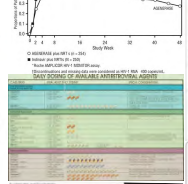



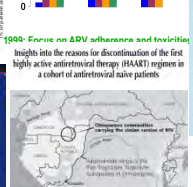



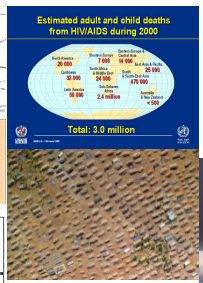


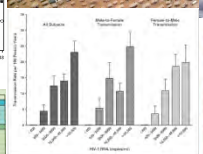




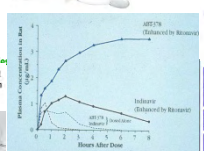
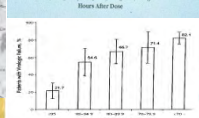


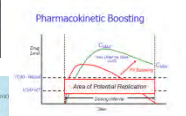



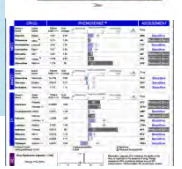
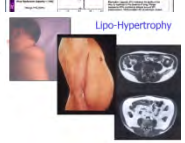


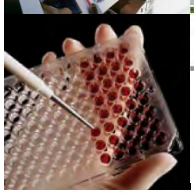


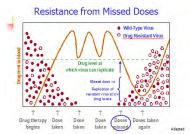




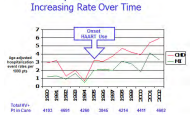


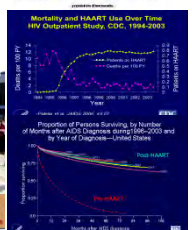


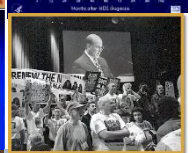



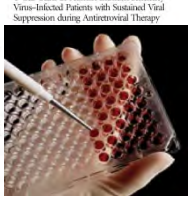









The Early-HAART Era: 1996-2005

2004: AIDS orphans number 15 million
12.1 million in Sub-Saharan Africa

The Early-HAART Era: 1996-2005

2004: WHO ARV “roll out” in developing countries

The Early-HAART Era: 1996-2005

2004: HIV spreading faster in Russia and Eastern Europe than anywhere else in the world

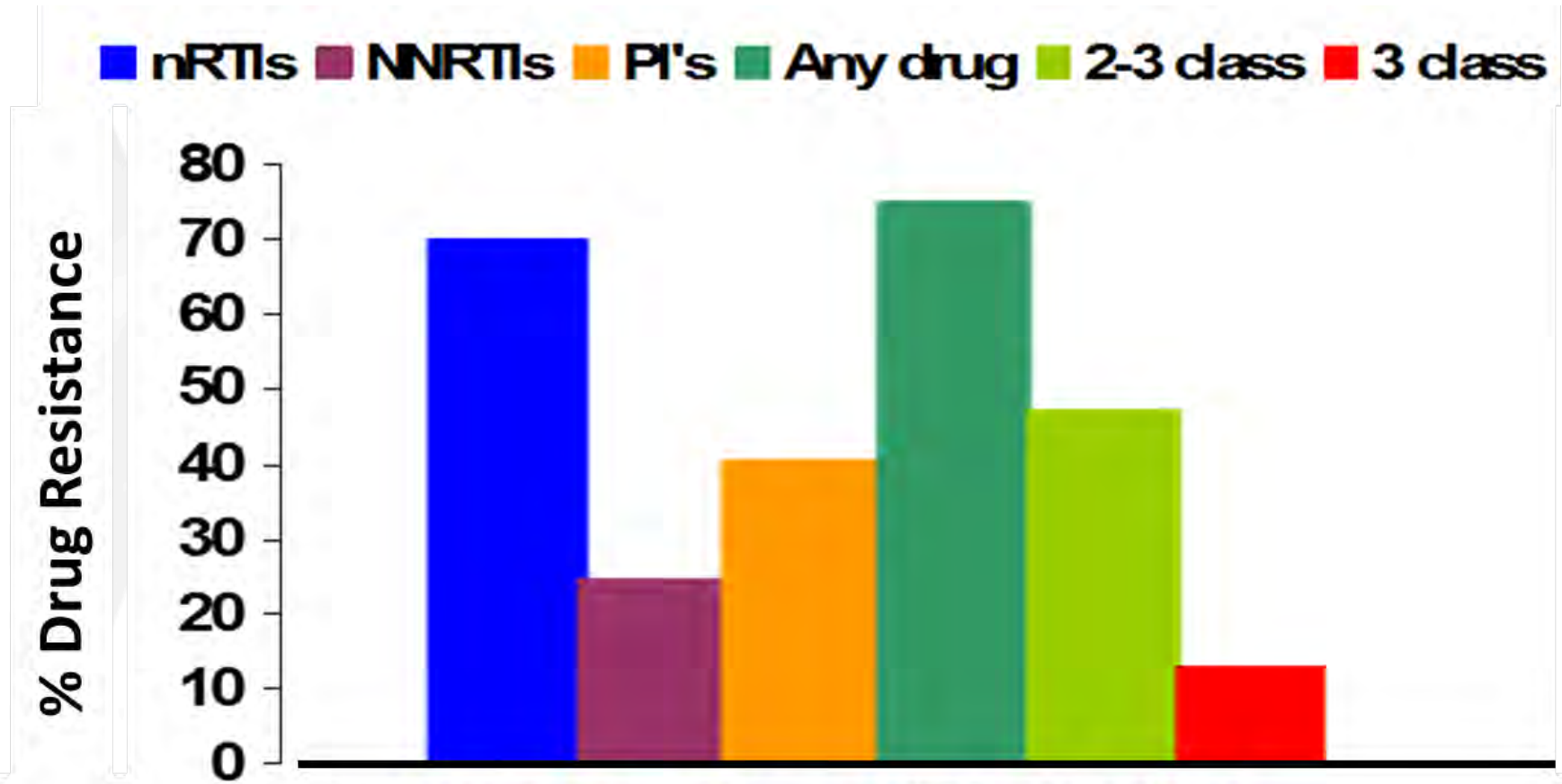
The Early-HAART Era: 1996-2005

2004: 2nd and 3rd 2-NRTI combination pills:

TDF-FTC (Truvada) ABC-3TC (Epzicom)

The Early-HAART Era: 1996-2005

2004: Long-term patients have high rates of resistance



Richman DD, AIDS 2004; 1393-1401

The Early-HAART Era: 1996-2005

2004: Accumulated resistance limits treatment options

	Trade Name	Generic Name	Interpretation	Associated Mutations	Comments
NNRTI	**– Mutation Summary** (100I, 103N)				
R	Rescriptor®	Delavirdine	Resistant	100I, 103N	
R	Sustiva®	Efavirenz	Resistant	100I, 103N	
R	Viramune®	Nevirapine	Resistant	100I, 103N	
NRTI	**– Mutation Summary** (41L, 67N, 70R, 74V, 118I, 184V, 210W, 215Y, 219E)				
R	Hivid®	Zalcitabine	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R, 74V	
R	Epivir®	Lamivudine	Resistant	118I, 184V	
R	Retrovir®	Zidovudine	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R	Mutations at 184 can suppress the effects of ZDV associated mutations.
R	Videx®	Didanosine	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R, 74V	
R	Zerit®	Stavudine	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R	Mutations at 184 can suppress the effects of ZDV associated mutations.
R	Ziagen®	Abacavir	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R, 74V	
R	Viread®	*Tenofovir(TDF)	Resistant	118I, 184V, 210W, 215Y, 219E, 41L, 67N, 70R	Mutations at 184 can suppress the effects of ZDV associated mutations.
R	Emtriva®	Emtricitabine	Resistant	184V	
PI	**– Mutation Summary** (10F, 20M, 71T, 84V, 90M)				
R	Agenerase®	Amprenavir	Resistant	10F, [84V], 90M	
R	Crixivan®	Indinavir	Resistant	10F, 20M, 71T, [84V], 90M	
R	Invirase®/Fortovase®	Saquinavir	Resistant	10F, 71T, 84V, [90M]	
R	Norvir®	Ritonavir	Resistant	10F, 20M, 71T, [84V], 90M	
R	Viracept®	Nelfinavir	Resistant	10F, 84V, [90M]	
S	Kaletra®	Lopinavir/r	Sensitive	10F, 20M, 71T, 84V, 90M	
RP	Rayataz®	Atazanavir	Resistance Possible	10F, 84V, 90M	

Legend: S Sensitive RP Resistance Possible R Resistant [ ] Denotes Major PI Mutation

The Early-HAART Era: 1996-2005

2004: CD4 depletion in the gut

$CD4^+$ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

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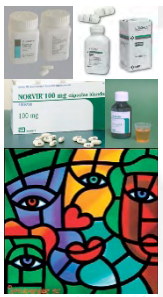
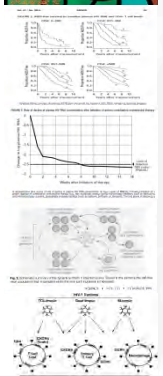
The Journal of Experimental Medicine • Volume 200, Number 6, September 20, 2004 749–759
http://www.jem.org/cgi/doi/10.1084/jem.20040874

The Early-HAART Era: 1996-2005

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





- AIDS Clinical Center at the International Medical Center of Japan
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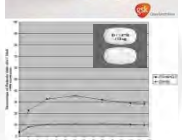
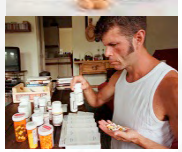
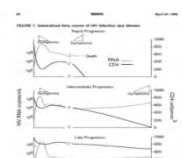




Identification of a Reservoir for HIV-1 Antiretroviral Therapy

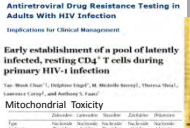
Conference Coverage (ICAAC)

T-Cell Gain Slow But Steady / Treatment



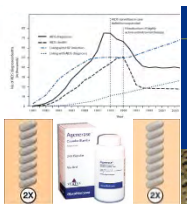
Antiretroviral Drug Resistance Testing in Adults With HIV Infection

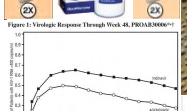
Implications for Clinical Management

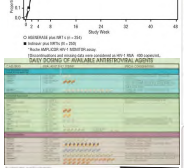


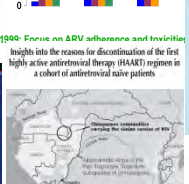
Early establishment of a pool of latently infected, resting $CD4^+$ T cells during primary HIV-1 infection

Mitochondrial Toxicity

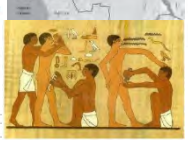


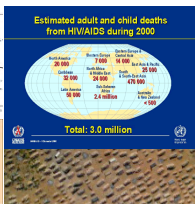


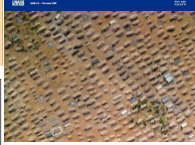


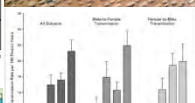


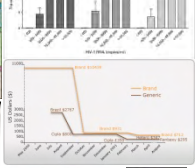
Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients

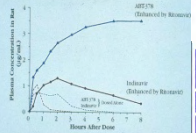


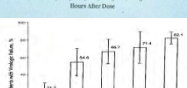




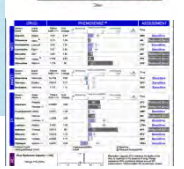


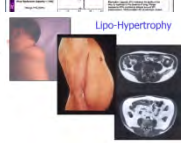




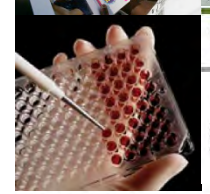


Pharmacokinetic Boosting



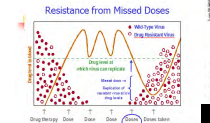


Lipo-Hypertrophy

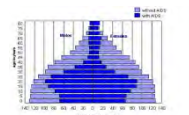


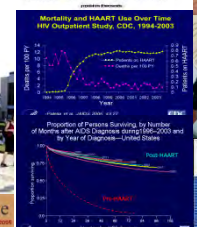
HIV-1 evolves rapidly, which i one or more error-prone steps

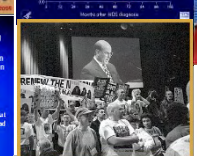
Resistance from Missed Doses

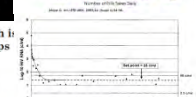


Coronary Heart Disease: Increasing Rate Over Time

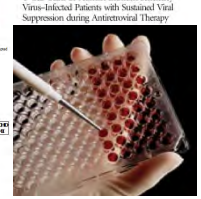


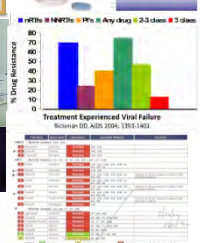






T Cell Activation Is Associated with Lower $CD4^+$ T Cell Gains in Human Immunodeficiency Virus–Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy





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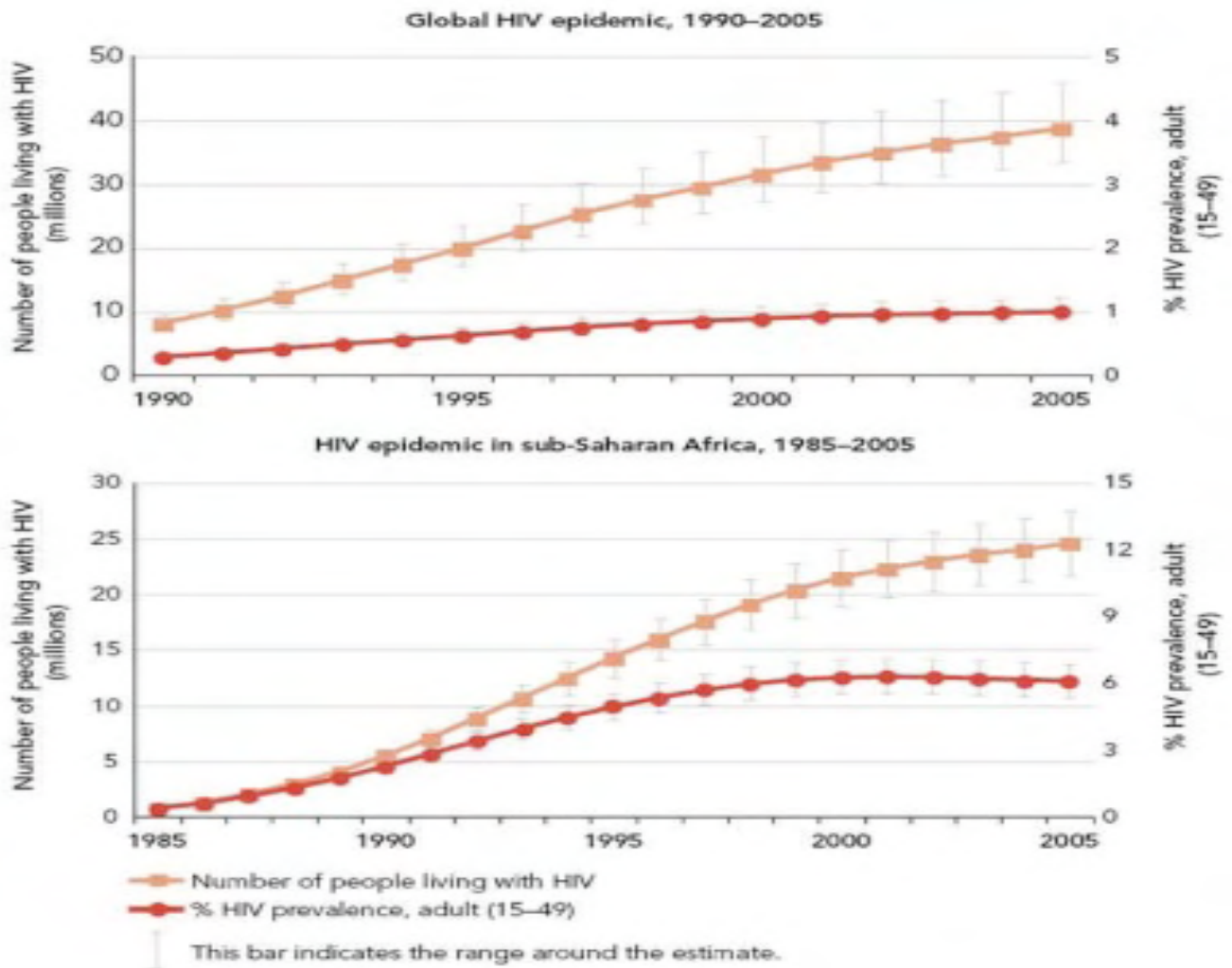
The Early-HAART Era: 1996-2005

2005: World AIDS deaths continue to increase



The Early-HAART Era: 1996-2005

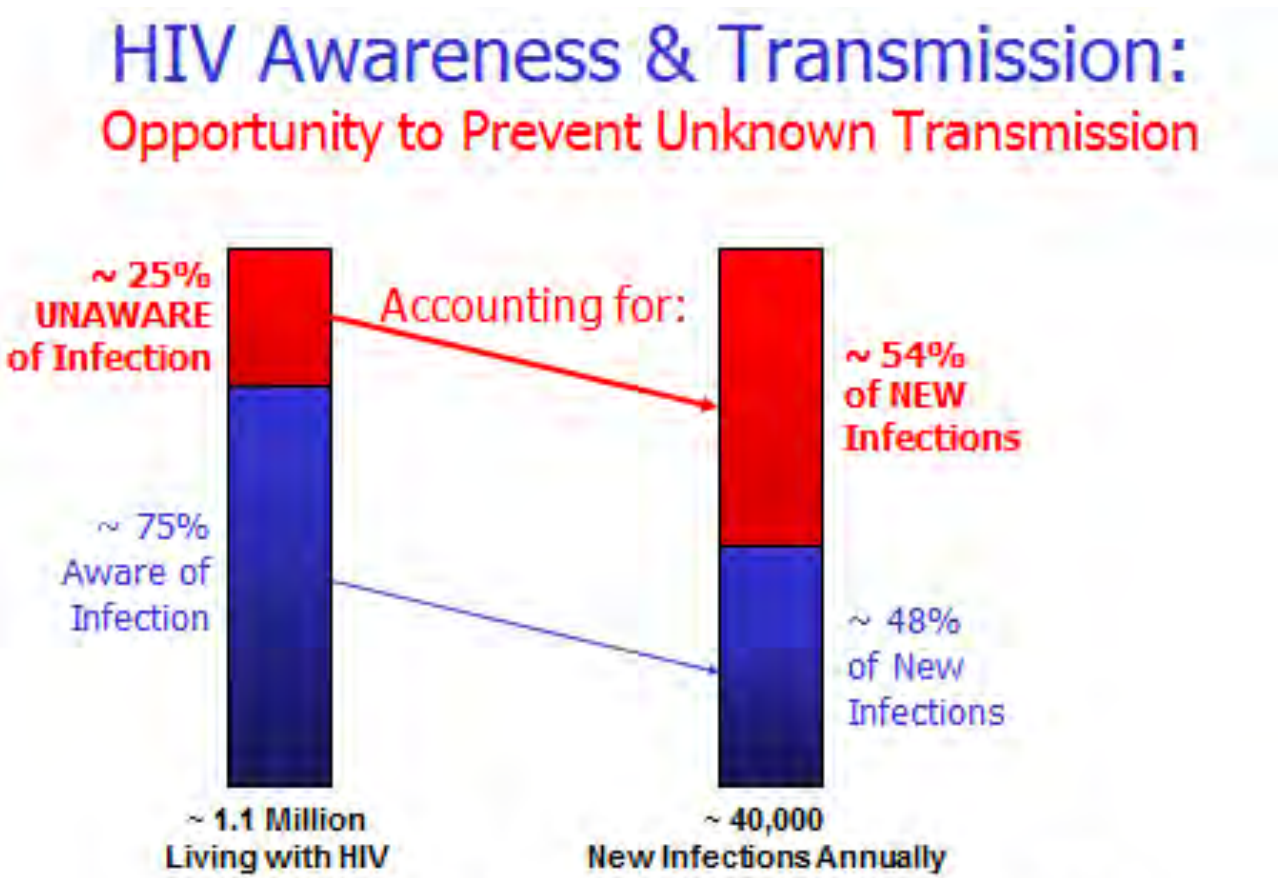
2005: “3 by 5” initiative achieves treatment for 1.3 million

"2005 is likely to be remembered more for the 3 million deaths and almost 5 million new infections it heralded than for the 300 000 lives saved through treatment for HIV“

Front cover of The Lancet Volume 366 Number 9500

The Early-HAART Era: 1996-2005

2005: >50% of US HIV transmission from the 25% who don't know they're infected



CDC. 2005 National HIV Conference. Marks, AIDS 2006;20:1447

The Early-HAART Era: 1996-2005

2005: AIDS deaths persist in the developed countries

Causes of Mortality in the HAART Era

2005 in the UK, N=397

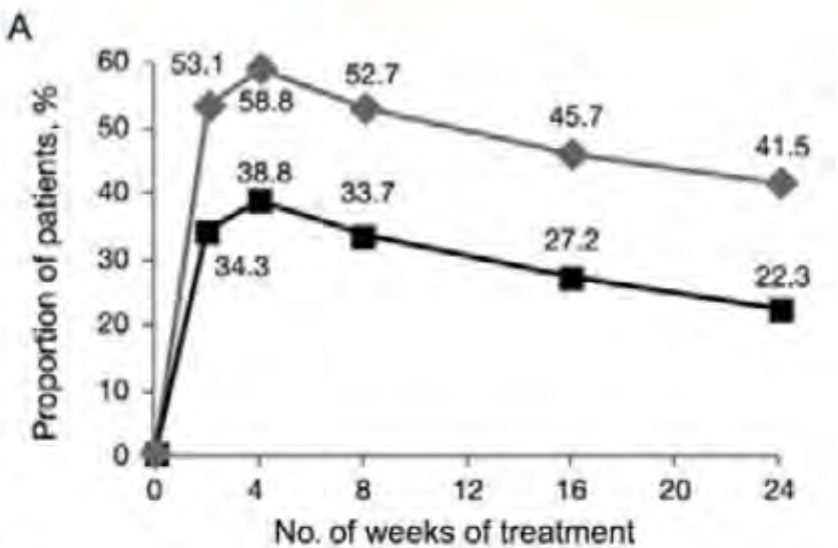
Scenario	% of AIDS deaths
Diagnosed too late for effective treatment	40%
Under care, but with untreatable complication	29%
Treatment ineffective due to poor adherence	12%
Chose not to receive treatment	8%
Known HIV, not under regular care, re-presented too late	6%
MDR HIV, ran out of options	5%

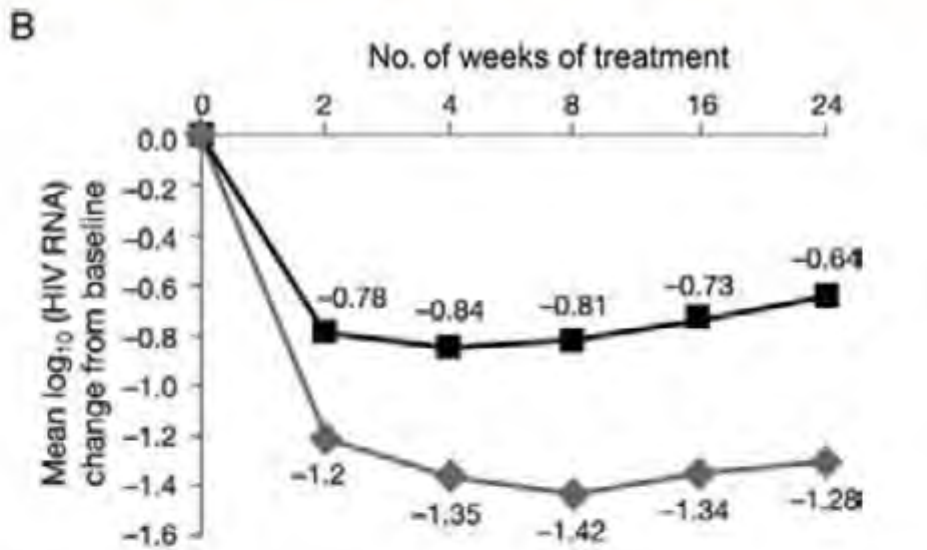
Philips A, Abstract 8, CROI 2008

The Early-HAART Era: 1996-2005

2005: 9th PI: Tipranavir

40 % success in treatment-experienced patients



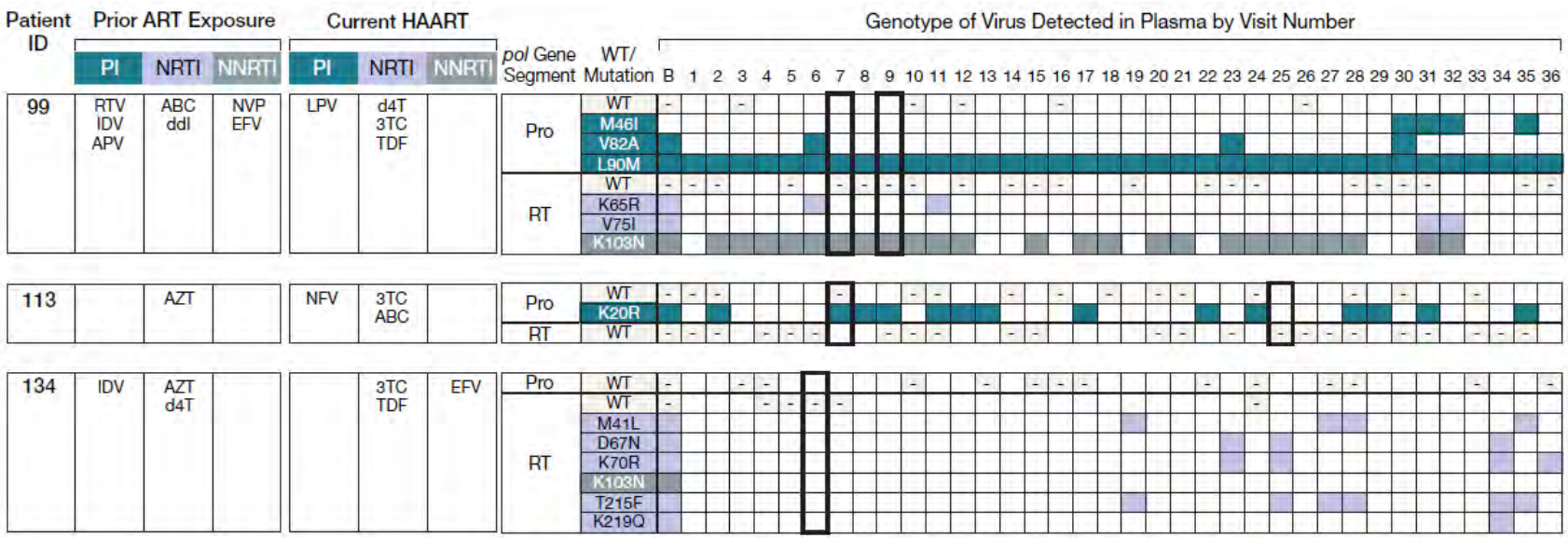


The Early-HAART Era: 1996-2005

2005: Viral load "Blips" don't lead to resistance

Intermittent HIV-1 Viremia (Blips) and Drug Resistance in Patients Receiving HAART

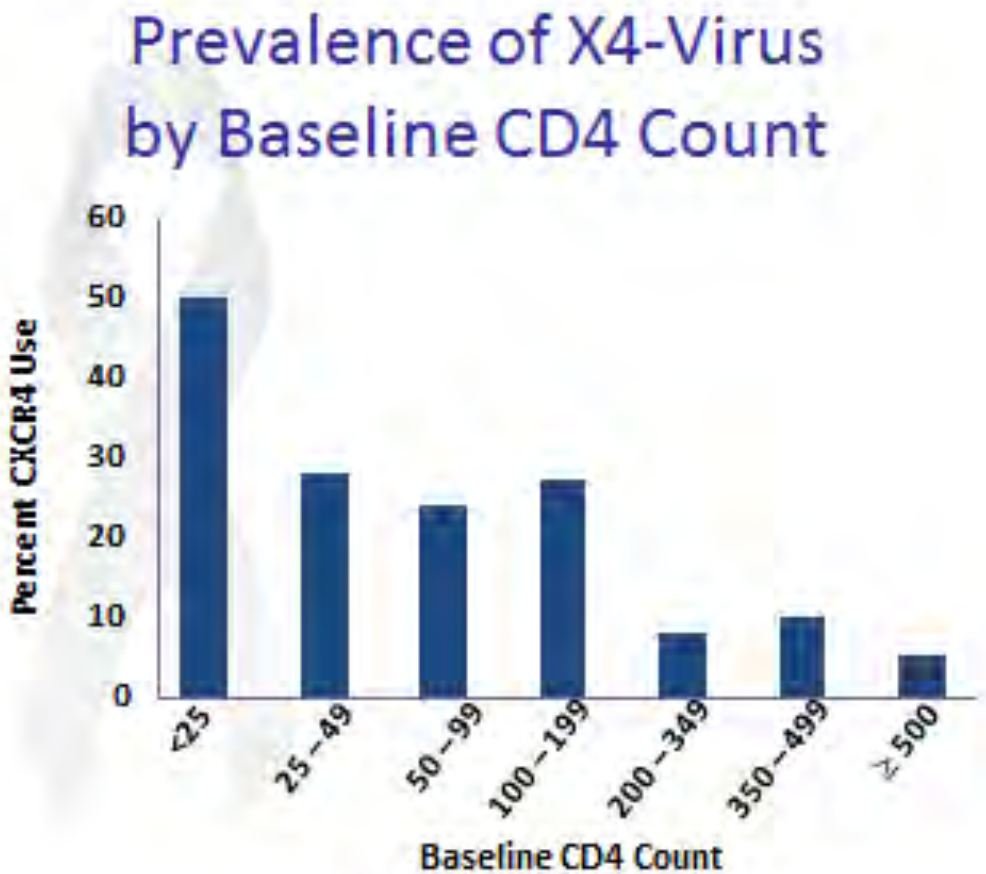
Figure 2. Lack of New Genotypic Resistance Mutations in Plasma Virus During or Immediately After Blips



JAMA. 2005;293:817-829

The Early-HAART Era: 1996-2005

2005: X4-Virus with baseline CD4 >200



Herrigan PR, et al. *J Infect Dis*. 2005. 192:466-474.

The Early-HAART Era: 1996-2005

2005: Transmitted multidrug resistant virus

Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report The Lancet, Volume 365, Issue 9464, Pages 1031 - 1038,

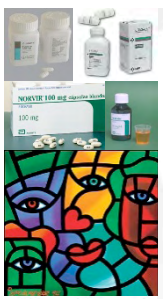
Case History:

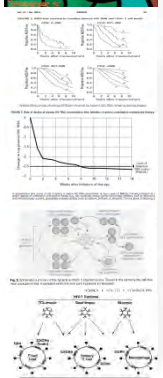
May 9, 2003:	**HIV seronegative**	**CD4+ 1500**
November 2004:	**Fever, pharyngitis, fatigue**	
December 15, 2004:	**HIV seropositive**	
December 29, 2004:	**VL 280,000**	**CD4+ 80**
January 12, 2005:	**Detuned HIV serology positive**	
February 2, 2005:		**CD4+ 39**

HIV strain: dual trophic, multiply resistant, replication capacity 136%.

The Early-HAART Era: 1996-2005

1996





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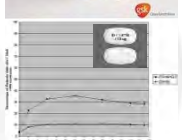
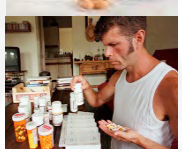
1997





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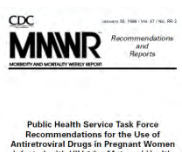
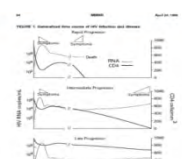
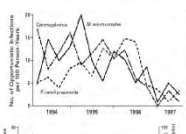
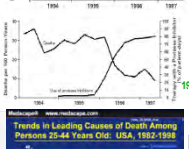
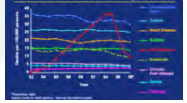


Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States









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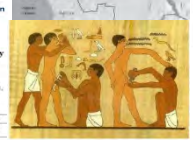


Early establishment of a pool of latently infected, resting $CD4^+$ T cells during primary HIV-1 infection

Mitochondrial Toxicity

1999

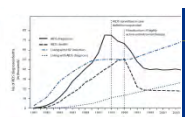
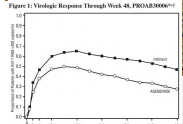
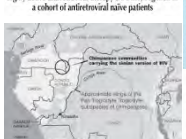


Figure 1: Virologic Response Through Week 48, PROAR3006

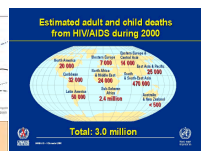


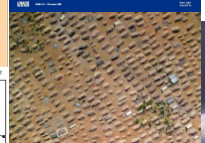
1999: Focus on ARV adherence and toxicities

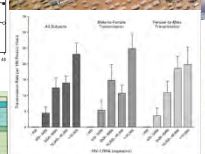
Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients

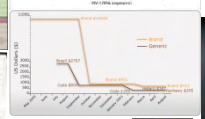


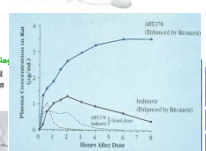
2000

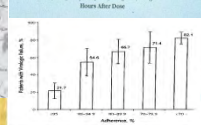




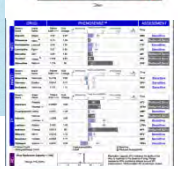




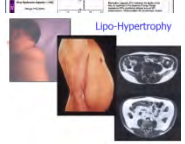




Pharmacokinetic Boosting



Lipo-Hypertrophy

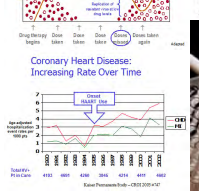


2001

HIV-1 evolves rapidly, which i

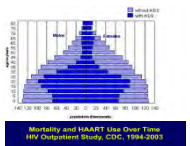
one or more error-prone steps

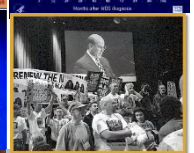
Resistance from Missed Doses



Coronary Heart Disease: Increasing Rate Over Time

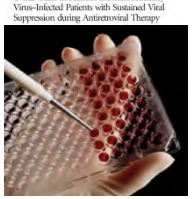
2002



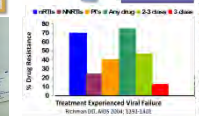


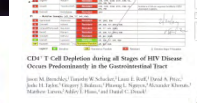
Patients Prefer Once-Daily Regimens With Low Pill Burden

T Cell Activation Is Associated with Lower $CD4^+$ T Cell Gains in Human Immunodeficiency Virus–Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy



2003

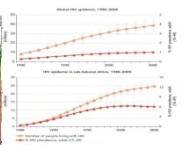




2004

$CD4^+$ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

2005

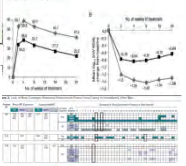


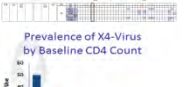
HIV Awareness & Transmission:
Opportunity to Prevent Unknown Transmission

Causes of Mortality in the HAART Era
2005 in the UK, N=397

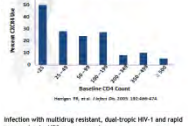
Scenario	% of AIDS deaths
Diagnosed too late for effective treatment	40%
Under care, but with untreatable complication	29%
Treatment ineffective due to poor adherence	12%
Chose not to receive treatment	8%
Known HIV, not under regular care,	6%
re-presented too late	
HIV+ UK, ran out of options	5%

Phillips A, Abstract 8, CROI 2006





Prevalence of X4-Virus by Baseline CD4 Count



Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report

Evolution of HIV treatment paradigms