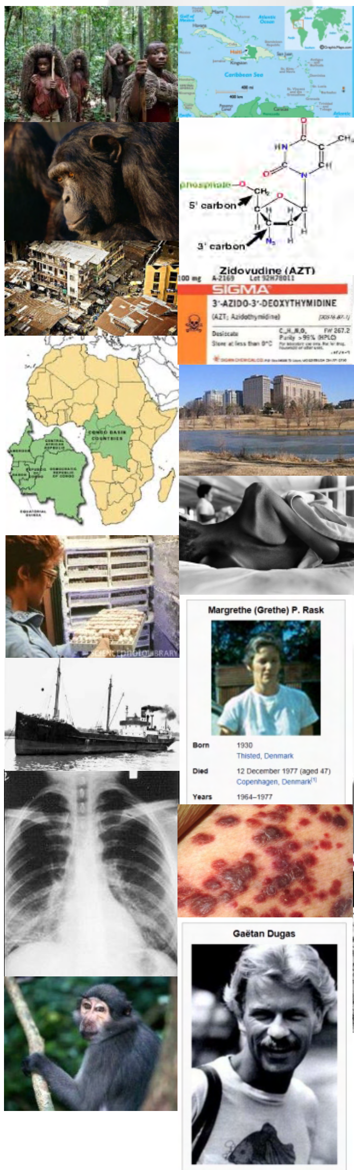
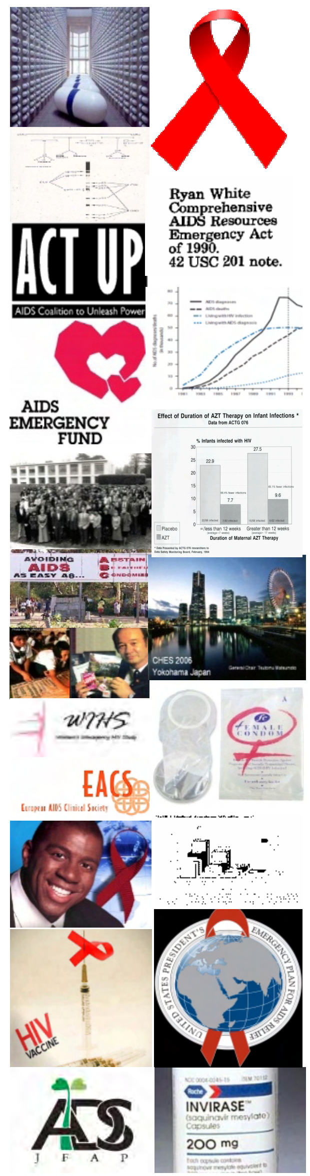
HIV流行の年代

1930-1980



1981-1986

1987-1995



HAART

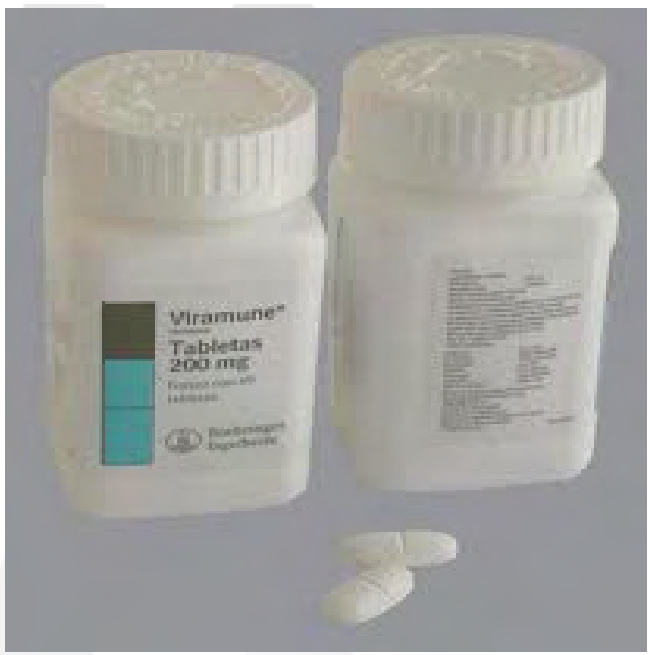
初期

1996-

2005年

HAART初期: 1996-2005年

1996年:最初のNNRTI
ネビラピン



2番目のPI
インジナビル

3番目のPI
リトナビル

HAART初期: 1996-2005年

1996年: 日本各地の拠点病院が設立され、USとのトレーニングコラボレーションが始まる

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.

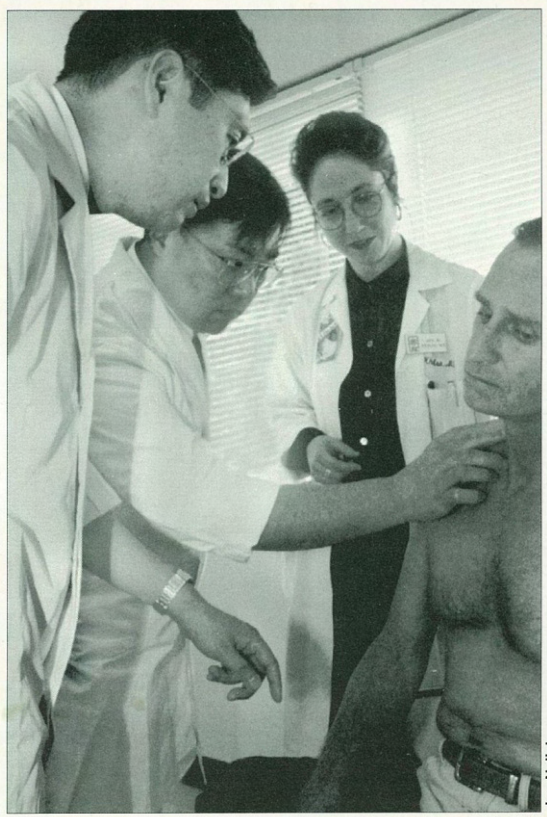
Khalsa, chief clinical trainer for the Aids Education and Training Program, had them particiapte in patient exams and interviews at the Rand Schrader Clinic for their training.

"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

HAART初期: 1996-2005年

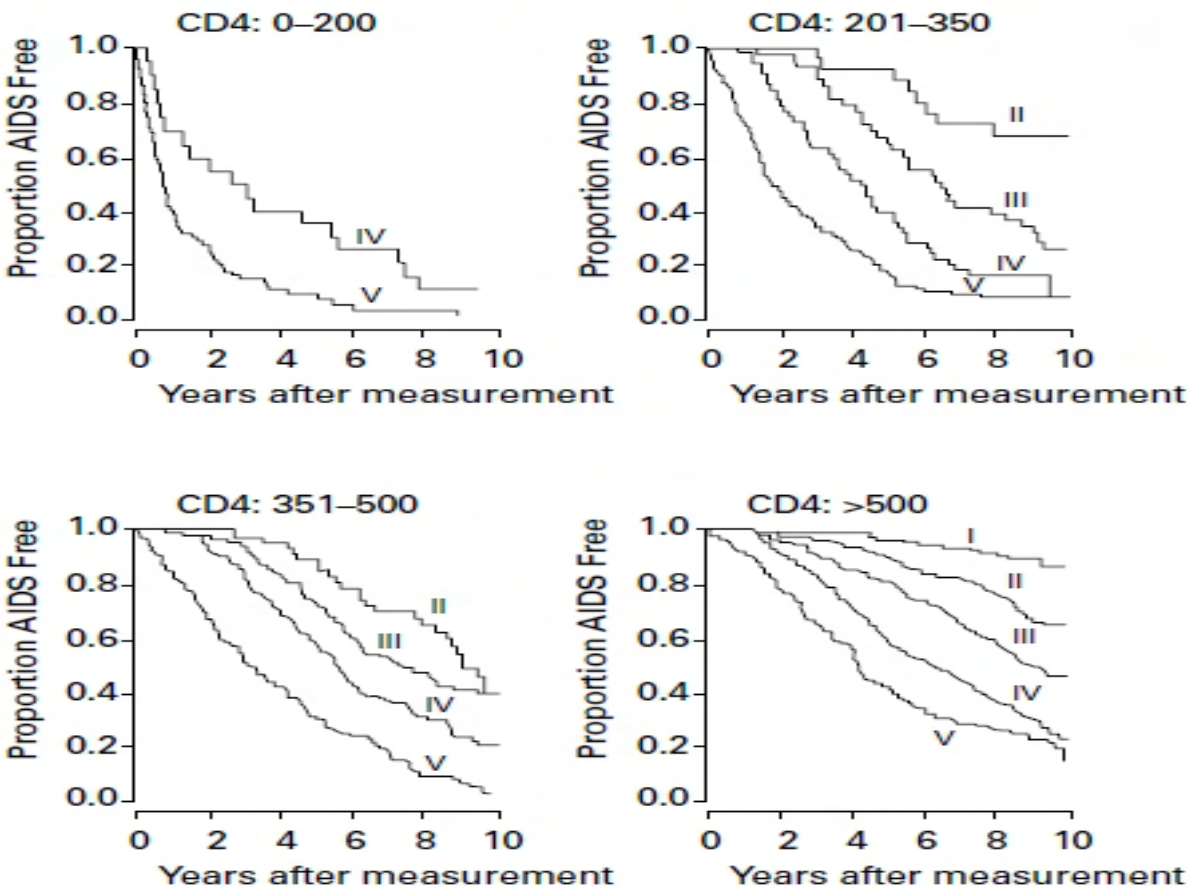
1996年: 第11回IAC:
“One World, One Hope”

“HAART”カクテル療法の時代の幕開け

HAART初期: 1996-2005年

1996年: 生存率はﾍﾞｰｽﾗｲﾝCD4値とｳｲﾙｽ量と相関

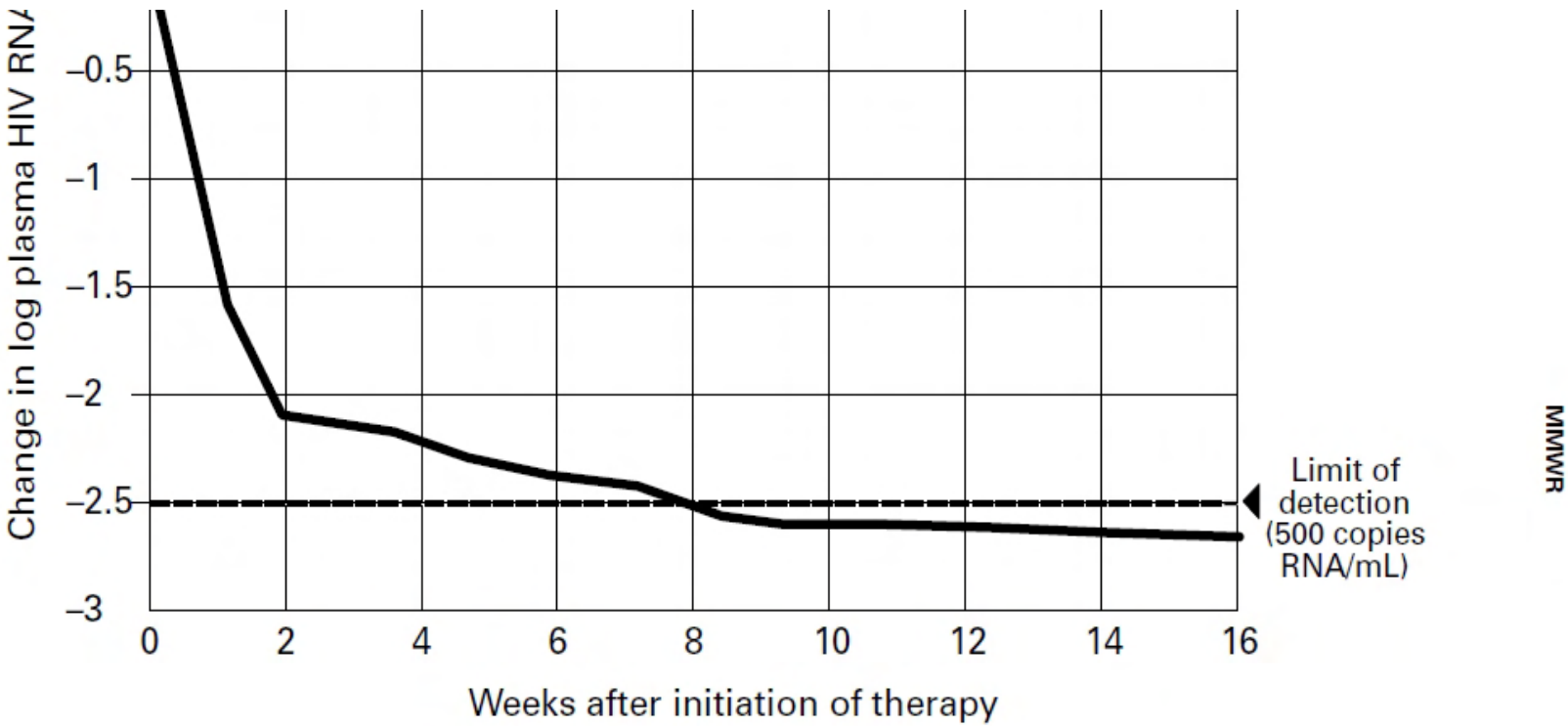
FIGURE 2. AIDS-free survival by baseline plasma HIV RNA and CD4+ T cell levels



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 Cohort Study (MACS) (27). The five categories of baseline HIV RNA levels were (I) <500;

HAART初期: 1996-2005年

1996年: ウイルス抑制が抗HIV療法の新たなゴール、商業的ウイルス量検査が可能となる



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

HAART初期: 1996-2005年

1996年: CD4とウイルス量を指標とすることで、臨床試験のエンドポイントが加速

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

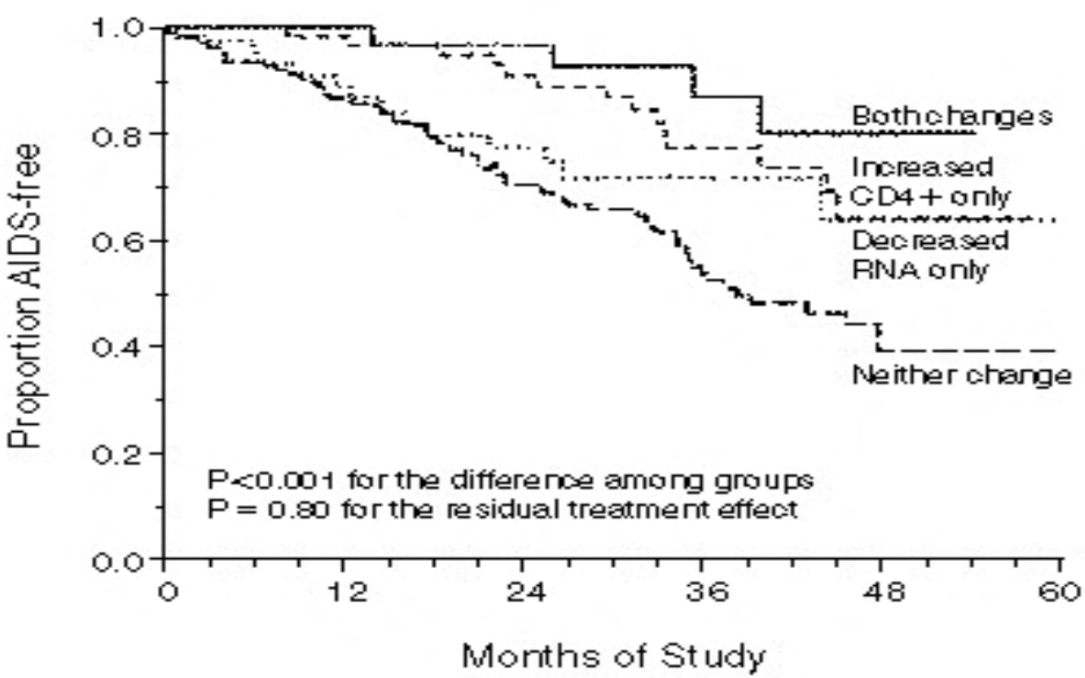


Figure 2. Kaplan–Meier Analysis of the Time to the Progression to AIDS in Patients Found to Have Both a Six-Month Mean Decrease of at Least 75 Percent in Plasma HIV-1 RNA and a Six-Month Mean Increase of at Least 10 Percent in the CD4+ Lymphocyte Count, One of These Changes, or Neither Change.

HAART初期: 1996-2005年

1996年: David Hoがウイルス増殖過程を定義

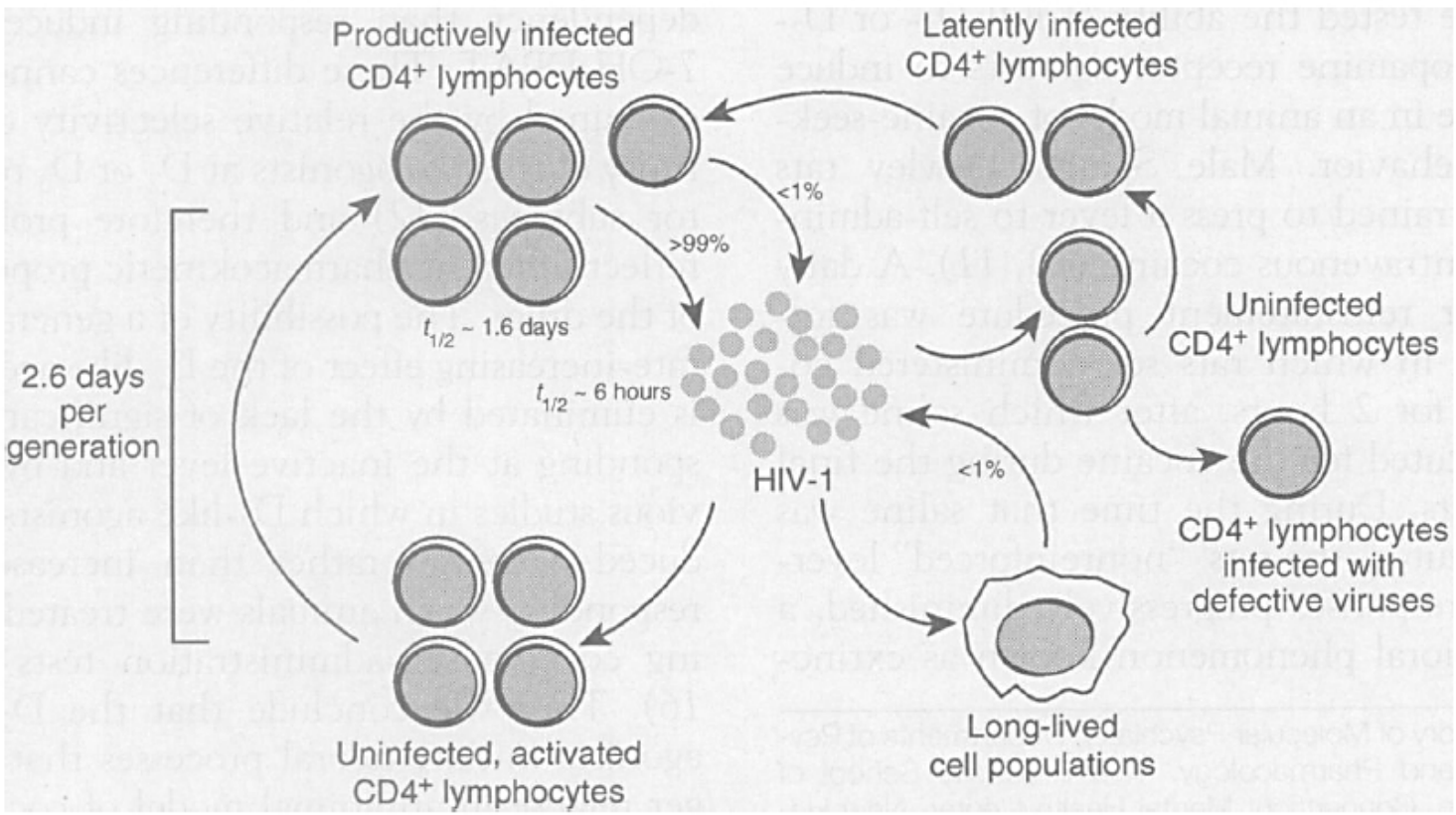
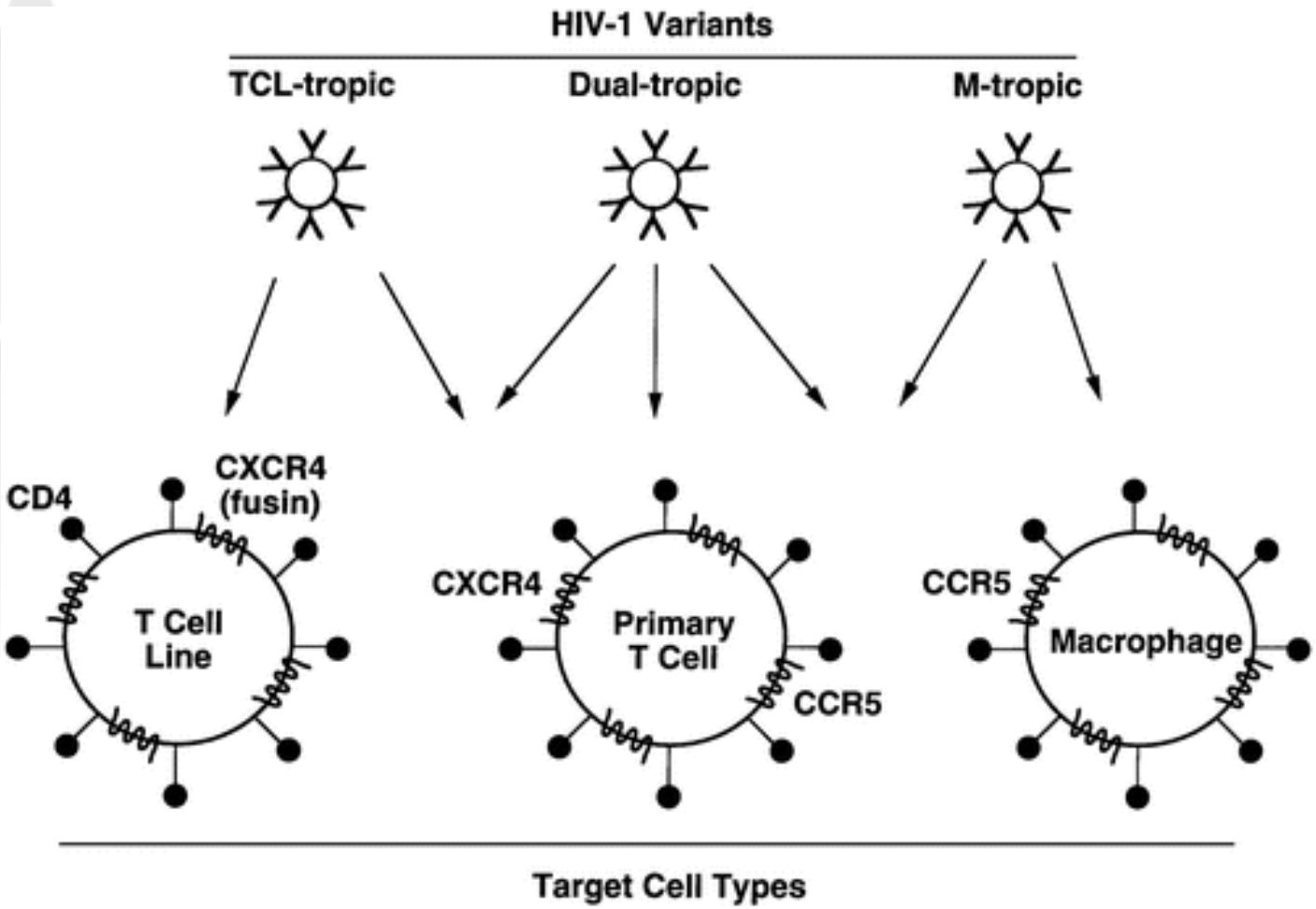


Fig. 2. Schematic summary of the dynamics of HIV-1 infection in vivo. Shown in the center is the cell-free virion population that is sampled when the viral load in plasma is measured.

SCIENCE • VOL. 271 • 15 MARCH 1996

HAART初期: 1996-2005年

1996年: ウイルス指向性を発見



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

HAART初期: 1996-2005年

1996年: コレセプター欠損がHIVに抵抗性を示す

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

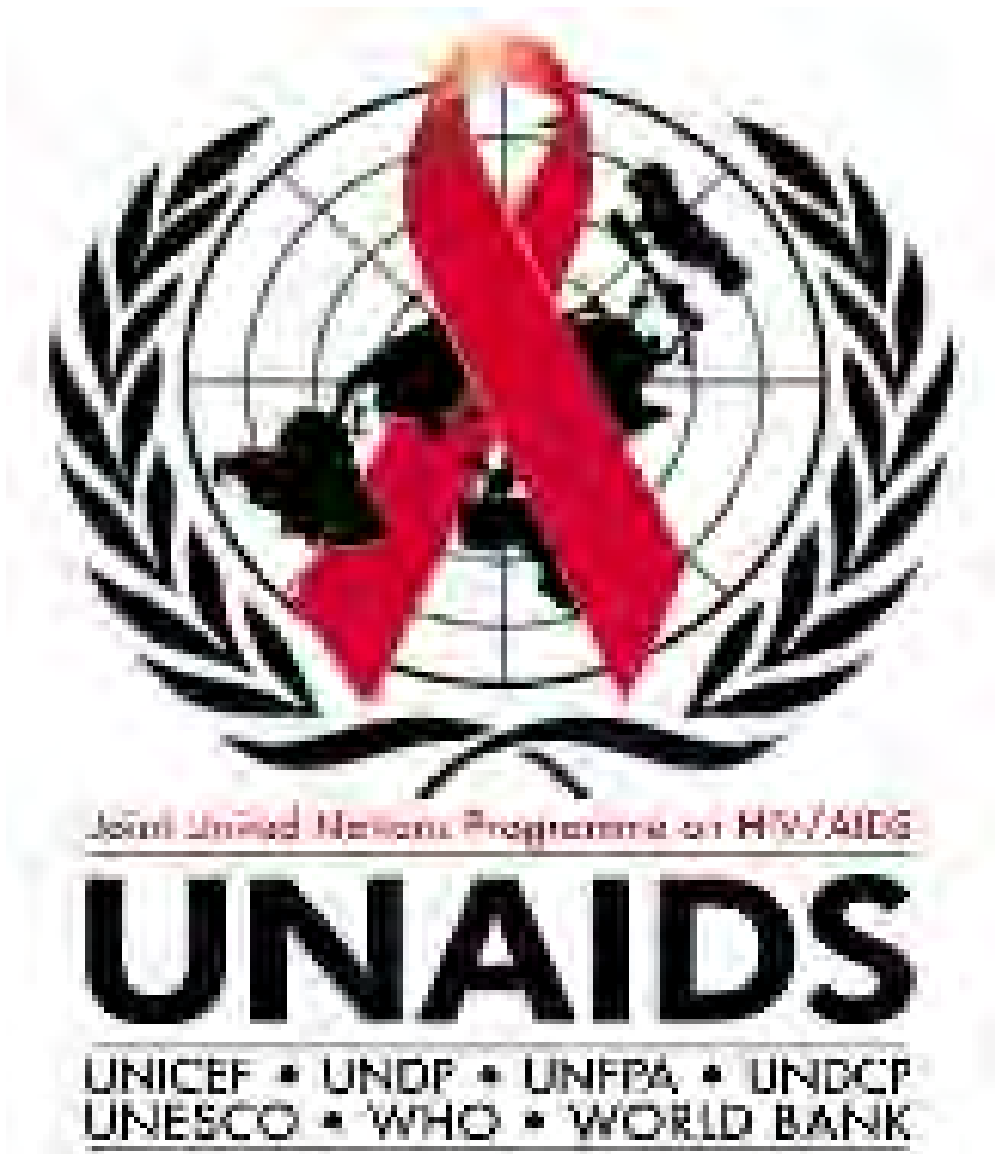
We show here that two individuals who are resistant to HIV-1 infection in spite of repeated exposures are homozygous for a defect in the gene encoding CKR-5, a major coreceptor for macrophage-tropic HIV-1 isolates.

HAART初期: 1996-2005年

1996年: ブラジルが発展途上国で初めてARVの供給を開始

HAART初期: 1996-2005年

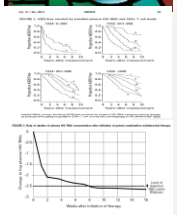
1996年: UNAIDS創設

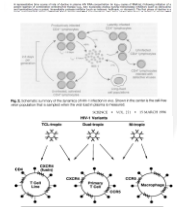


HAART初期: 1996-2005年

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



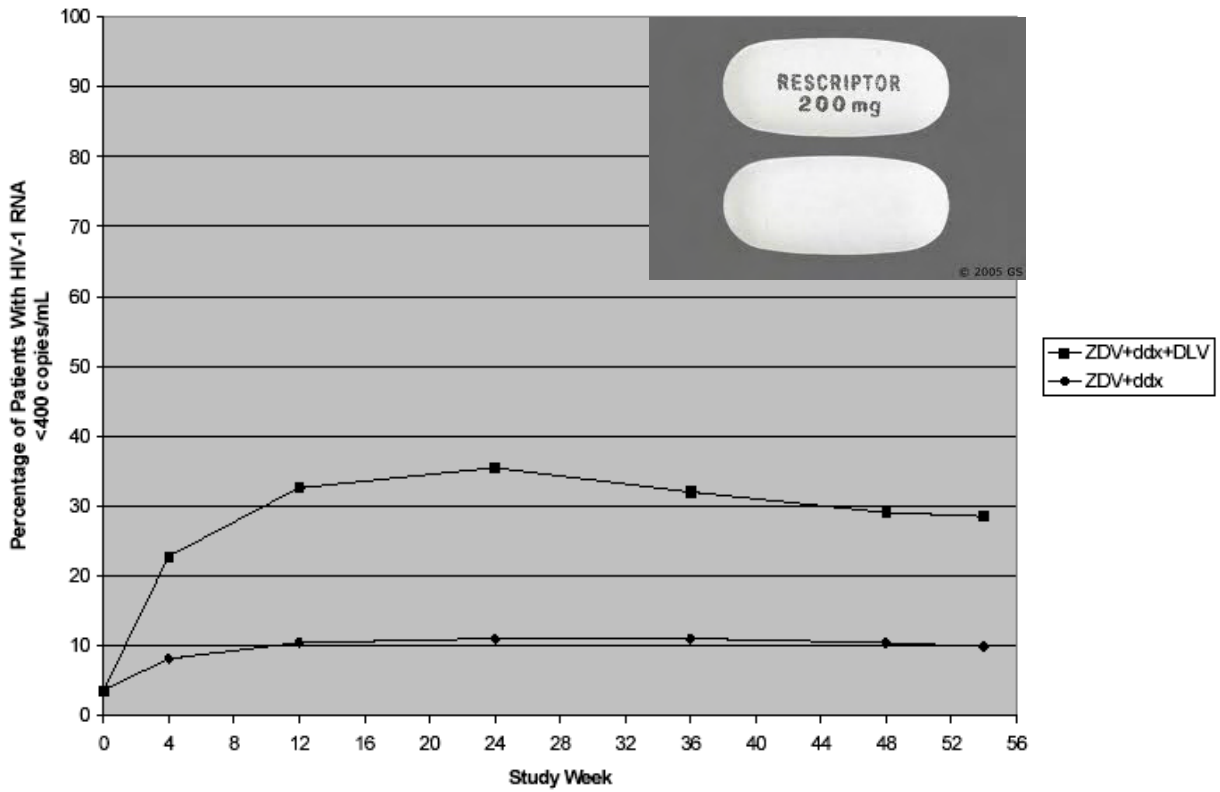


Joint United Nations Programme on HIV/AIDS
UNAIDS
UNICEF • UNDP • UNFPA • UNDCP
UNESCO • WHO • WORLD BANK

HAART初期: 1996-2005年

1997年: 最初のNRTI合剤
コンビビル

2番目のNNRTI:
DLV デラビルジ



HAART初期: 1996-2005年

1997年: 4番目のPI:
ネルフィナビル

PI剤形変更:
サキナビル軟カプセル

HAART初期: 1996-2005年

1997年: 大量の薬剤との戦い

HAART初期: 1996-2005年

1997年: HAARTでもHIVリザーバー消失せず

Science

AAAS

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*

HAART初期: 1996-2005年

1997年: HAARTでCD4が持続的に増加

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.

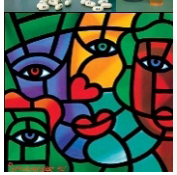
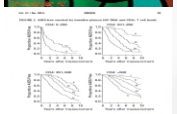
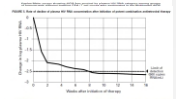
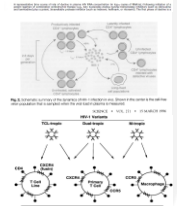
"Data suggest that there can really be repopulation of naive T cells that might have a full expression of the T-cell repertoire and might result in effective immune reconstitution, eventually," said Donald E. Mosier of The Scripps Research...

HAART初期: 1996-2005年

1997年: 米国各地でAIDSウォーク

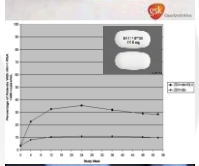
HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

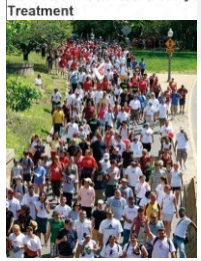
- AIDS Clinical Center at the International Medical Center of Japan
- Regional AIDS Care Core Hospitals
- Japan – US AETC clinical training

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



Identification of a Reservoir for HIV-1 Antiretroviral Therapy

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



HAART初期: 1996-2005年

1998年: US DHHS 抗HIV療法ガイドライン

CDC

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

April 17, 1998 / Vol.

Recommen
and
Repor

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

CDC

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

January 30, 1998 / Vol. 47 / No. RR-2

Recommendations and Reports

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

CDC

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

April 24, 1998 / Vol. 47 / No. RR-5

Recommendations and Reports

Report of the NIH Panel to Define Principles of Therapy of HIV Infection

and

Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

HAART初期: 1996-2005年

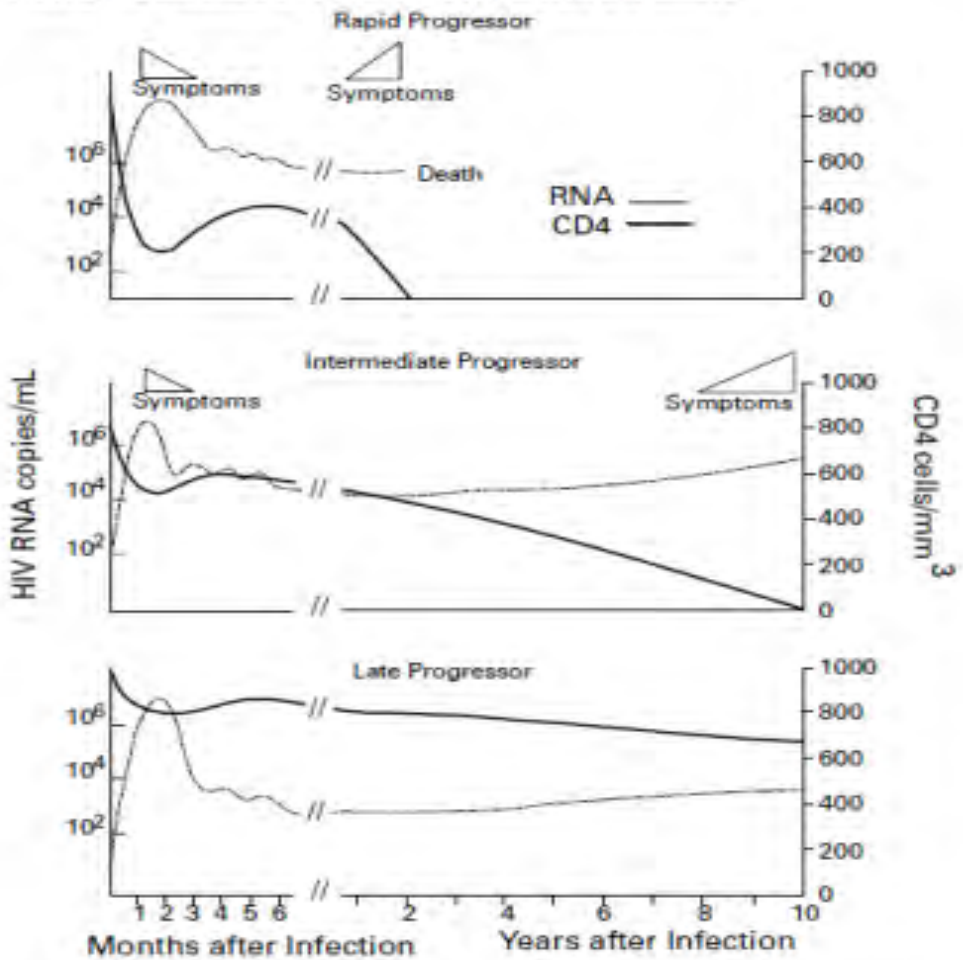
1998: 5番目のNRTI: アバカビル

3番目のNNRTI: エファビレンツ

HAART初期: 1996-2005年

1998年: いくつかの異なった病期進展パターン

FIGURE 1. Generalized time course of HIV infection and disease



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

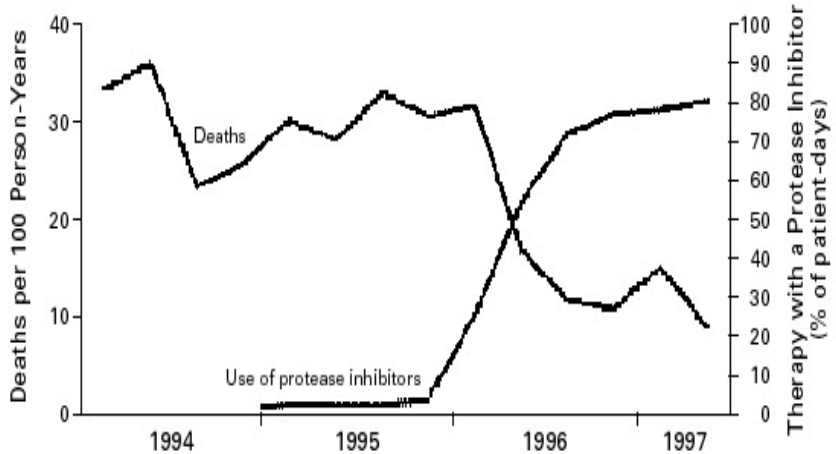
HAART初期: 1996-2005年

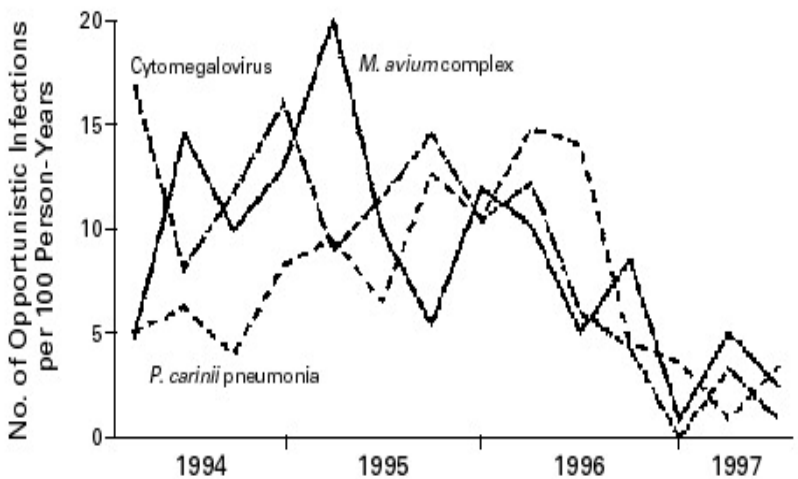
1998年: HAARTがAIDS罹患・死亡率を低下させる

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

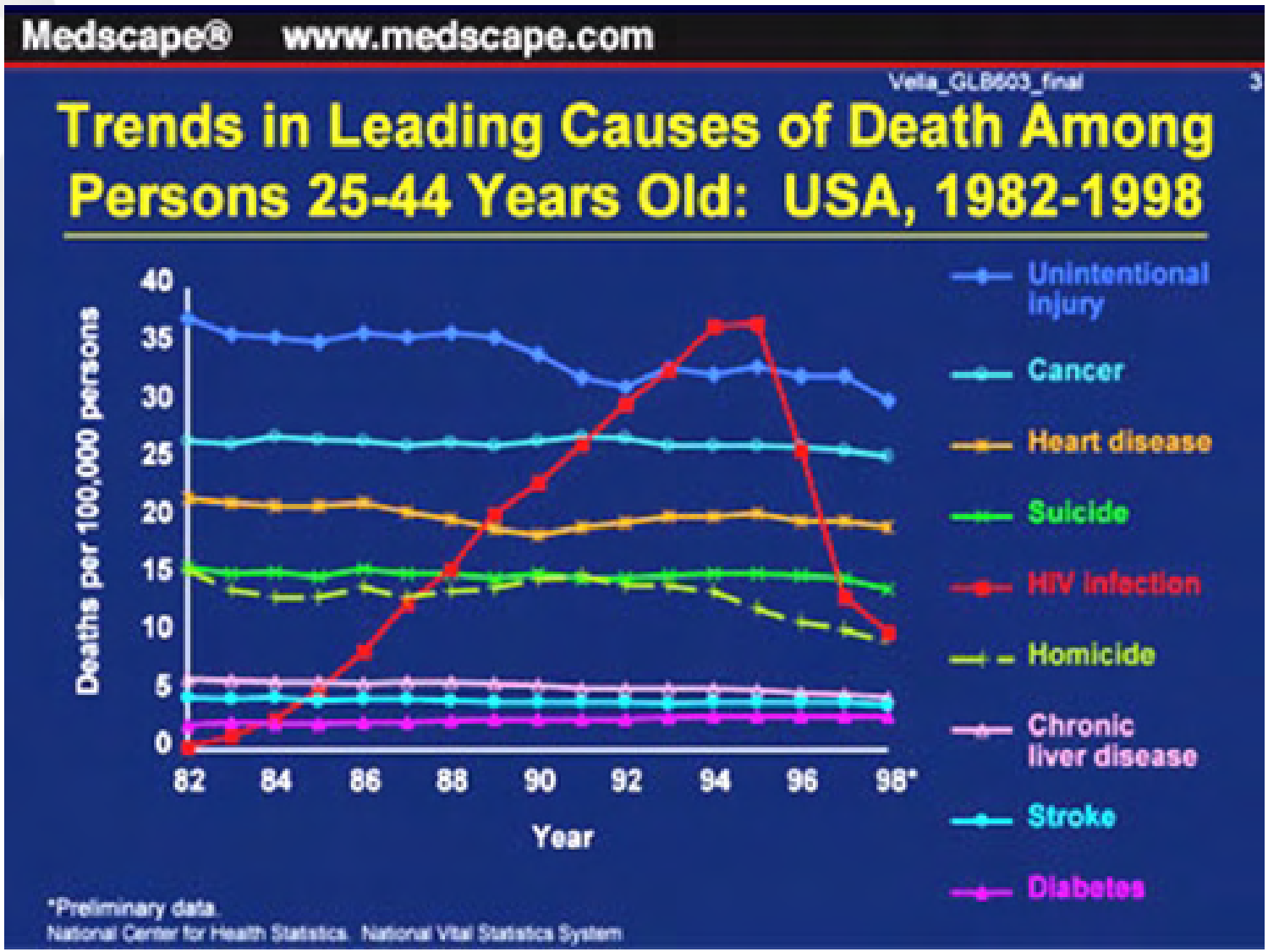
N Engl J Med 1998; 338:853-860 | March 26, 1998





HAART初期: 1996-2005年

1998年: AIDSが死亡原因のトップではなくなる



HAART初期: 1996-2005年

1998年: 臨床現場での耐性検査の開始

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

HAART初期: 1996-2005年

1998年: 急性感染期に潜在感染リザーバーが確立

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

HAART初期: 1996-2005年

1998年: NRTIによるミトコンドリア毒性

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

HAART初期: 1996-2005年

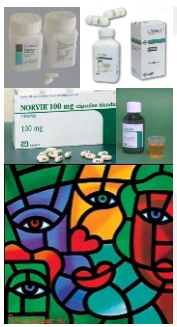
1998年: リポジストロフィーによるART長期安全性への疑問

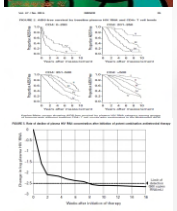
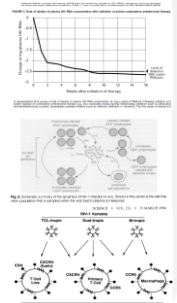
HAART初期: 1996-2005年

1998年: 最初のHIVワクチン臨床試験が開始

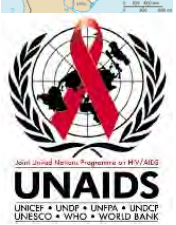
HAART初期: 1996-2005年

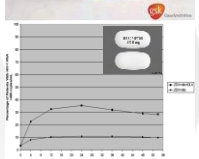
1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



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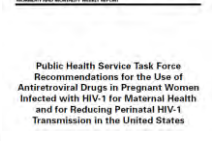
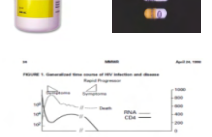
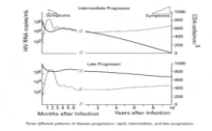
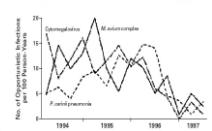
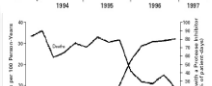
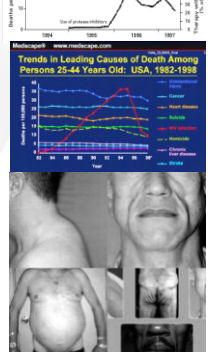
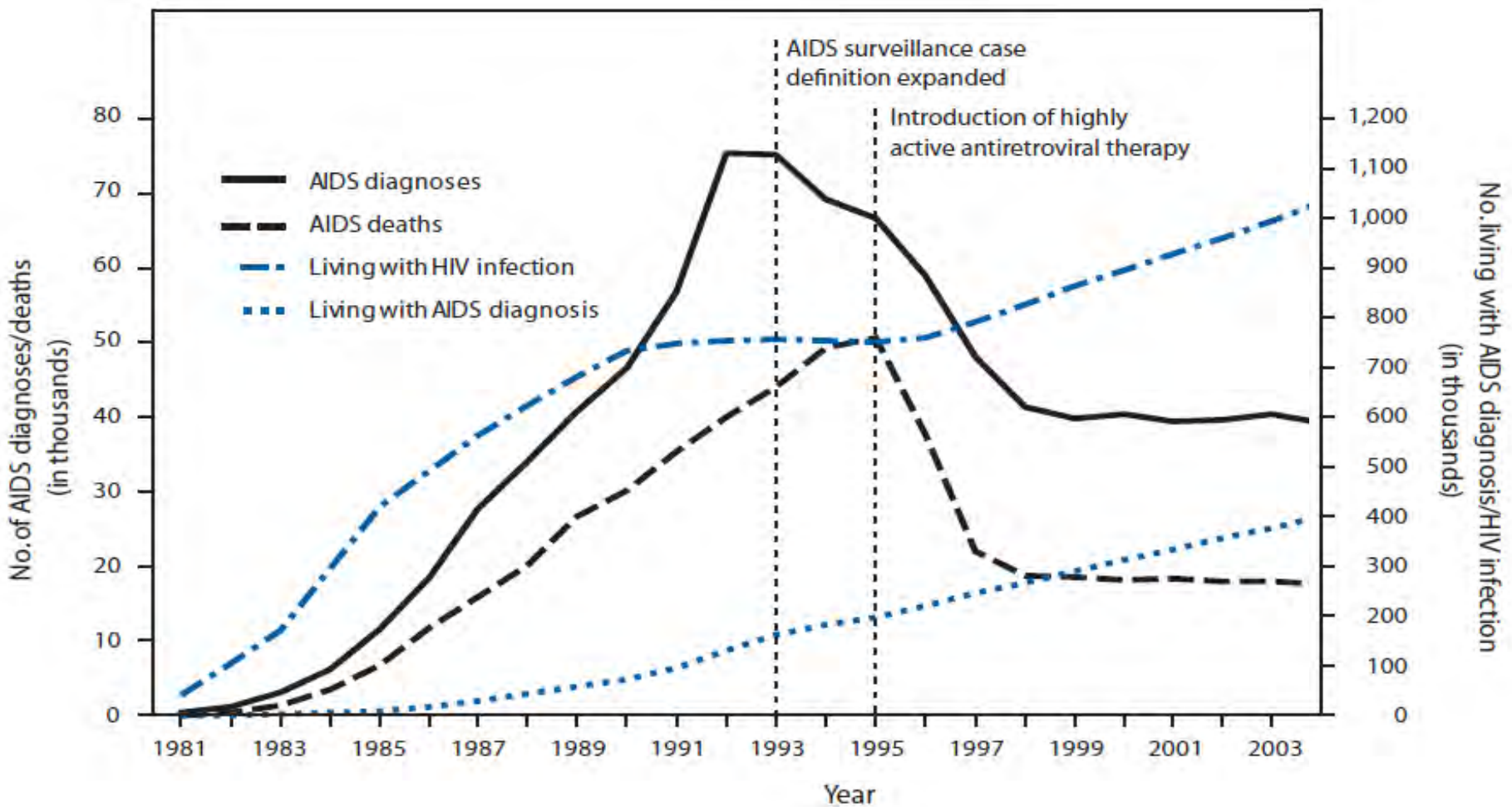


HAART初期: 1996-2005年

1999年: AIDS症例数と死亡数が横ばい

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



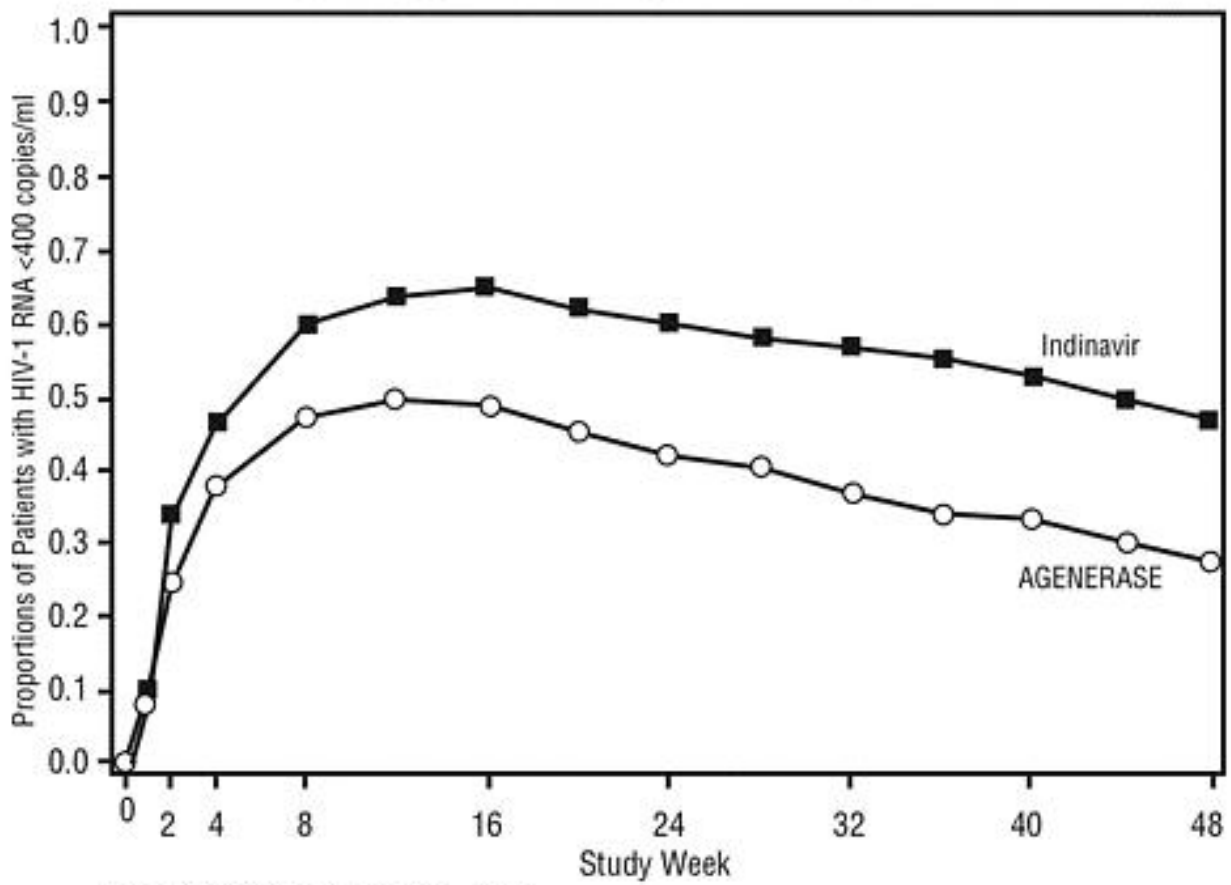
HAART初期: 1996-2005年

1999年: 5番目PI:アンプレナビル

HAART初期: 1996-2005年

1999年: HAARTの成功率は50%止まり

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.

HAART初期: 1996-2005年

1999年: 大量服薬が必要なレジメン

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.

HAART初期: 1996-2005年

1999年: 第1世代ARTにおける高度交叉耐性

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)

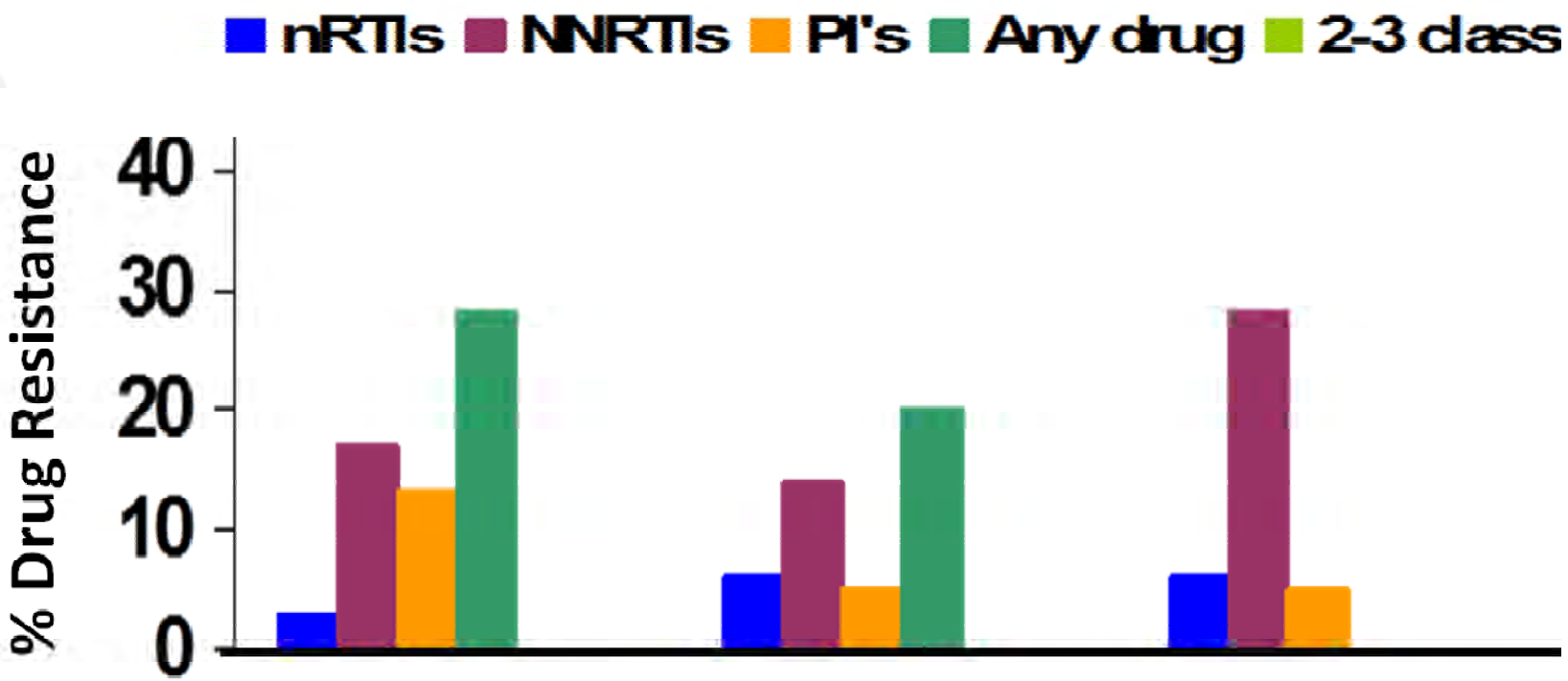
DLV		103				181				236	NNRTI resistance occurs quickly if viral suppression is incomplete. K103N and Y181C are the most common mutations and lead to cross-resistance. Y181C alone may not lead to EFV resistance.
EFV	100	103		108	179	181	188		225		
NVP	100	103	106	108		181	188	190			

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

HAART初期: 1996-2005年

1999年: 異なった抗HIV薬の内服を順次的に繰り返すことにより、耐性変異が高率に出現



HAART初期: 1996-2005年

1999年: ARVのｱﾄﾞﾋｱﾗﾝｽと副作用に注目

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

HAART初期: 1996-2005年

1999年: 西アフリカのチンパンジーがHIVの発生源との報告

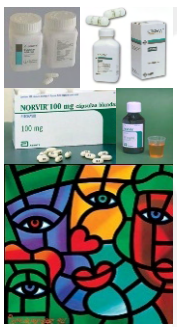
HAART初期: 1996-2005年

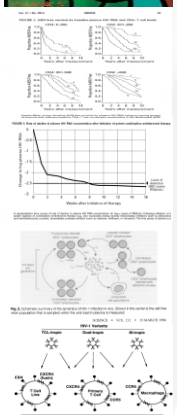
1999年: 男性の割礼をHIV感染予防に

Halperin, Lancet 1999; 1813354:

HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





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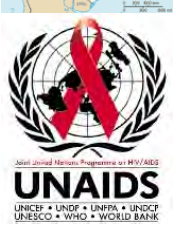

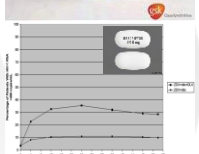

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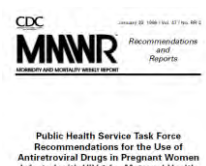

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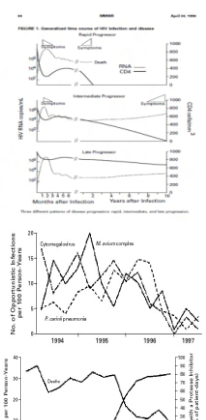

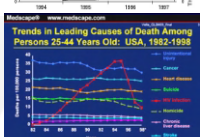

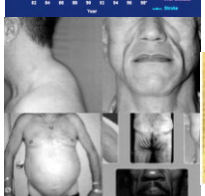

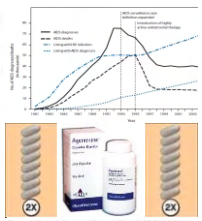

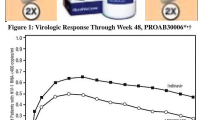

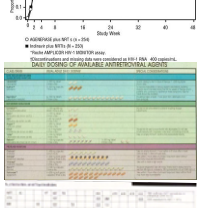

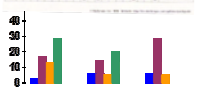

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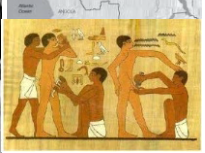
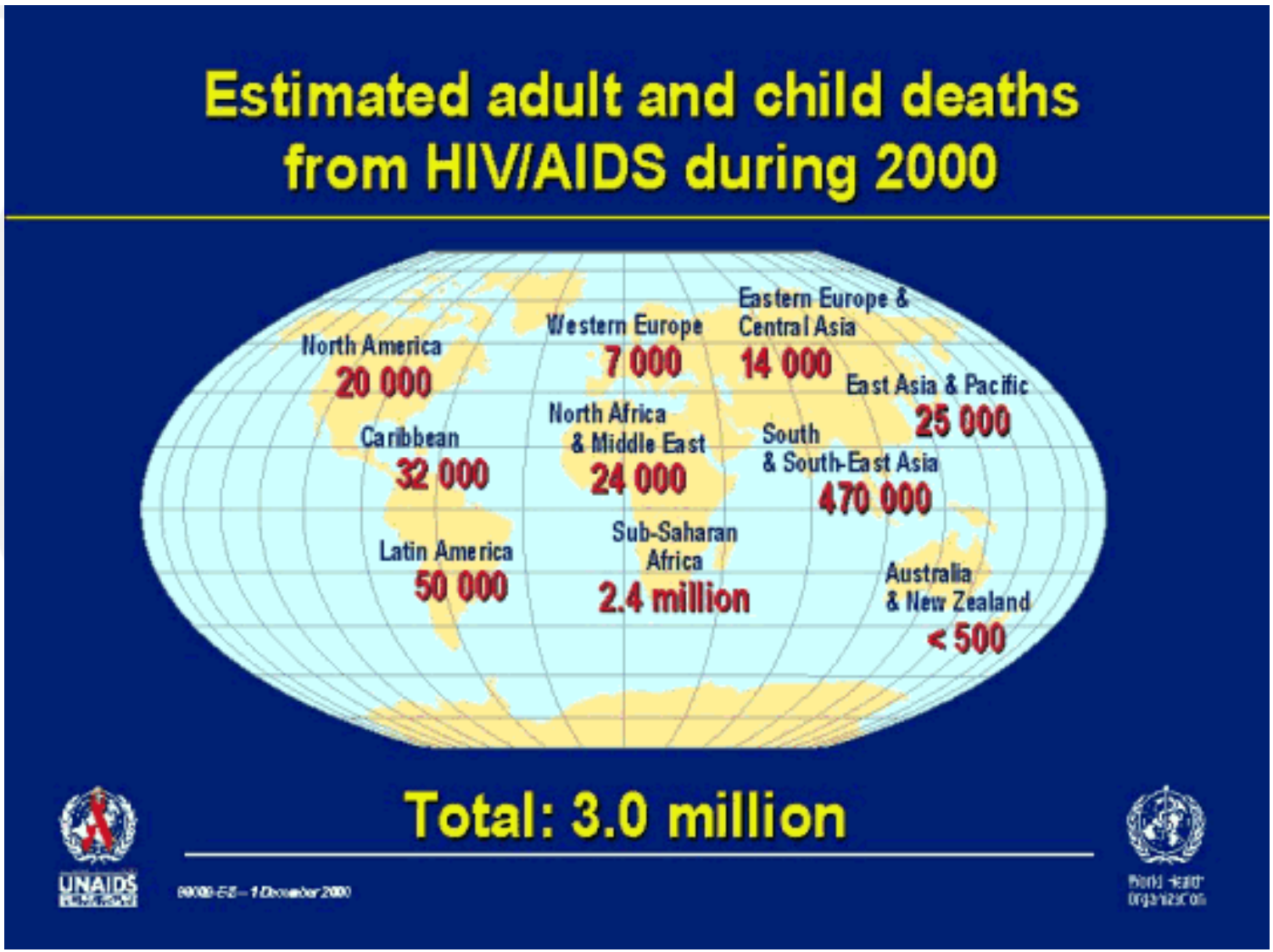


HAART初期: 1996-2005年

2000年: AIDS死は発展途上国に偏る



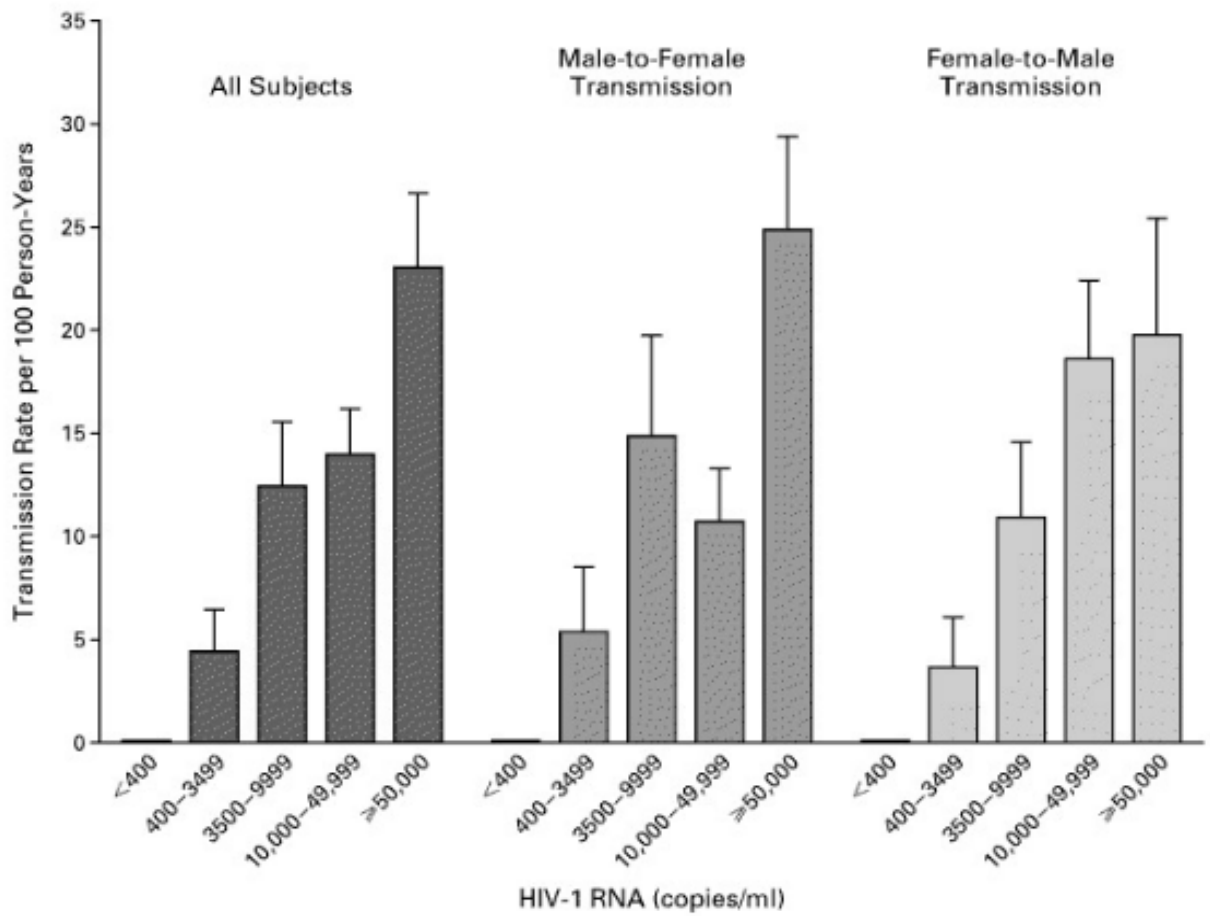
HAART初期: 1996-2005年

2000年: アフリカの墓標なきAIDSの墓

HAART初期: 1996-2005年

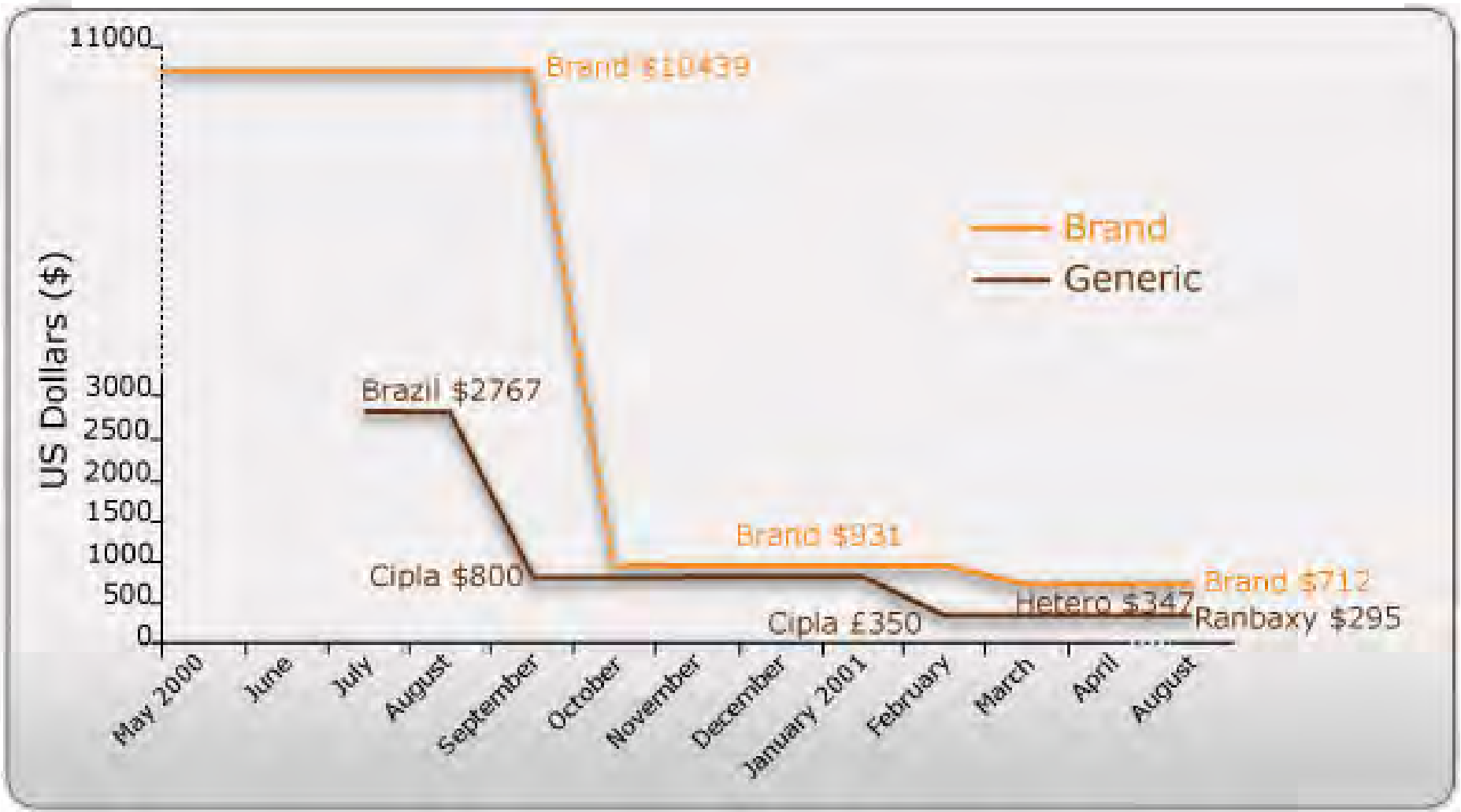
2000年: ウイルス量抑制でHIV伝播も抑制

Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1 Rakai Project. NEJM 2000; 342:921



HAART初期: 1996-2005年

2000年: 発展途上国でもARVは購入可能な価格に



HAART初期: 1996-2005年

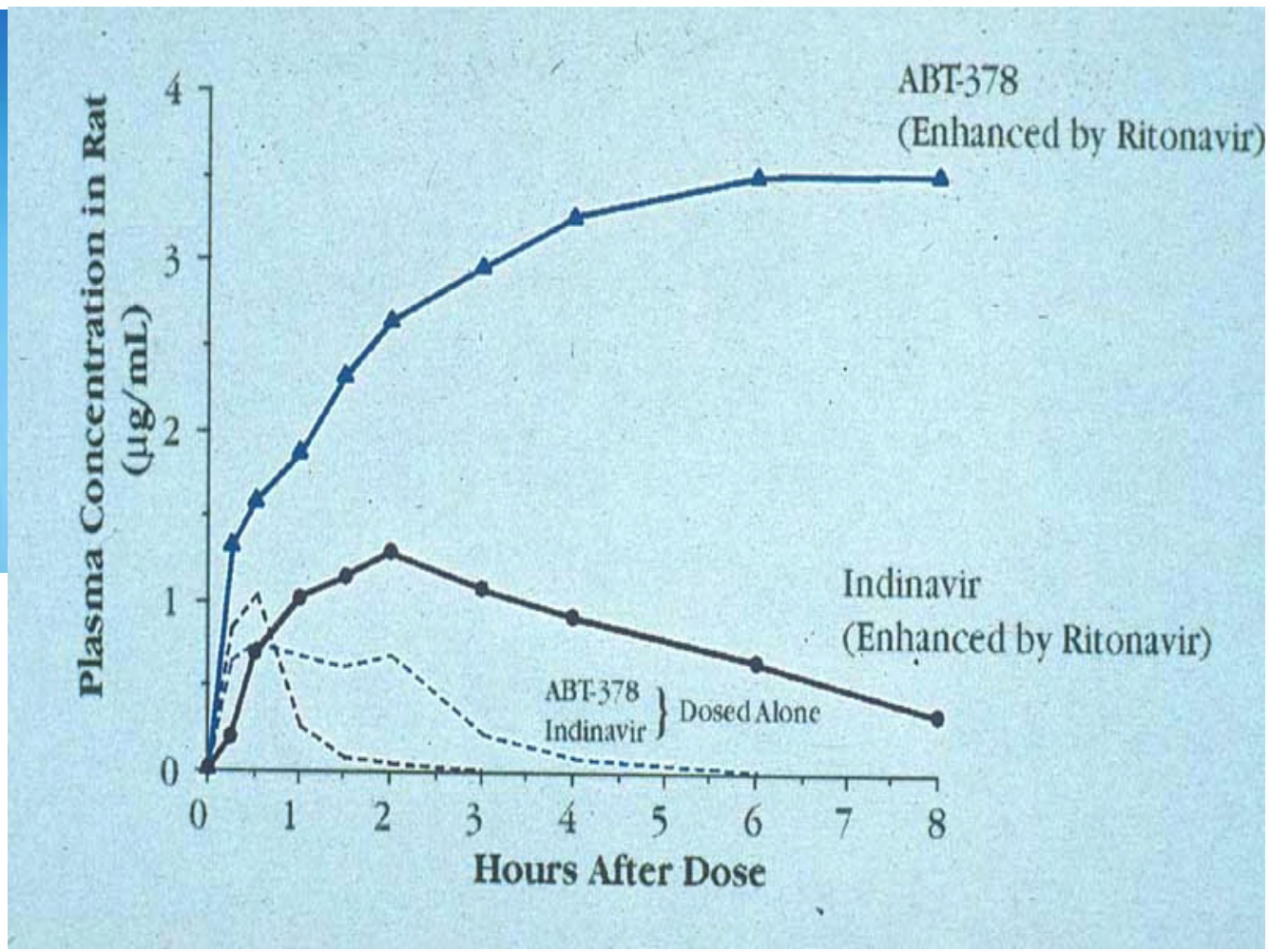
2000年: 2番目のNRTI合剤 Trizivir

NRTI剤形変更 ヴァイデックスEC

HAART初期: 1996-2005年

2000年: 最初のブーストPI合剤: カレトラ

Kaletra SGCs



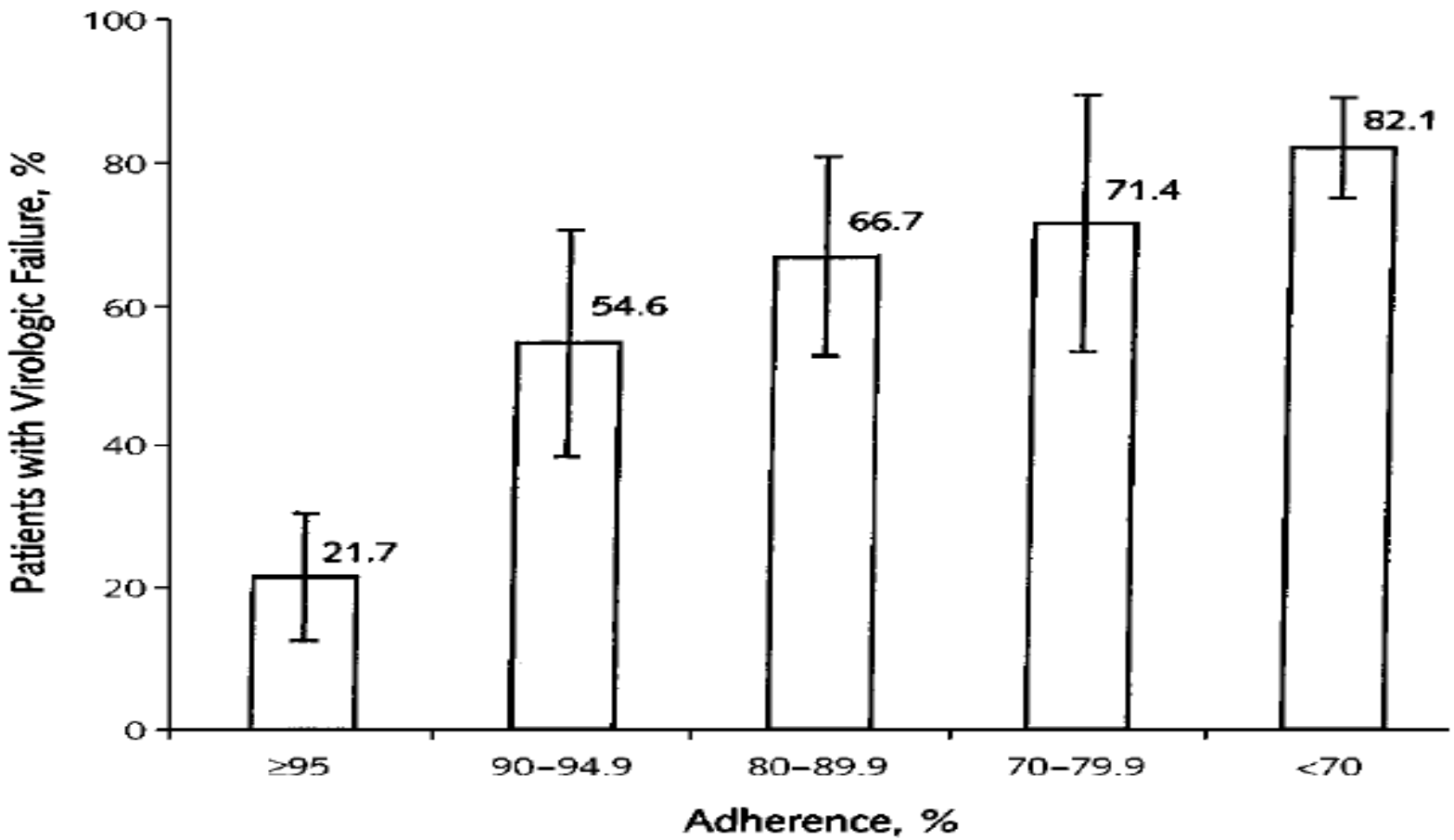
HAART初期: 1996-2005年

2000年: ｱﾄﾞﾋｱﾗﾝｽ<95%で高いｳｲﾙｽ学的失敗

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

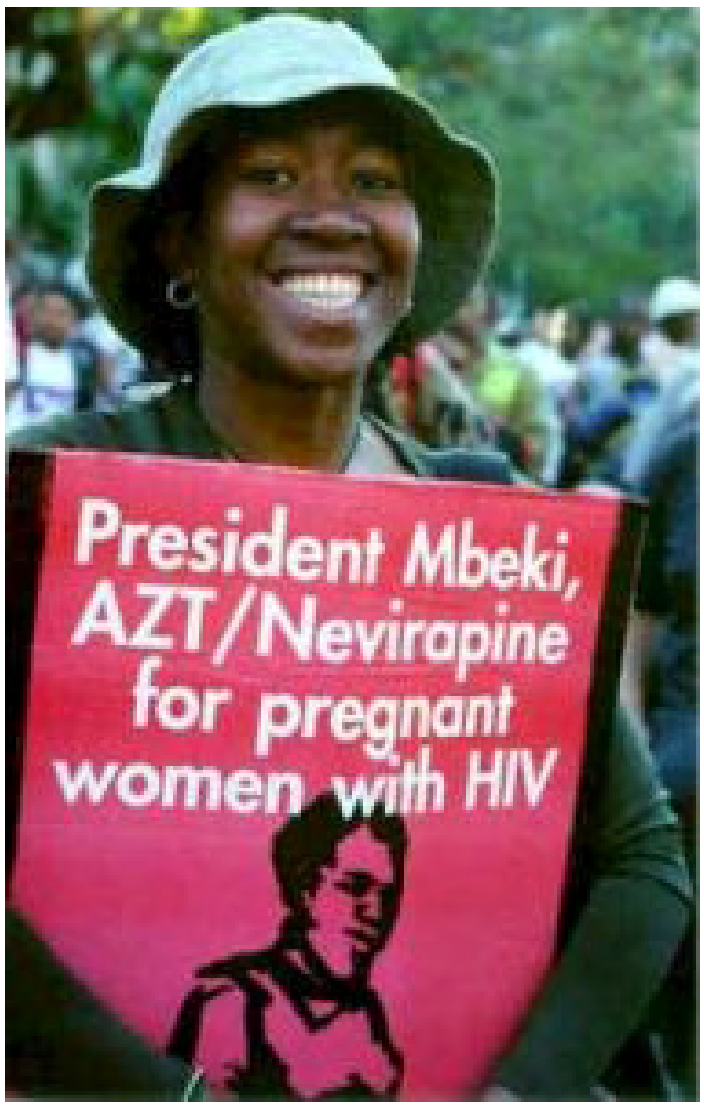
David L. Paterson, MB, BS, FRACP; Susan Swindells, MD; Jeffrey Mohr, MSW; Cheryl Squier, RN; Marilyn M. Wagener, MPH; and Nina Singh, MD

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



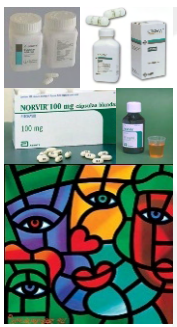
HAART初期: 1996-2005年

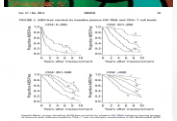
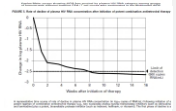
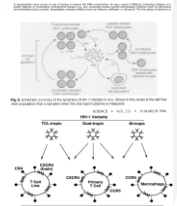
2000年: 南アでIAC開催



HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



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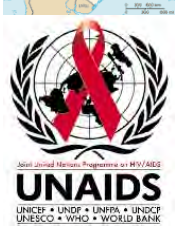


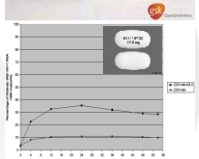


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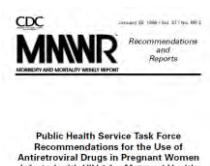

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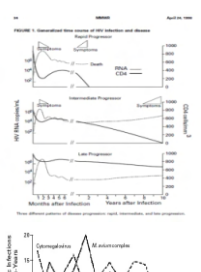
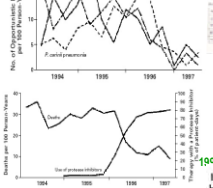
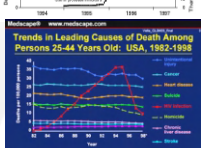
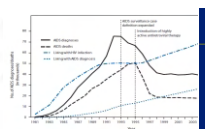




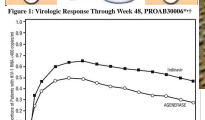
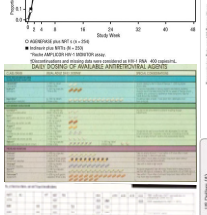
Antiretroviral Drug Resistance Testing in Adults With HIV Infection

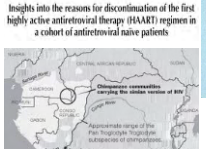
Implications for Clinical Management

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

Mitochondrial Toxicity



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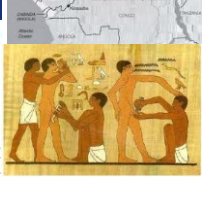
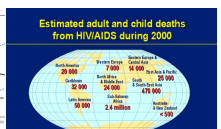
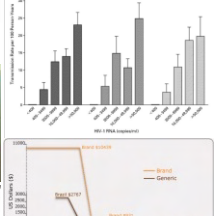
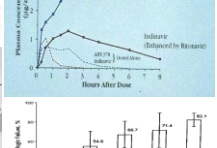
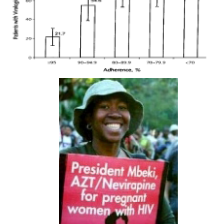
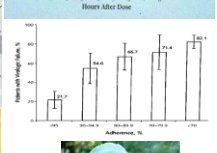






HAART初期: 1996-2005年

2001年: 中国が高いHIV感染率を認める

HAART初期: 1996-2005年

2001年: 国連アナン事務総長が世界エイズ基金を宣言

HAART初期: 1996-2005年

2001年: CDCが50歳以上で倍以上の速さで HIVが増加していることを報告

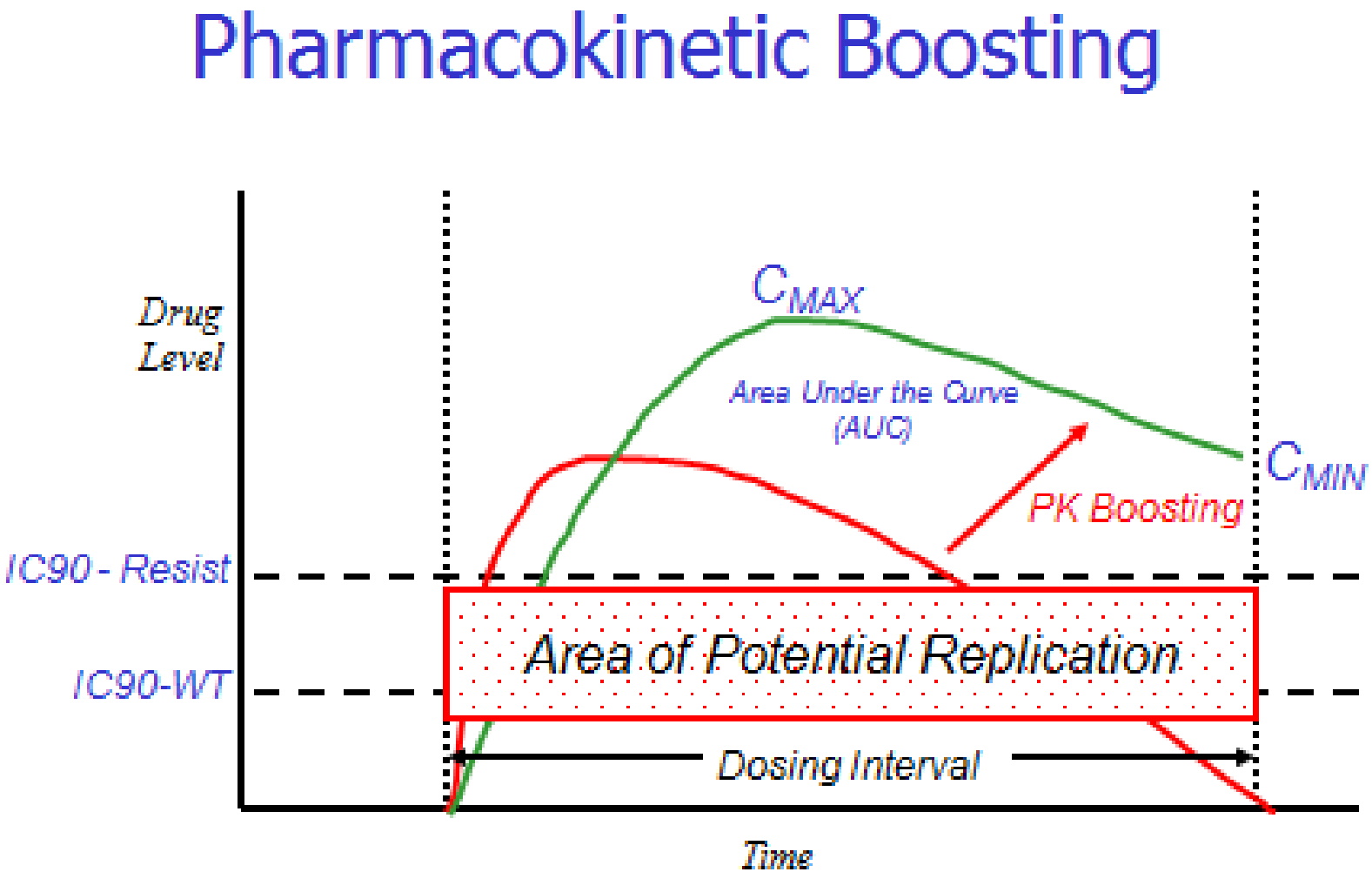
Officials have speculated that a more open society, people entering the dating scene after the monogamy of a marriage and the absence of a fear of pregnancy is causing the alarming rise in sexually transmitted infections.

HAART初期: 1996-2005年

2001年: 7番目のNRTI: テノホビル

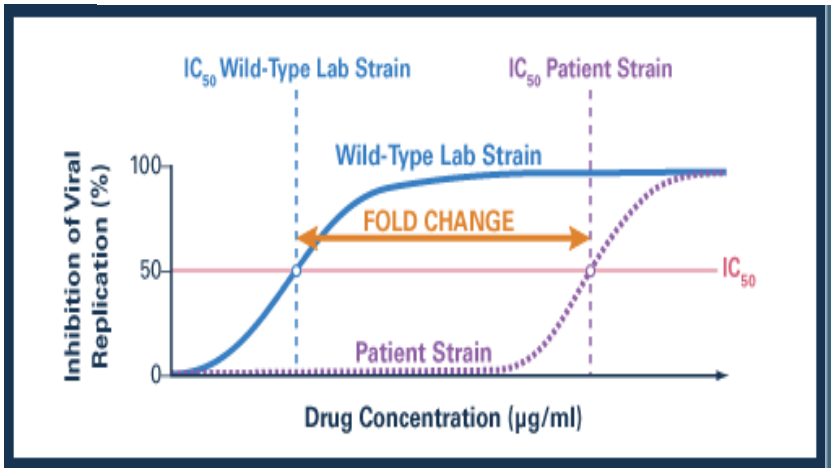
HAART初期: 1996-2005年

2001年: PI治療においてブーストが標準となる



HAART初期: 1996-2005年

2001年: フェノタイプ検査がより汎用されるようになる



DRUG			PHENOSENSE™			ASSESSMENT	
	Generic Name	Brand Name	Patient IC50* (µM)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (1, 10, 100, 1000)	Drug	
NRTI	Abacavir	Ziagen	4.02	2.26		ABC	Sensitive
	Didanosine	Videx *	6.13	1.39		ddI	Reduced Susc.
	Emtricitabine	Emtriva§	2.49	2.25		FTC	Sensitive
	Lamivudine	Epivir	5.57	1.83		3TC	Sensitive
	Stavudine	Zerit	0.88	1.80		d4T	Reduced Susc.
	Tenofovir	Viread *	1.602	2.43		TFV	Reduced Susc.
	Zidovudine	Retrovir	1.219	39		ZDV	Reduced Susc.
NNRTI	Delavirdine	Rescriptor	0.0139	0.63		DLV	Sensitive
	Efavirenz	Sustiva	0.0014	0.77		EFV	Sensitive
	Nevirapine	Viramune	0.101	1.10		NVP	Sensitive
PI	Atazanavir	Reyataz	0.00897	5.89		ATV	Reduced Susc.
		Reyataz / r‡				ATV/r	Reduced Susc.
	Fosamprenavir	Lexiva	0.0151	1.26		AMP	Sensitive
	Indinavir	Crixivan	0.0206	2.86		IDV	Reduced Susc.
		Crixivan / r‡				IDV/r	Sensitive
	Lopinavir	Kaletra	0.006	1.49		LPV/r	Sensitive
	Nelfinavir	Viracept	0.6017	80		NFV	Reduced Susc.
	Ritonavir	Norvir	0.0214	1.72		RTV	Sensitive
	Saquinavir	Invirase	0.0052	1.17		SQV	Sensitive
	Tipranavir	Aptivus / r‡	0.0241	0.33		TPV/r	Sensitive

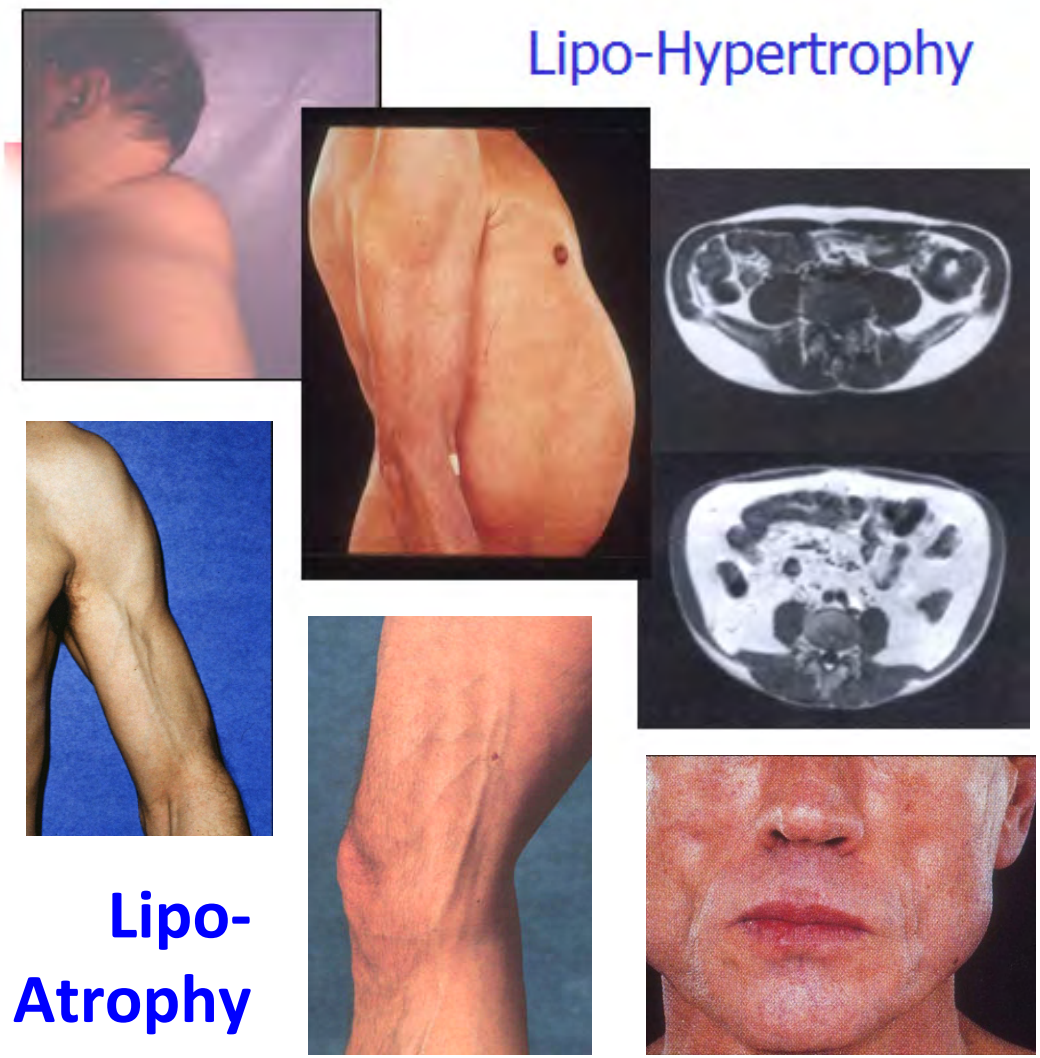
Clinical Cutoff
Biological/Assay Cutoff
Hypersusceptibility Cutoff
Sensitive
Reduced Susceptibility

RC — Virus Replication Capacity = 118%
(Range 74%-187%)
0 50 100 150 200
Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%=median RC of wild-type viruses.

Monogram Biosciences, Inc.

HAART初期: 1996-2005年

2001年: リポジストロフィによりART開始が遅らされる



HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

HAART初期: 1996-2005年

2003年: サハラ以南アフリカで女性患者数が男性を上回る

HAART初期: 1996-2005年

2002年: 抗議団体が貧困国へのARVを要求　スペインIAC

HAART初期: 1996-2005年

2002年: ARTの国際的目標が宣言される

SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS:

TREATMENT GUIDELINES FOR A PUBLIC HEALTH APPROACH

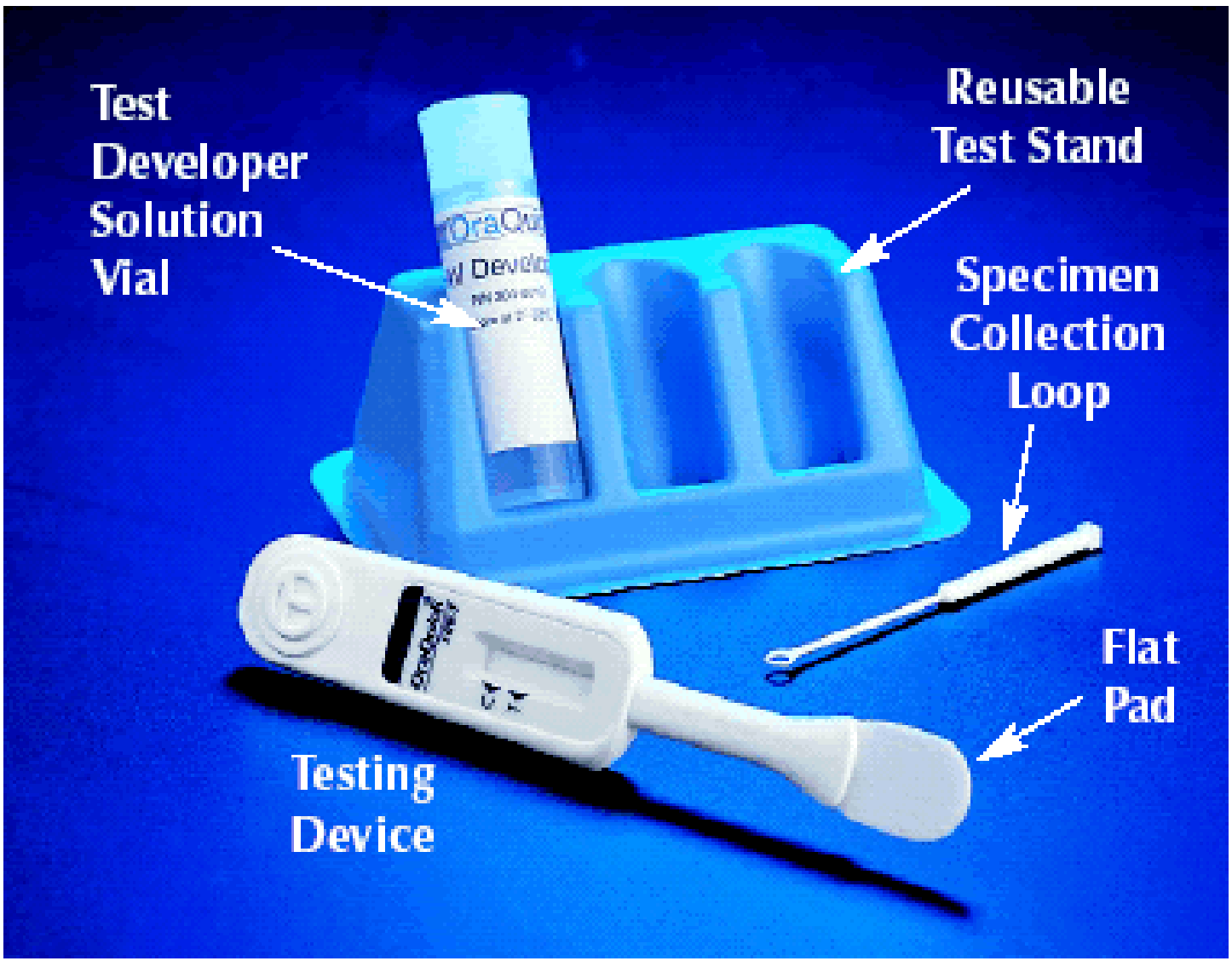
WHO recommends that, in resource-limited settings, HIV-infected adults and adolescents should start ARV therapy when the infection has been confirmed and one of the following conditions is present.

- 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

HAART初期: 1996-2005年

2002年: FDAが初の20分迅速HIV検査を承認



HAART初期: 1996-2005年

2002年: HIV検査が米国各地のコミュニティに提供される

HAART初期: 1996-2005年

2002年: HIV複製は高頻度に変異を起こす

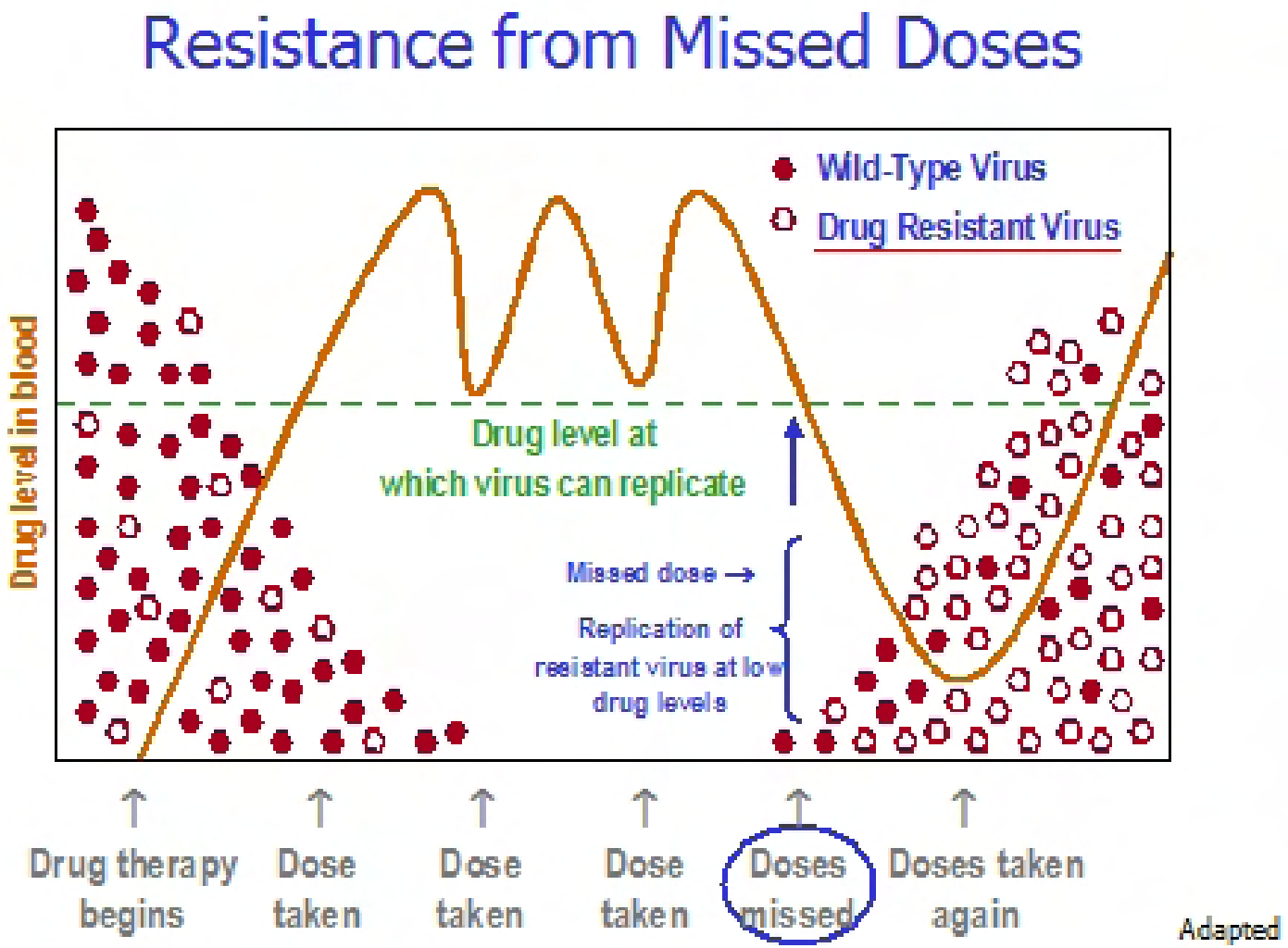
J Biol Chem. 2002 Oct 11;277(41):38053-61. Epub 2002 Jul 31.

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

HAART初期: 1996-2005年

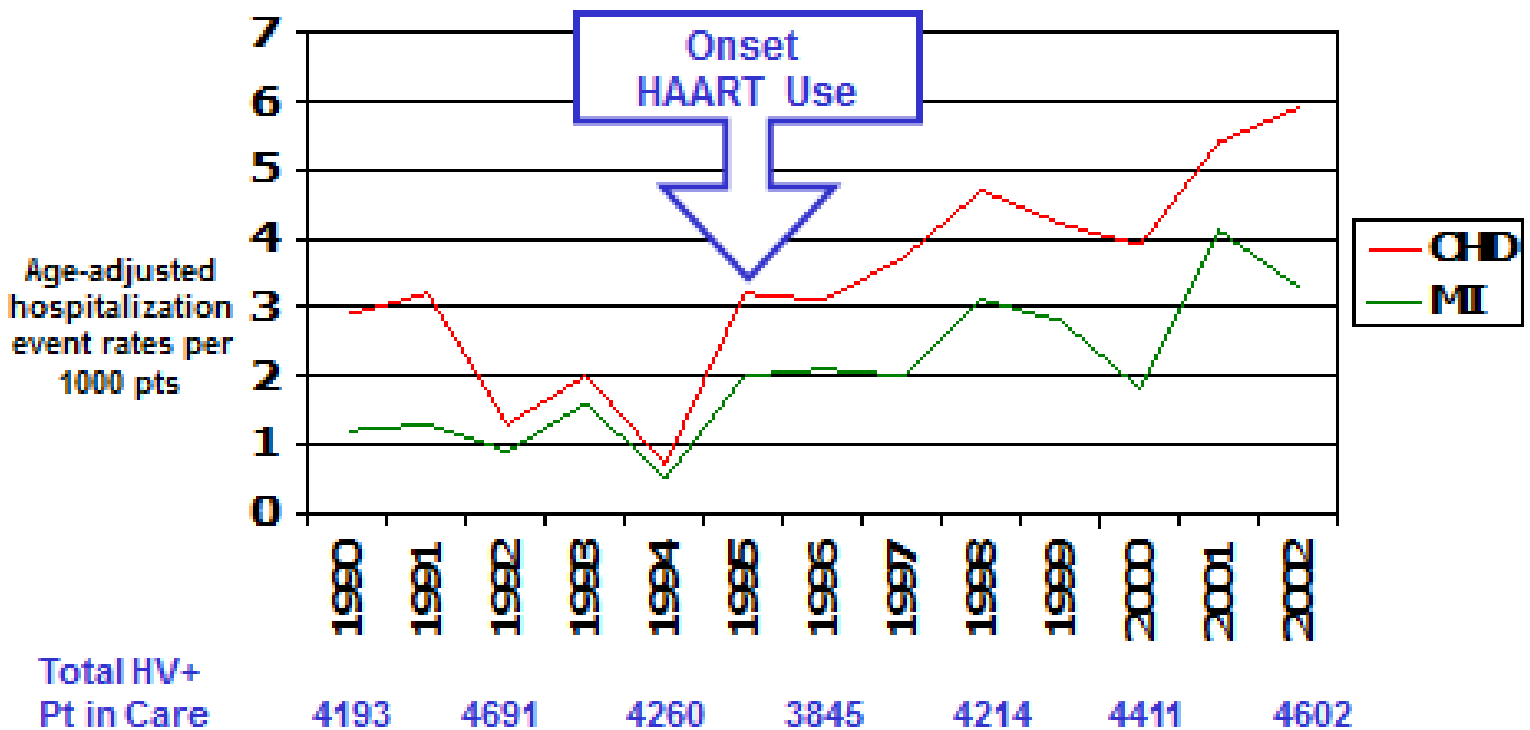
2002年: 既存の耐性ウイルスの選択による耐性



HAART初期: 1996-2005年

2002年: 代謝・心血管系合併症が増加

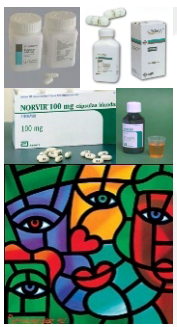
Coronary Heart Disease: Increasing Rate Over Time



Kaiser Permanente Study – CROI 2003 #747

HAAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



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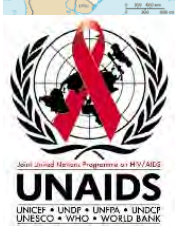
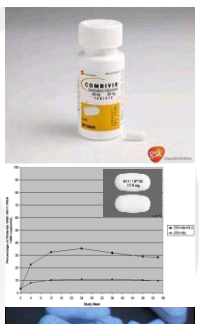
- Regional AIDS Care Core Hospitals
- Japan – US AETC clinical training





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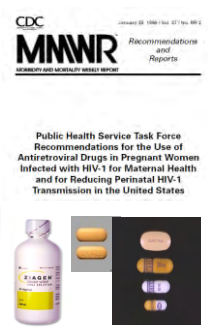
Conference Coverage (ICAAC)
T-Cell Gain Slow But Steady
Treatment



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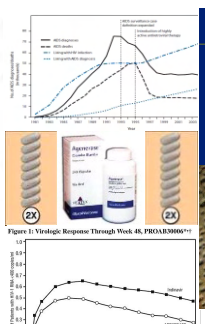
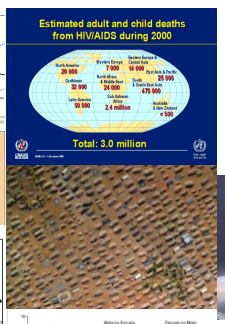


1999: Focus on ARV adherence and toxicities

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



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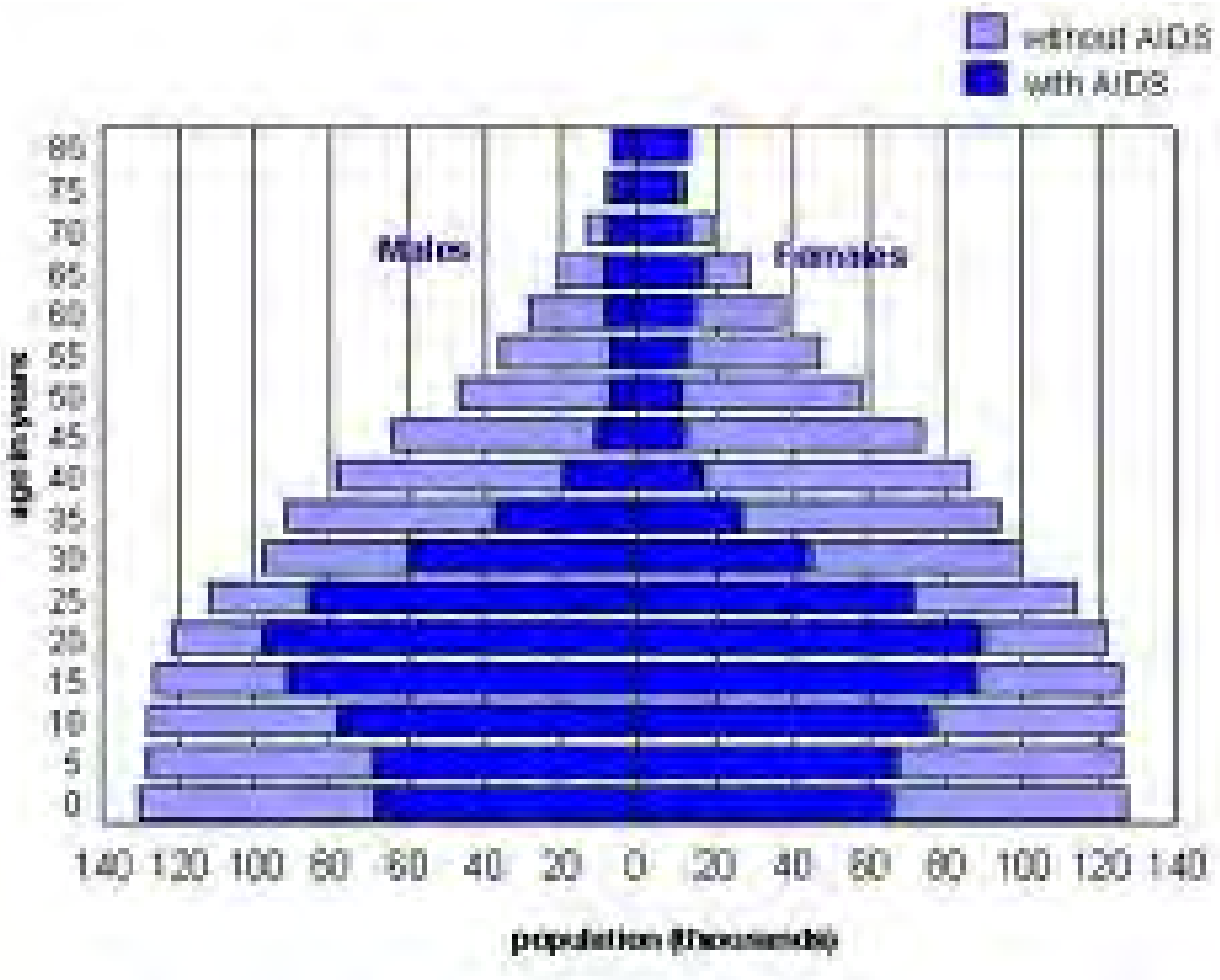
one or more error-prone steps

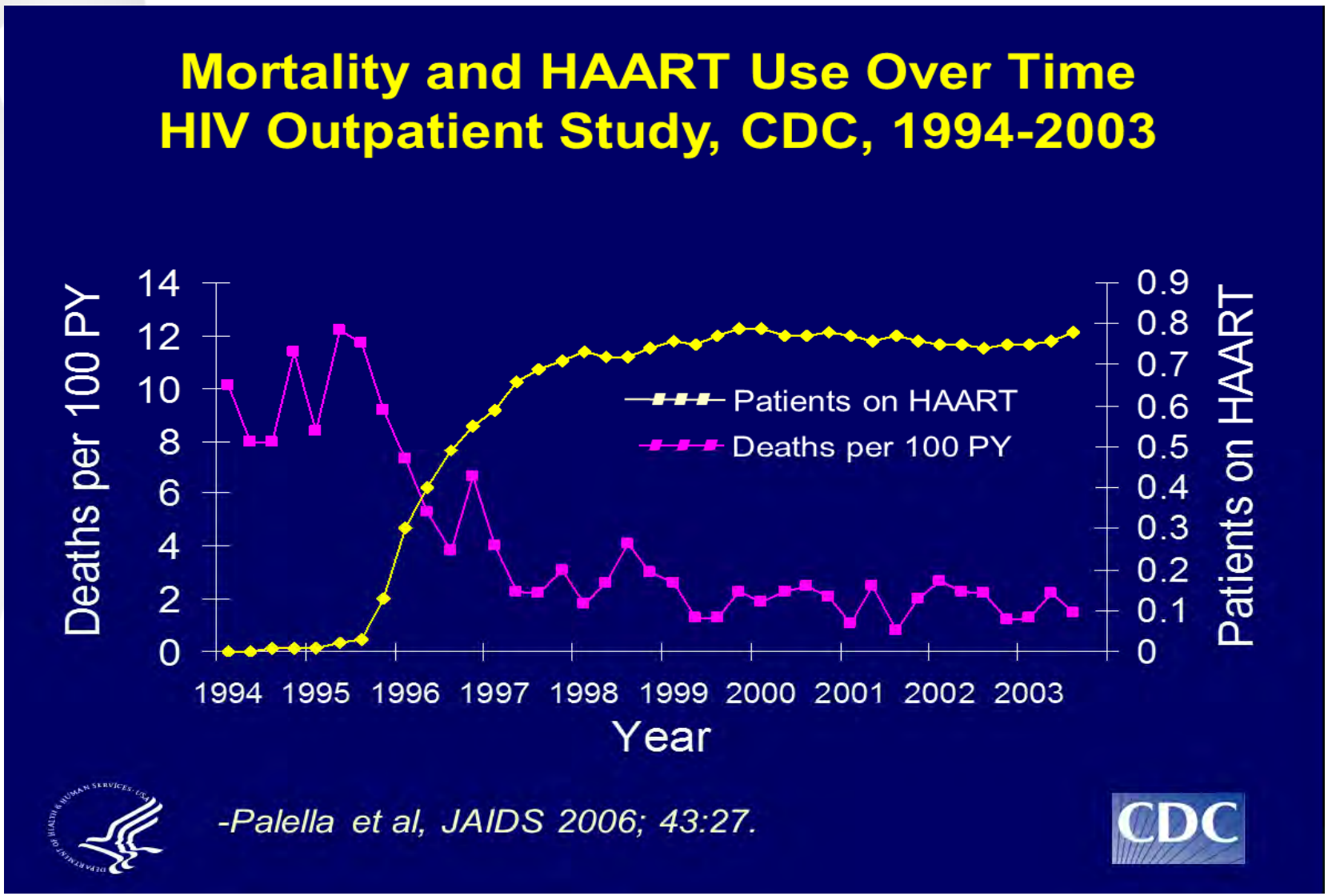
HAART初期: 1996-2005年

2003年: ﾎﾞﾂﾜﾅがHIV有病率最大の国に: 38.8%



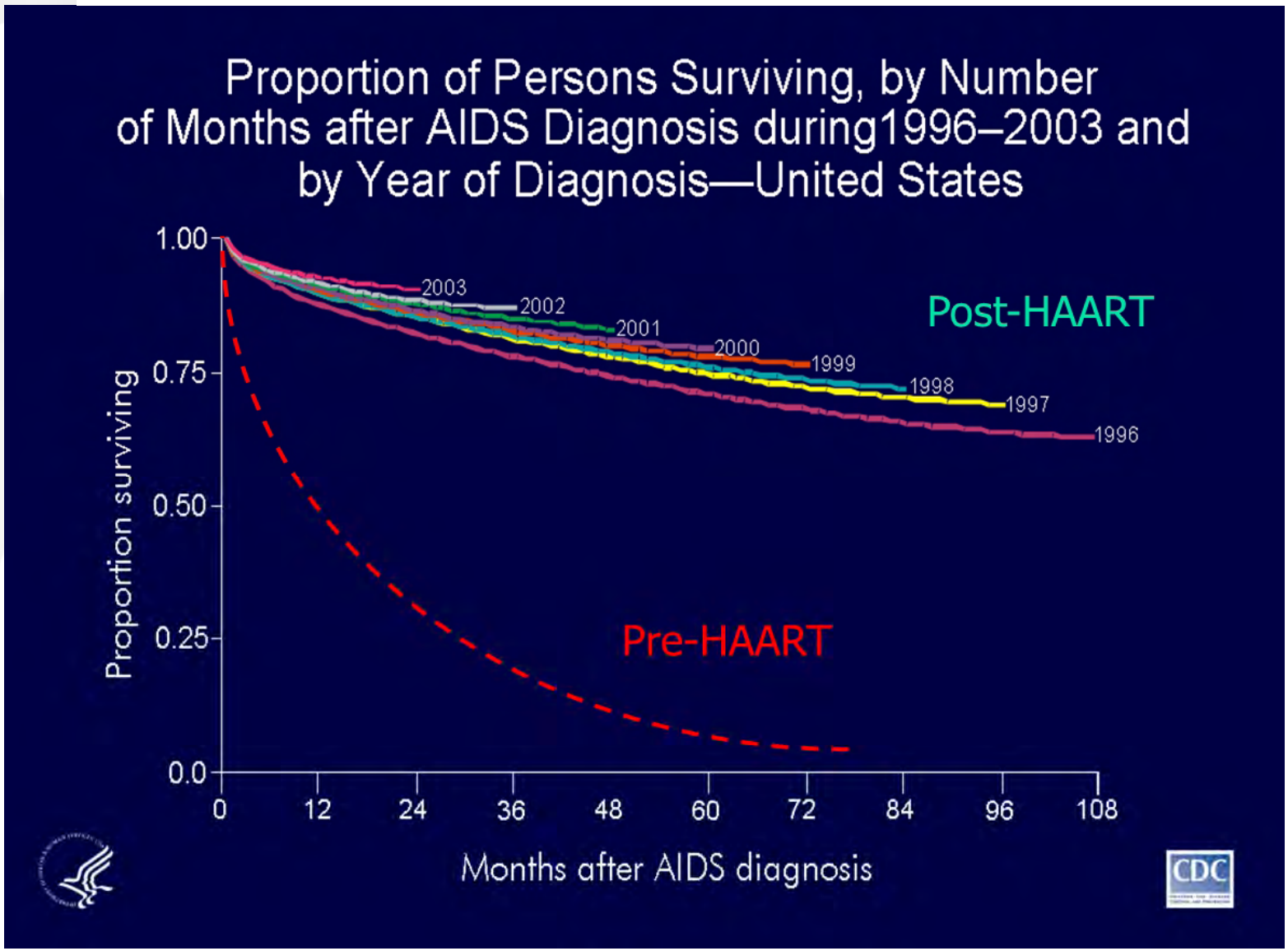
HAART初期: 1996-2005年

2003年: HAART普及とともに死亡率は低下を続ける



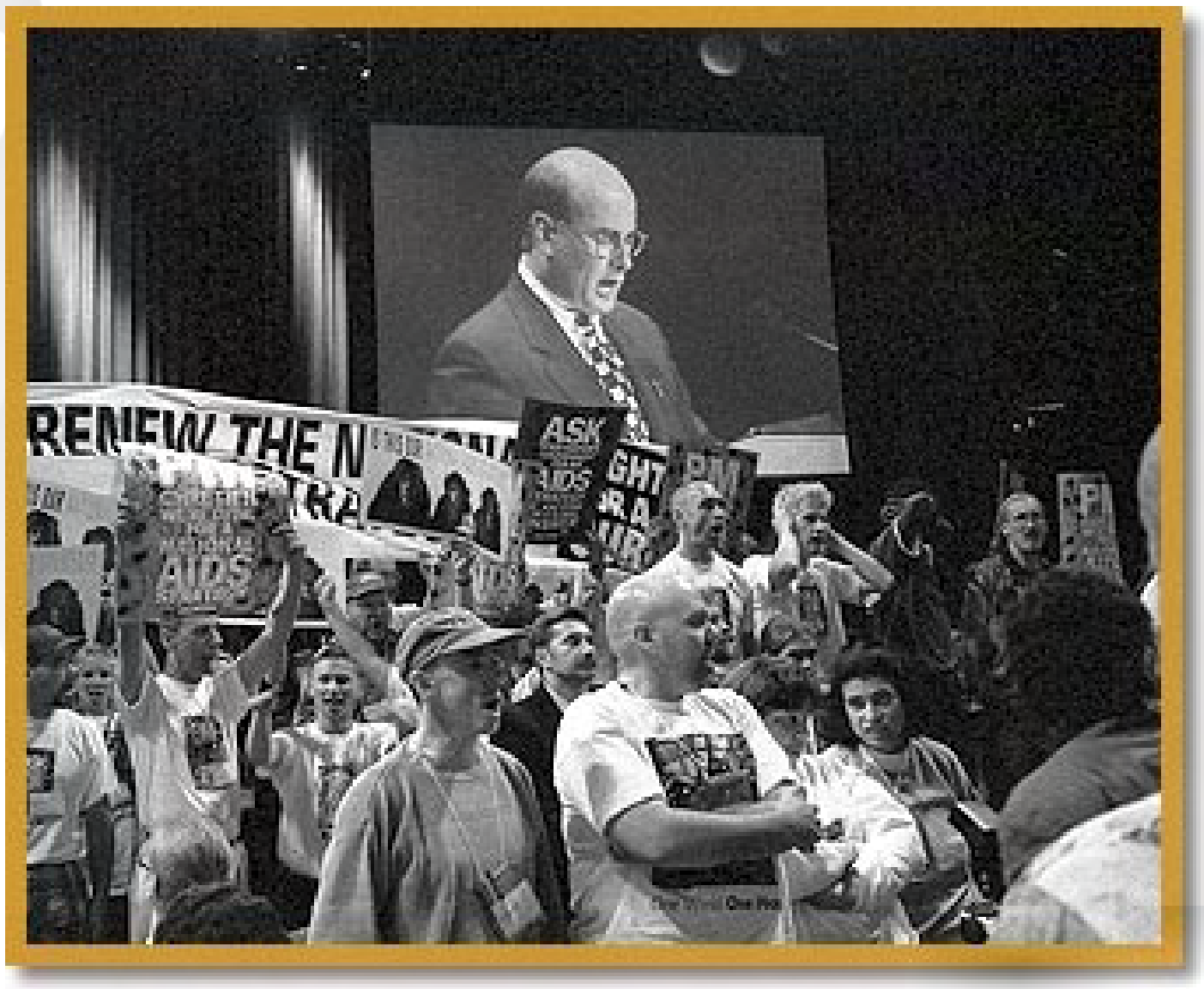
HAART初期: 1996-2005年

2003年: AIDSはもはや“死の宣告”でなくなる



HAART初期: 1996-2005年

2003年: AIDS活動家が学会で発言



HAART初期: 1996-2005年

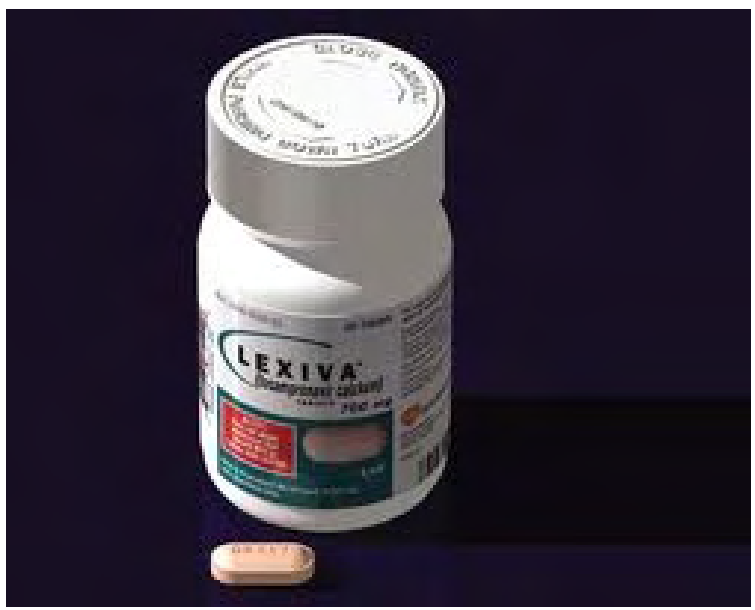
2003: 初の侵入阻害剤
Enfuvirtide (T-20)

8番目のNRTI
エムトリシタビン

HAART初期: 1996-2005年

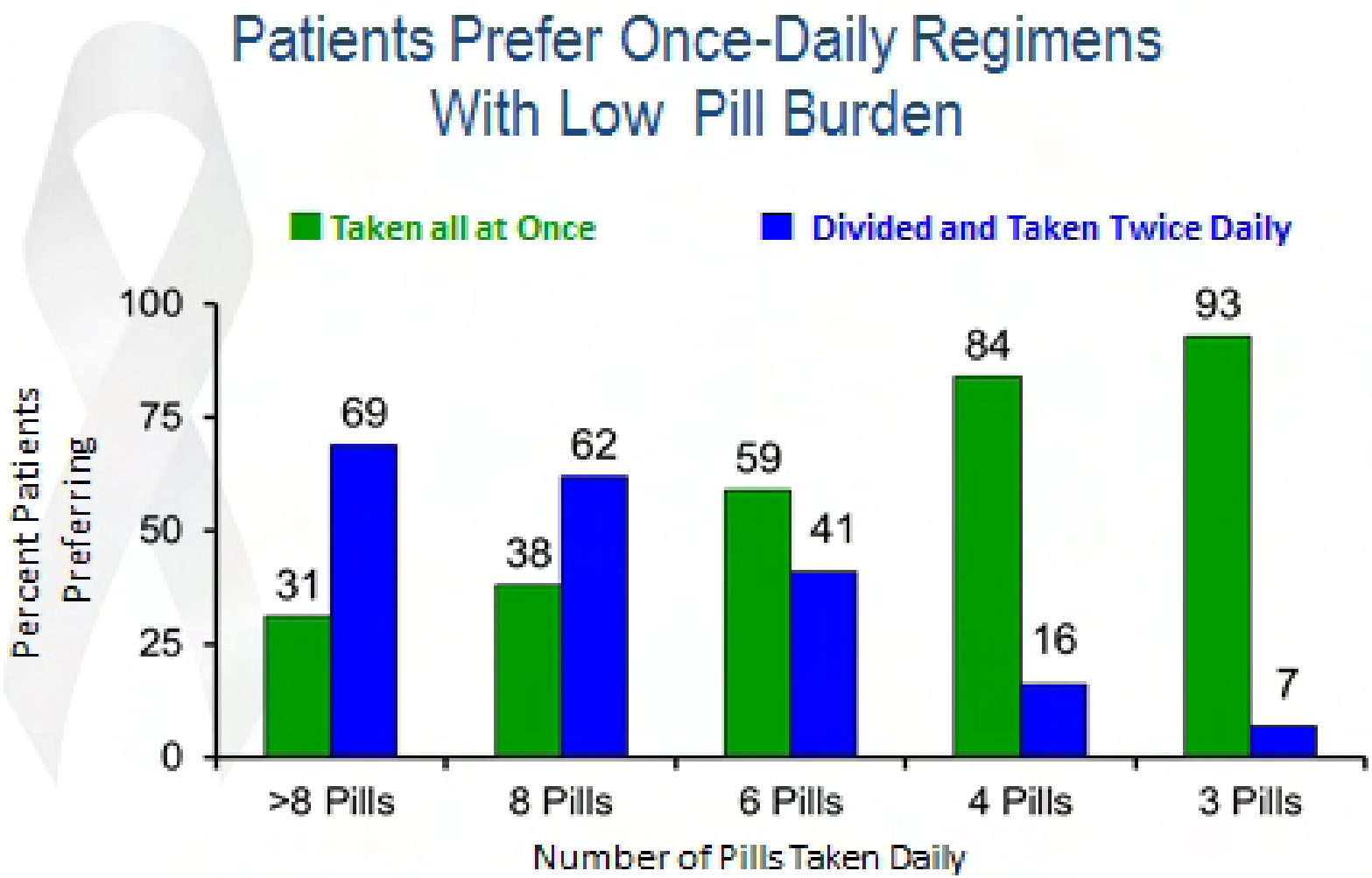
2003年: 8番目のPI
アタザナビル

9番目のPI
ホスアンプレナビル



HAART初期: 1996-2005年

2003年: 患者は服薬しやすさを好む

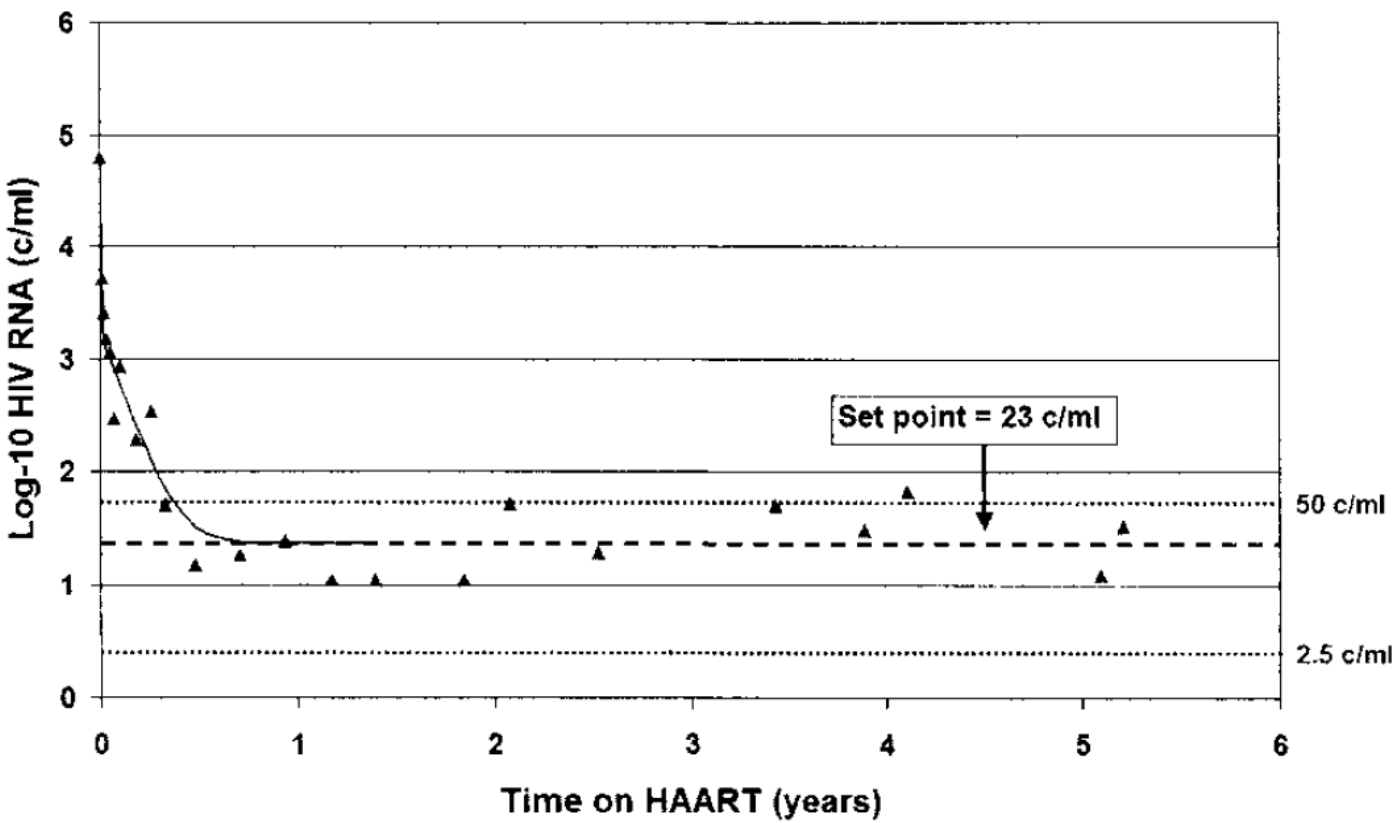


Moyle G. *Int J STD AIDS.* 2003;14: (Suppl 1):34-36.

HAART初期: 1996-2005年

2003年: HAARTでウイルスを抑えてもウイルス血症は残存

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



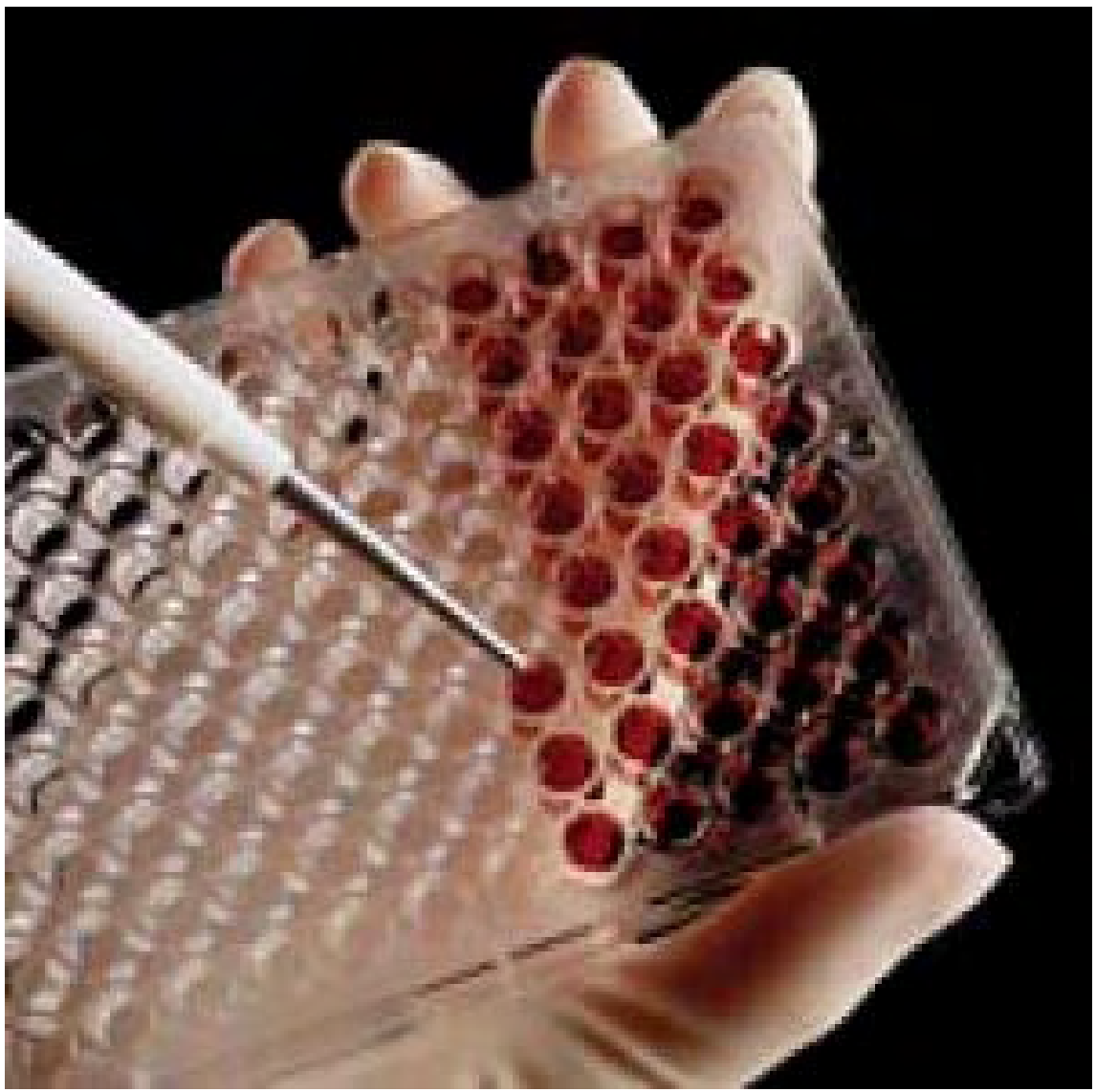
HAART初期: 1996-2005年

2003年: CD8活性化によりCD4増加が阻害

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

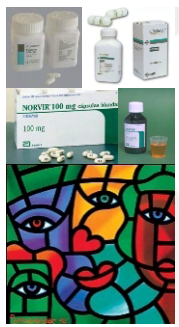
HAART初期: 1996-2005年

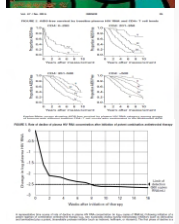
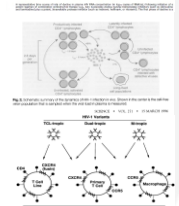
2003年: AIDSワクチン試験で免疫獲得不十分の報告

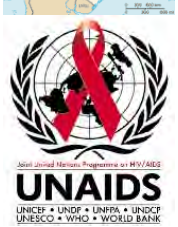


HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005





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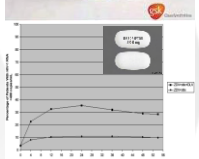


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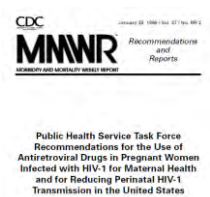

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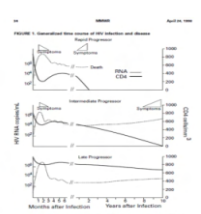
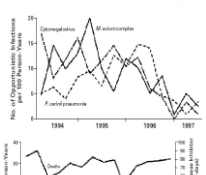
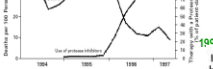
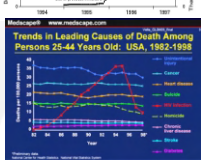

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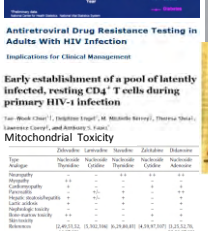

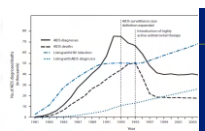

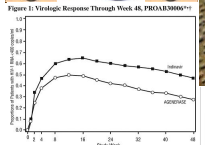

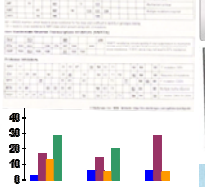

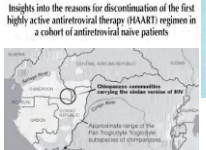
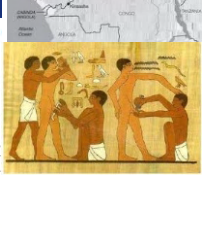

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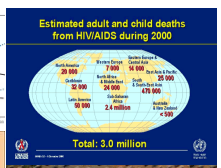
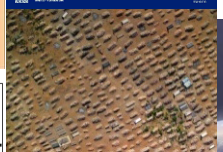
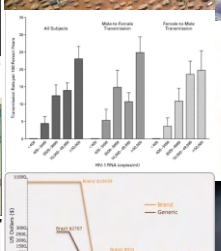
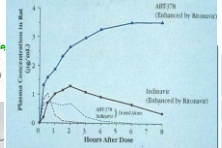
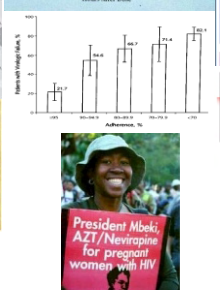
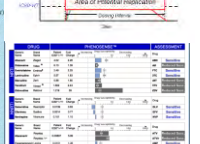
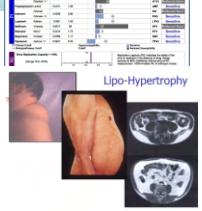
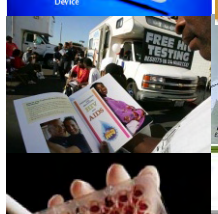
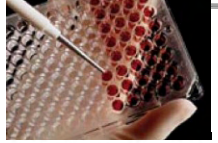


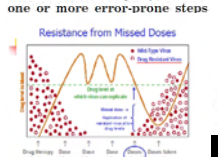



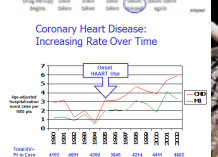



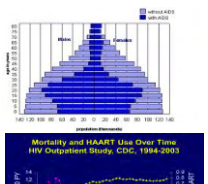
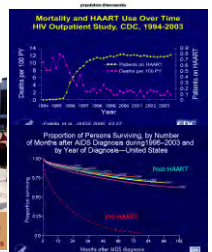




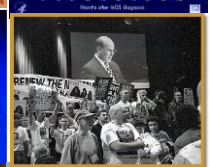




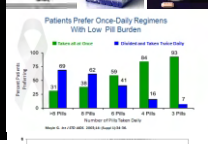
HIV-1 evolves rapidly, which i
one or more error-prone steps

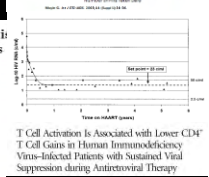


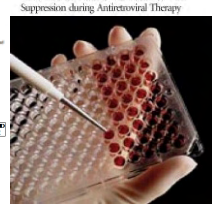








HAART初期: 1996-2005年

2004年: AIDS孤児が1,500万人に
うち1,210万人はサハラ以南アフリカに

HAART初期: 1996-2005年

2004年: WHOが発展途上国でARVを “展開”

HAART初期: 1996-2005年

2004年: HIVが世界のどこよりもロシア及び東欧で急速に拡大

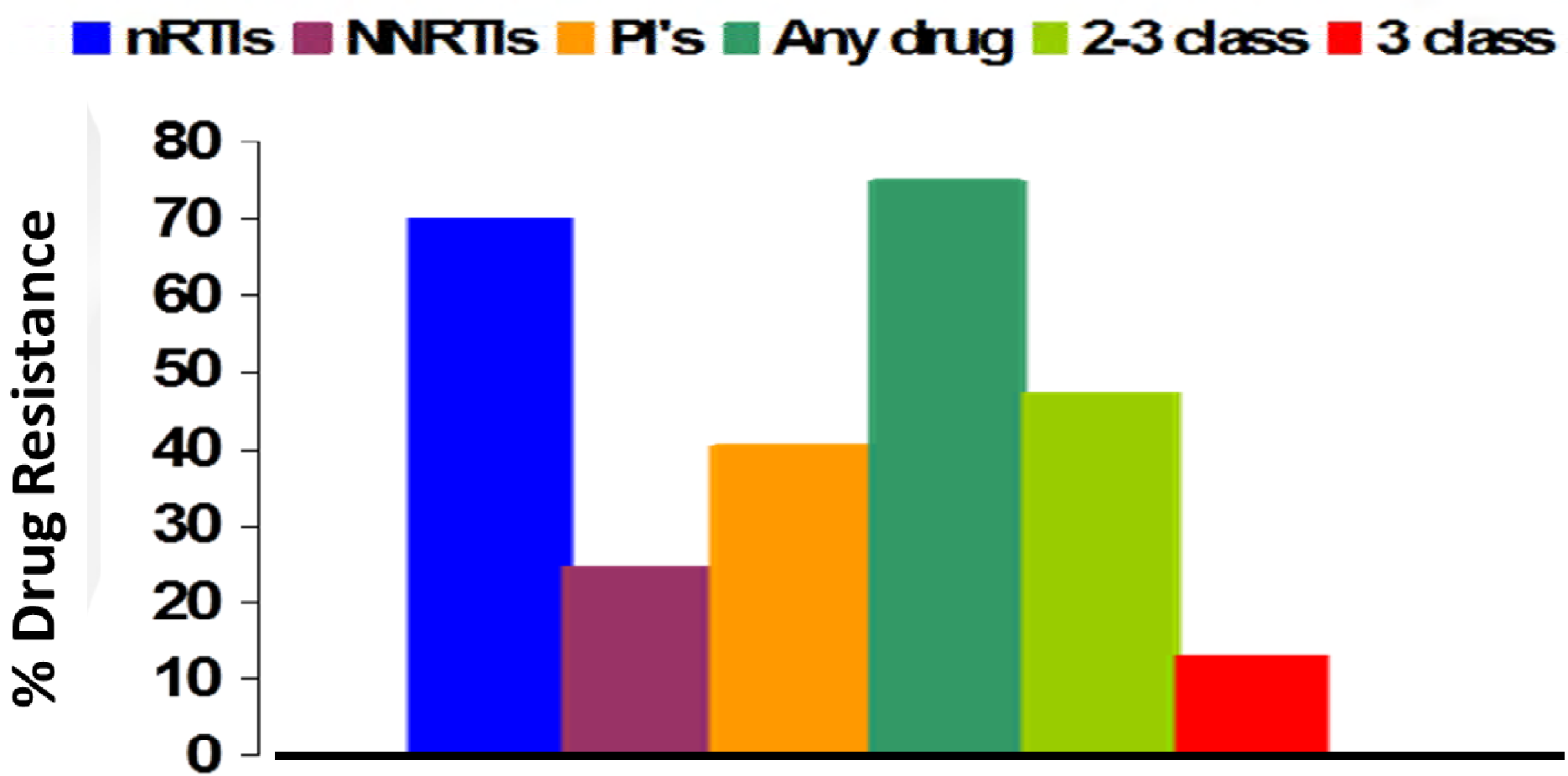
HAART初期: 1996-2005年

2004年: 2番目、3番目の2-NRTI合剤:

TDF-FTC (ツルバダ)　　ABC-3TC (エプジコム)

HAART初期: 1996-2005年

2004年: 長期治療の患者で耐性が高率



Richman DD, AIDS 2004; 1393-1401

HAART初期: 1996-2005年

2004年: 耐性変異蓄積で治療選択肢が限定される

	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

HAART初期: 1996-2005年

2004年: 消化管におけるCD4枯渇

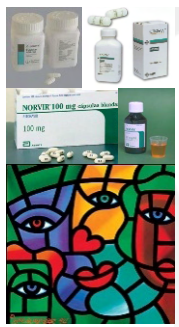
CD4$^+$ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

Jason M. Brenchley,[1] Timothy W. Schacker,[2] Laura E. Ruff,[1] David A. Price,[1] Jodie H. Taylor,[3] Gregory J. Beilman,[3] Phuong L. Nguyen,[5] Alexander Khoruts,[2] Matthew Larson,[2] Ashley T. Haase,[4] and Daniel C. Douek[1]

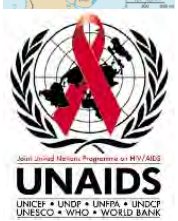
The Journal of Experimental Medicine • Volume 200, Number 6, September 20, 2004 749–759
http://www.jem.org/cgi/doi/10.1084/jem.20040874

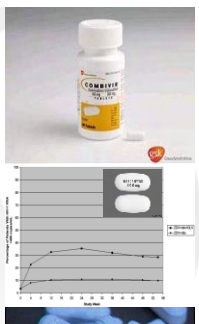
The Early-HAART Era: 1996-2005

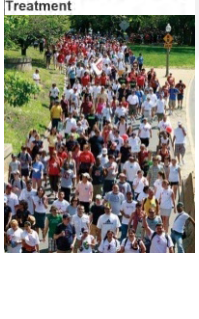
1996 1997 1998 1999 2000 2001 2002 2003 2004 2005



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

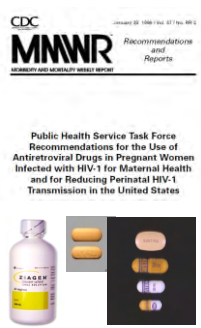


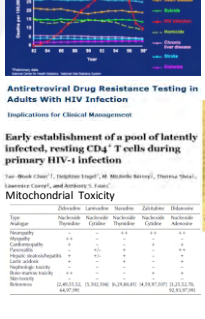




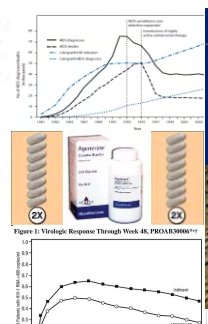
Identification of a Reservoir for HIV-1 Antiretroviral Therapy

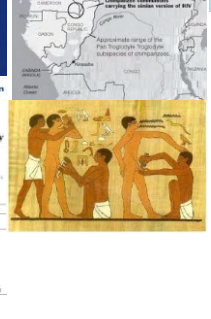
Conference Coverage (ICAAC)
T-Cell Gain Slow But Steady
Treatment





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





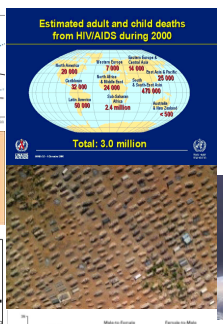
Trends in Leading Causes of Death Among Persons 25-44 Years Old: USA, 1982-1998

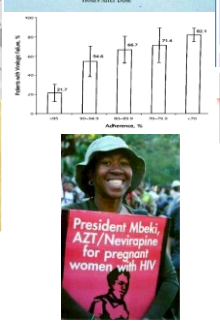
Antiretroviral Drug Resistance Testing in Adults With HIV Infection

Implications for Clinical Management

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

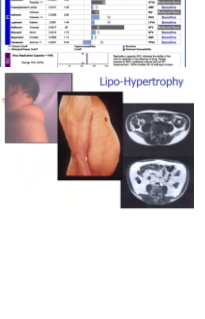
Mitochondrial Toxicity





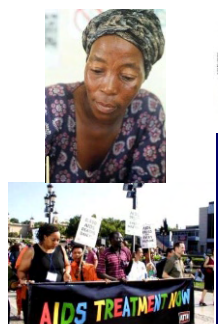
1999: Focus on ARV adherence and toxicities

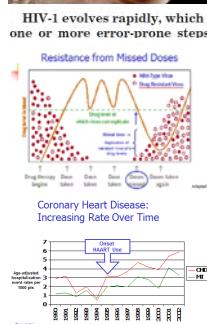
Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients



Estimated adult and child deaths from HIV/AIDS during 2000

Total: 3.0 million



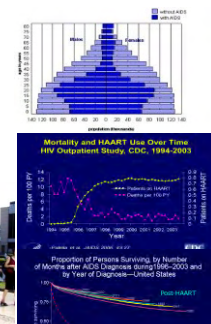


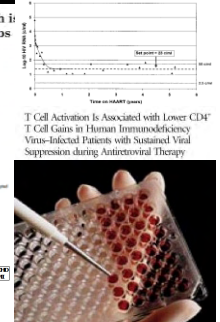
The Global Fund

Dating Over 50

Pharmacokinetic Boosting

Lipo-Hypertrophy





AIDS TREATMENT NOW

The 3 by 5 initiative

TREAT THREE MILLION PEOPLE WITH HIV/AIDS BY 2005

Test Developer Solution Vial

Reusable Test Stand

Specimen Collection Loop

Flat Pad

Testing Device

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

Resistance from Missed Doses

Coronary Heart Disease:
Increasing Rate Over Time

Mortality and HAART Use Over Time
HIV Outpatient Study, CDC, 1994-2003

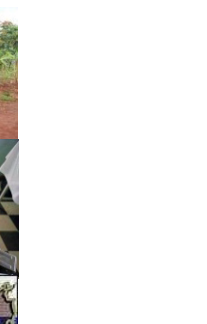
Proportion of Persons Surviving, by Number of Months after AIDS Diagnosis during1996–2003 and by Year of Diagnosis—United States

Fuzeon™ 90 mg/ml

Emtriva

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

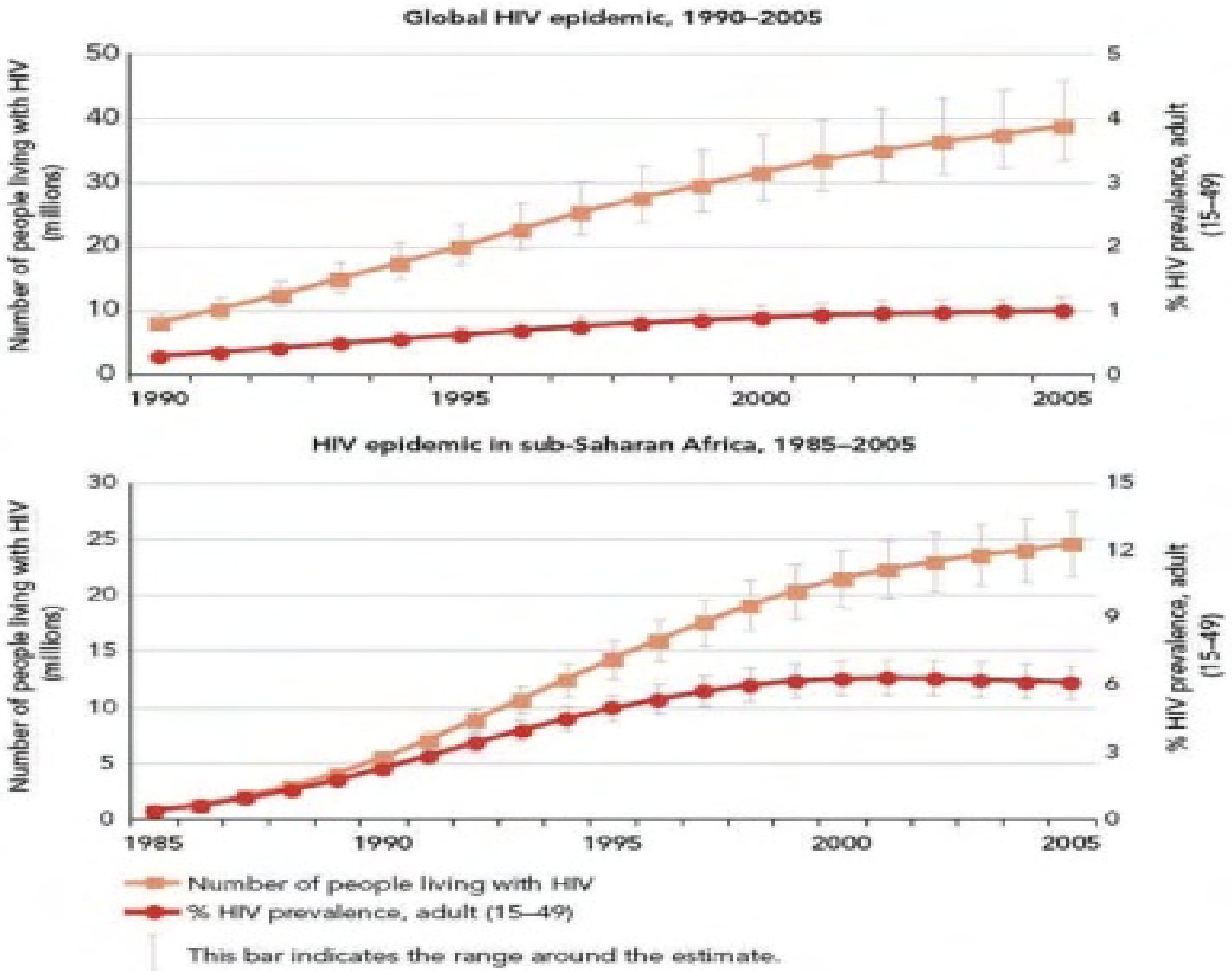


Treatment Experienced Viral Failure
Richman DD, AIDS 2004; 1393-1401

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

HAART初期: 1996-2005年

2005年: 世界のAIDS死の増加が続く



HAART初期: 1996-2005年

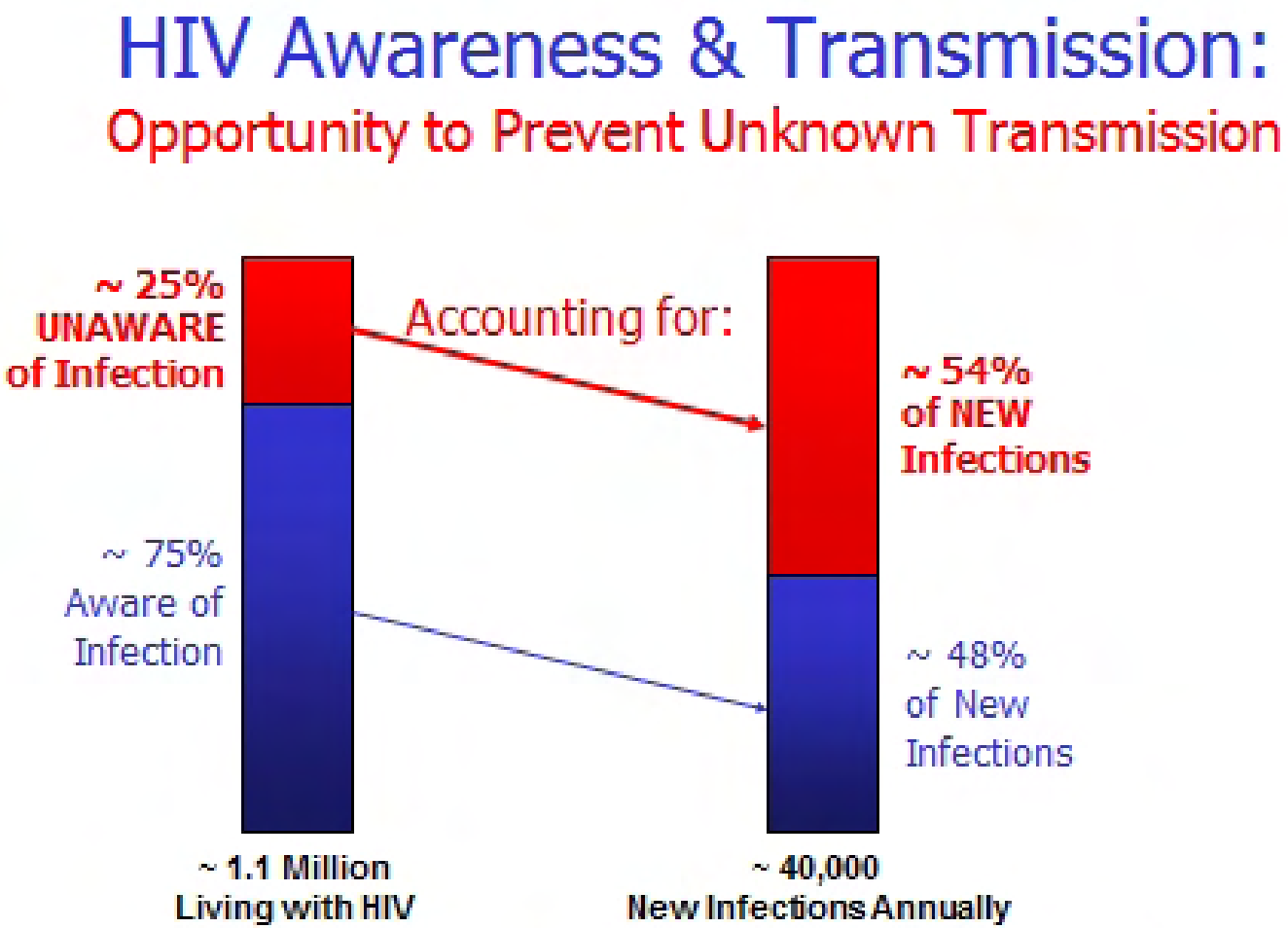
2005年: “3 by 5”ｲﾆｼｬﾁﾌﾞにより治療130万人達成

"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

HAART初期: 1996-2005年

2005年:米国のHIV感染者の50%以上が25%の感染未診断者からの感染



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

HAART初期: 1996-2005年

2005年: 先進国でAIDS死なくならず

Causes of Mortality in the HAART Era

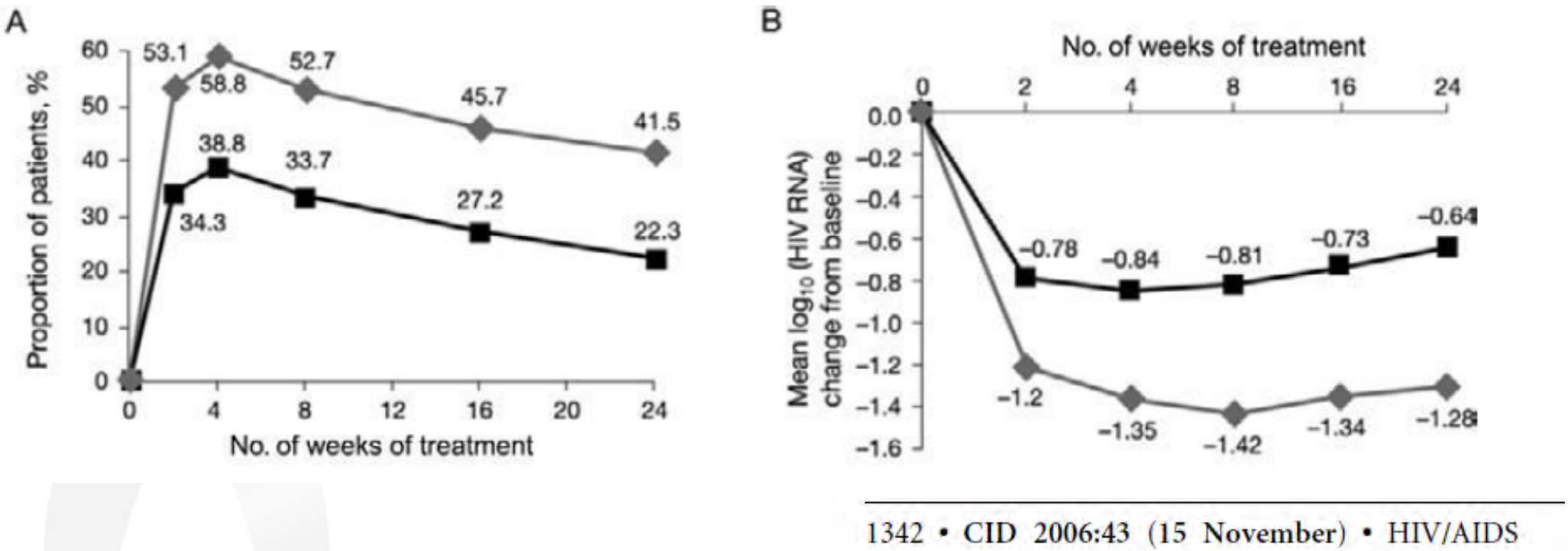
2005 in the UK, N=397

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

HAART初期: 1996-2005年

2005年: 9番目の: Tipranavir
既治療患者での成功率40 %

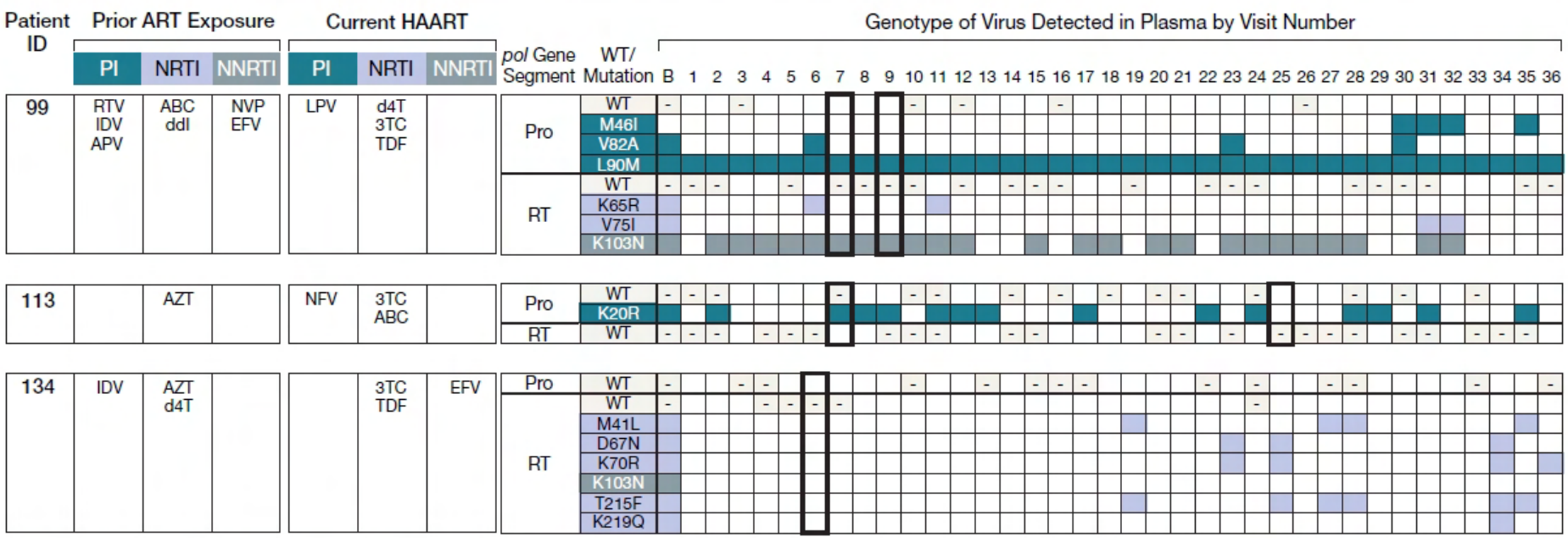


HAART初期: 1996-2005年

2005年: “ブリップ”は耐性を引き起こさない

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

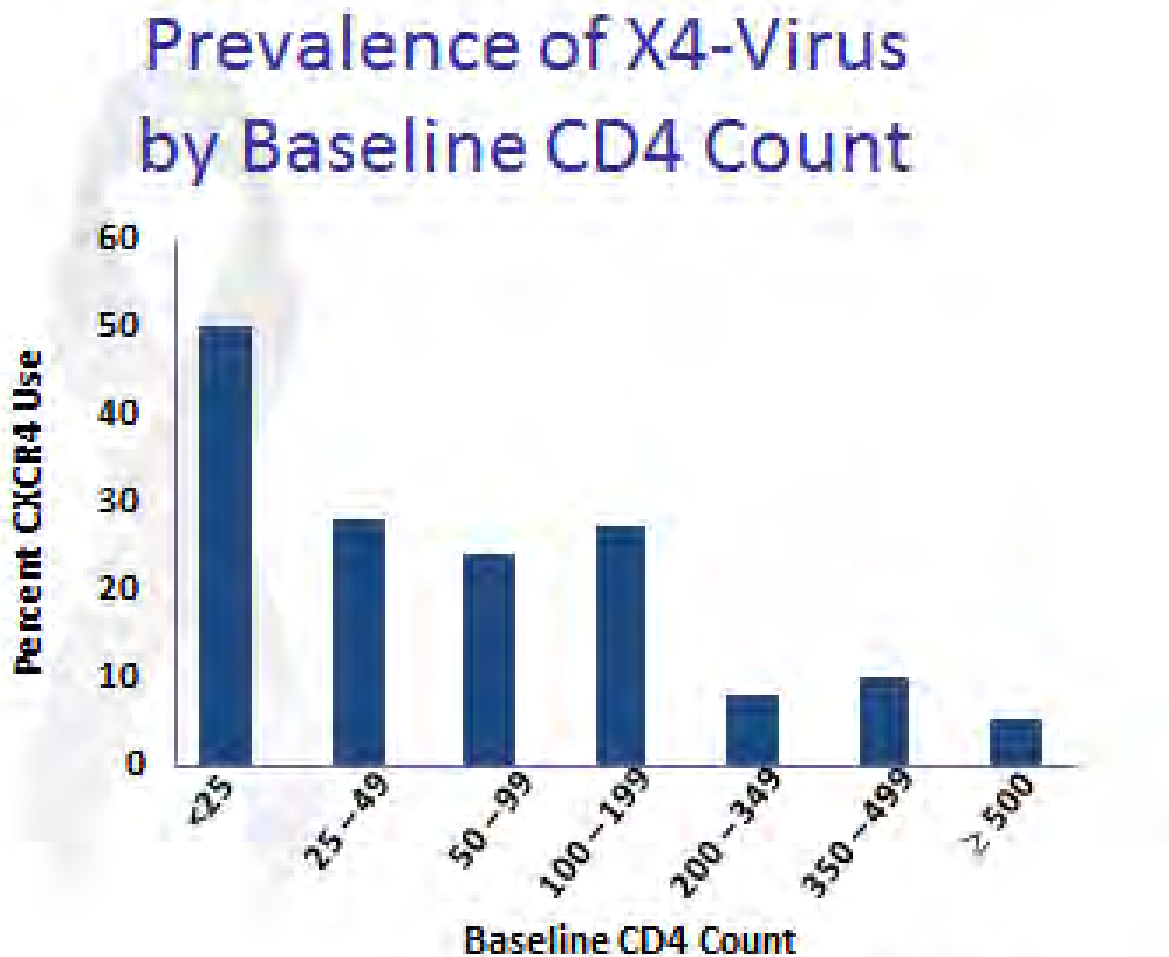
Figure 2. Lack of New Genotypic Resistance Mutations in Plasma Virus During or Immediately After Blips



JAMA. 2005;293:817-829

HAART初期: 1996-2005年

2005年: ベースラインCD4 >200でX4ウイルス存在



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

HAART初期: 1996-2005年

2005年: 多剤耐性ウイルスの伝播

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:

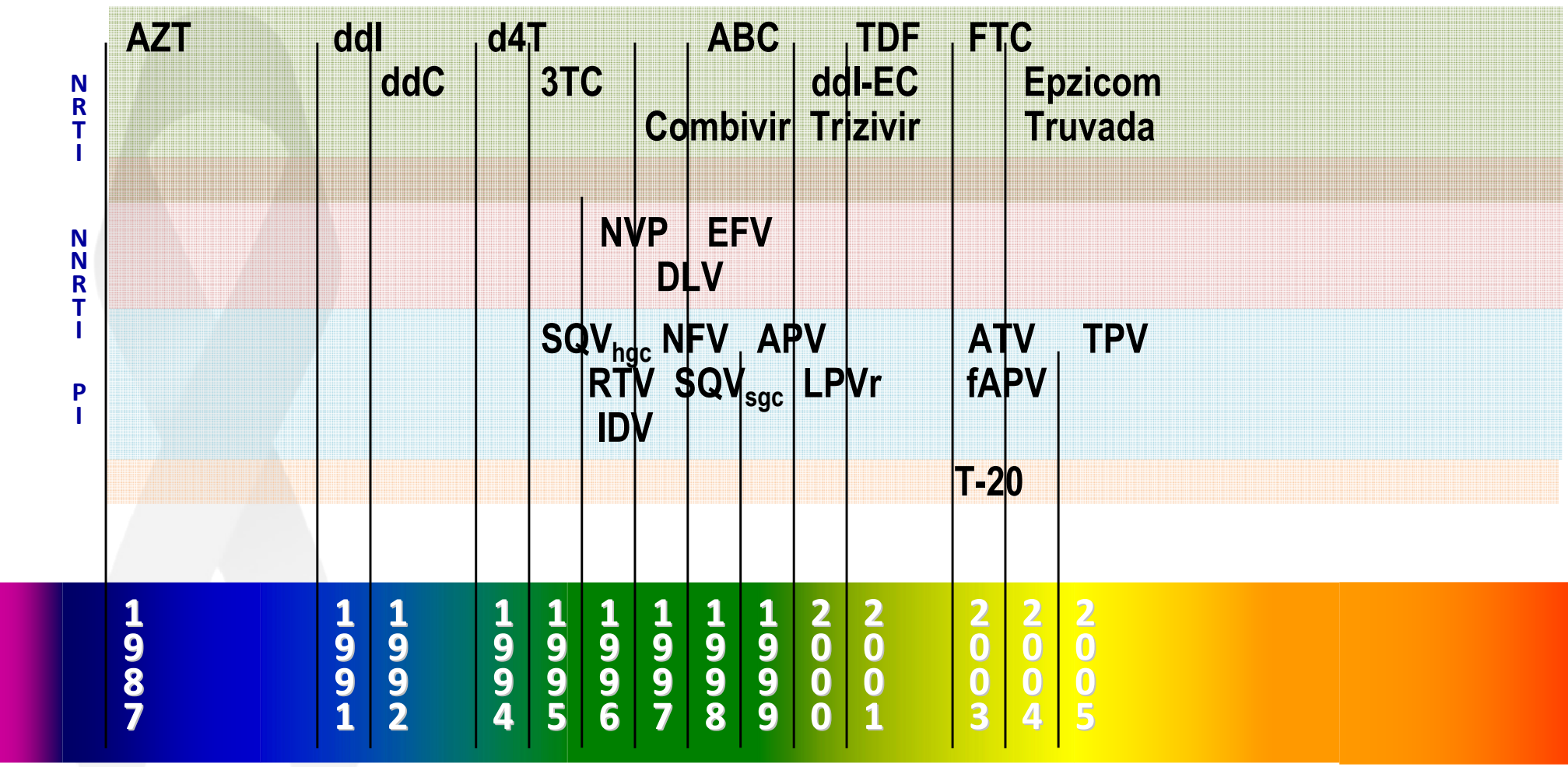
May 9, 2003:	**HIV seronegative**	**CD4+ 1500**
November 2004:	**Fever, pharyngitis, fatigue**	
December 15, 2004:	**HIV seropositive**	
December 29, 2004:	**VL 280,000**	**CD4+ 80**
January 12, 2005:	**Detuned HIV serology positive**	
February 2, 2005:		**CD4+ 39**

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

HAART初期: 1996-2005年

1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

HIV治療パラダイムの進化



治療薬なし　AZT単剤治療　連続的なNRTI単剤治療 2-NRTI治療　……3-剤HAARTの初期……(NRTI順次使用)　(ブーストPI)

CD4 <500　CD4<200