

# History of ART

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UKZN

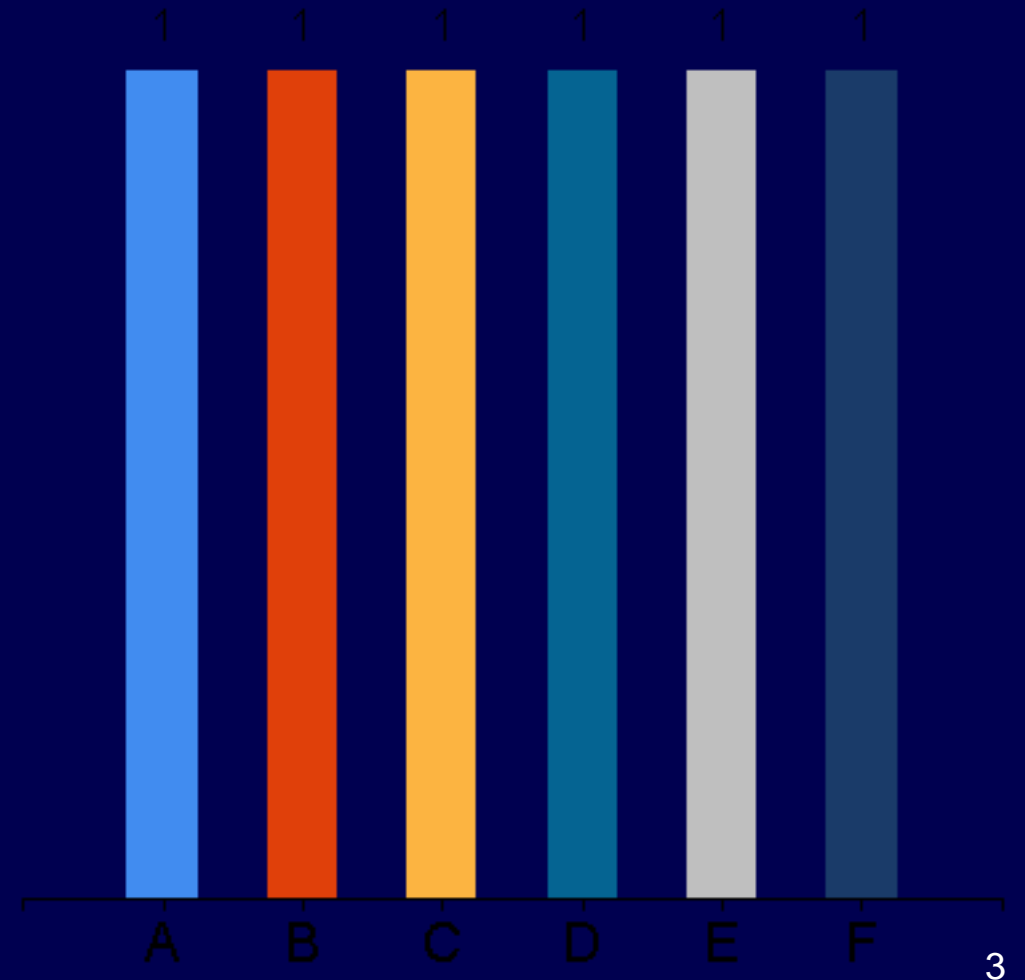
# In the beginning ...



- 1981 rare diseases, KS/PCP, among gay community
  - New York
  - California
- Strong suspicion - infectious disease.
- Initially exclusively MSMs  $\Rightarrow$  mid-1982 spread to other groups  $\Rightarrow$  haemophiliacs, heroin users.
- September 1982 disease was recognised as a new entity and named AIDS

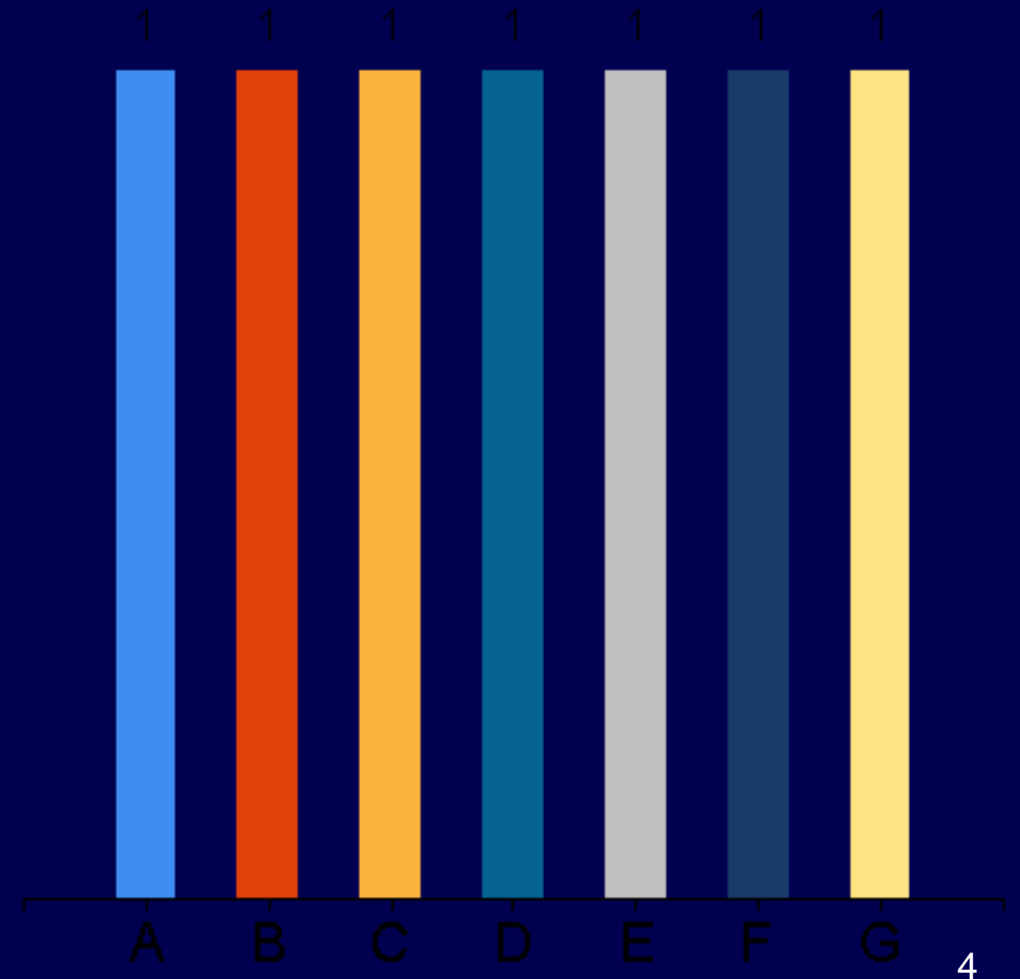
# Age of Delegates

- A. 60+
- B. 50+
- C. 40+
- D. 30+
- E. 20+
- F. I don't know



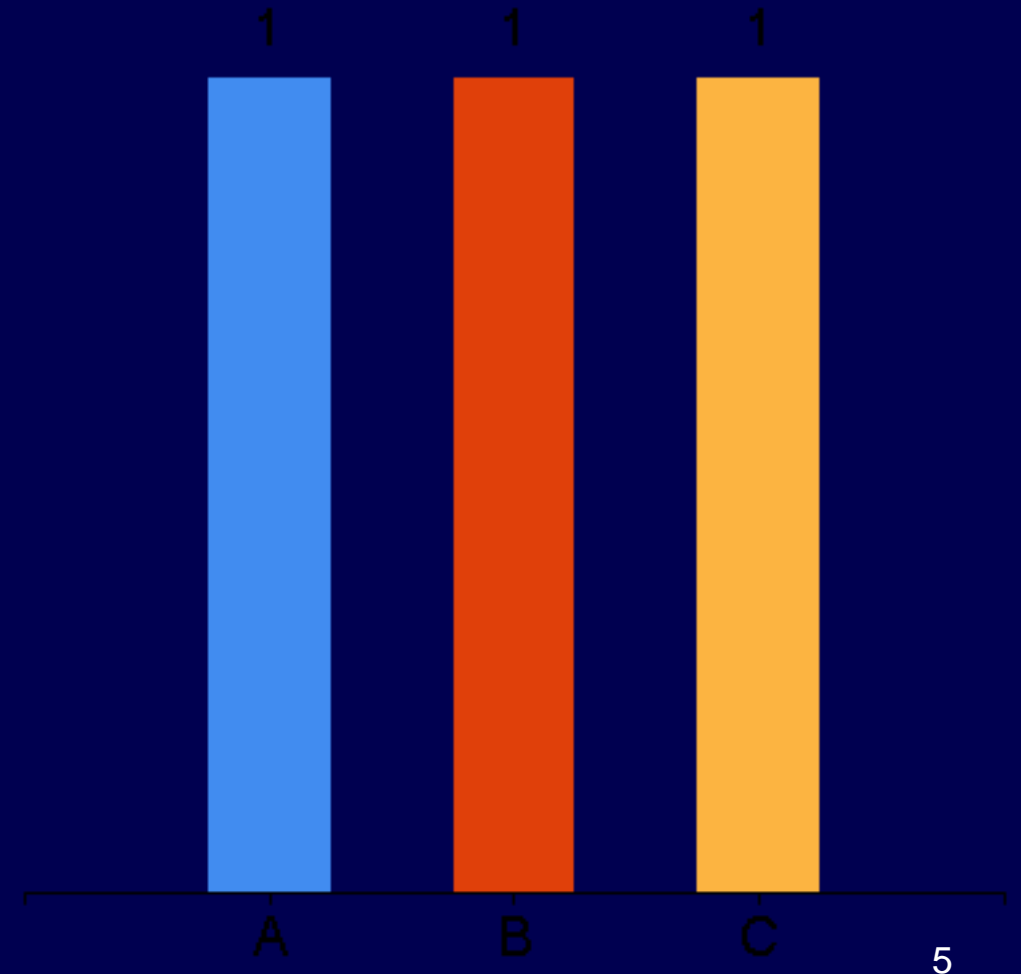
# In 1987 I was...

- A. 60+
- B. 50+
- C. 40+
- D. 30+
- E. 20+
- F. 10+
- G. Not yet conceived.



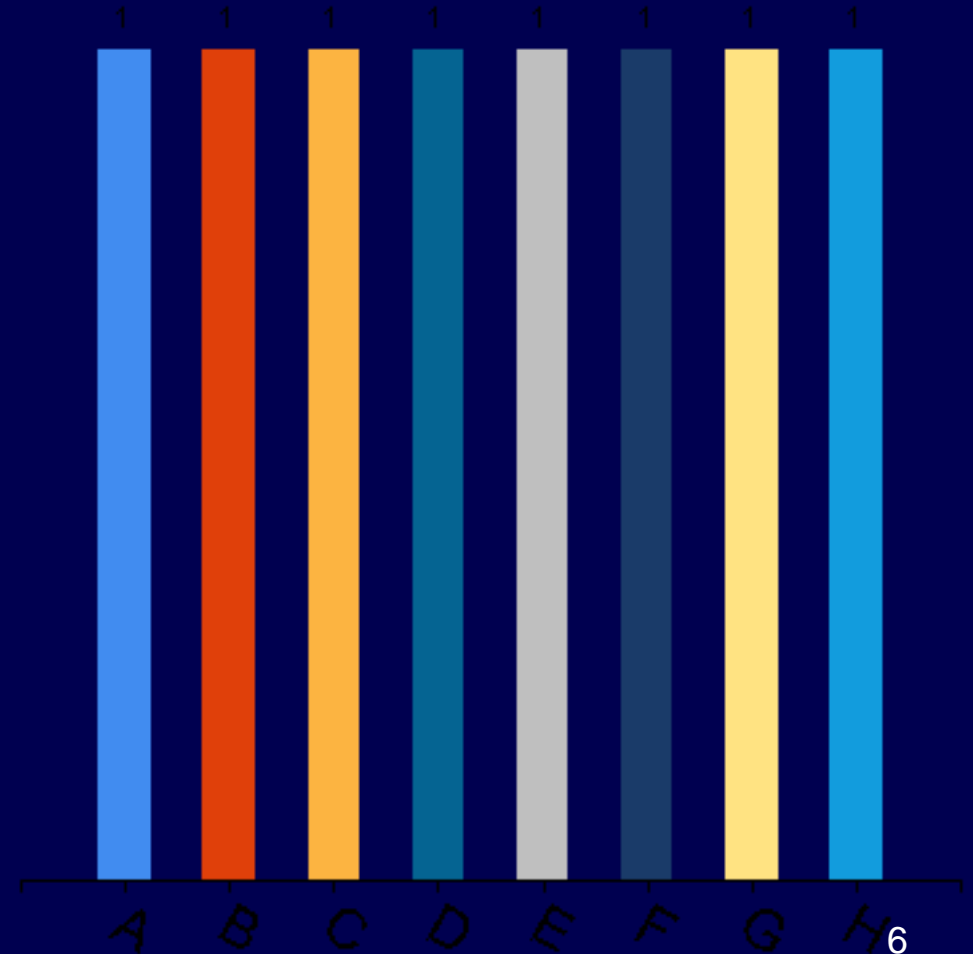
# What was the first Class of Drugs used to treat HIV/AIDS

- A. NRTIs
- B. NNRTIs
- C. PIs



# What was the first drug used to treat HIV/AIDS?

- A. AZT- zidovudine
- B. DDI - didanosine
- C. d4T- stavudine
- D. 3TC - lamivudine
- E. RTV - Ritonavir
- F. LPV- Lopinavir
- G. EFV - Efavirenz
- H. NVP - Nevirapine



# Early history

- 1983: virus was first isolated
- 1985: diagnostic test developed – serology
- Soon after clinical trials with dideoxynucleoside RTI (NRTIs) started.
- 1987 AZT approved

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

**A Double-Blind, Placebo-Controlled Trial**

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D.,

# Clinical Outcomes

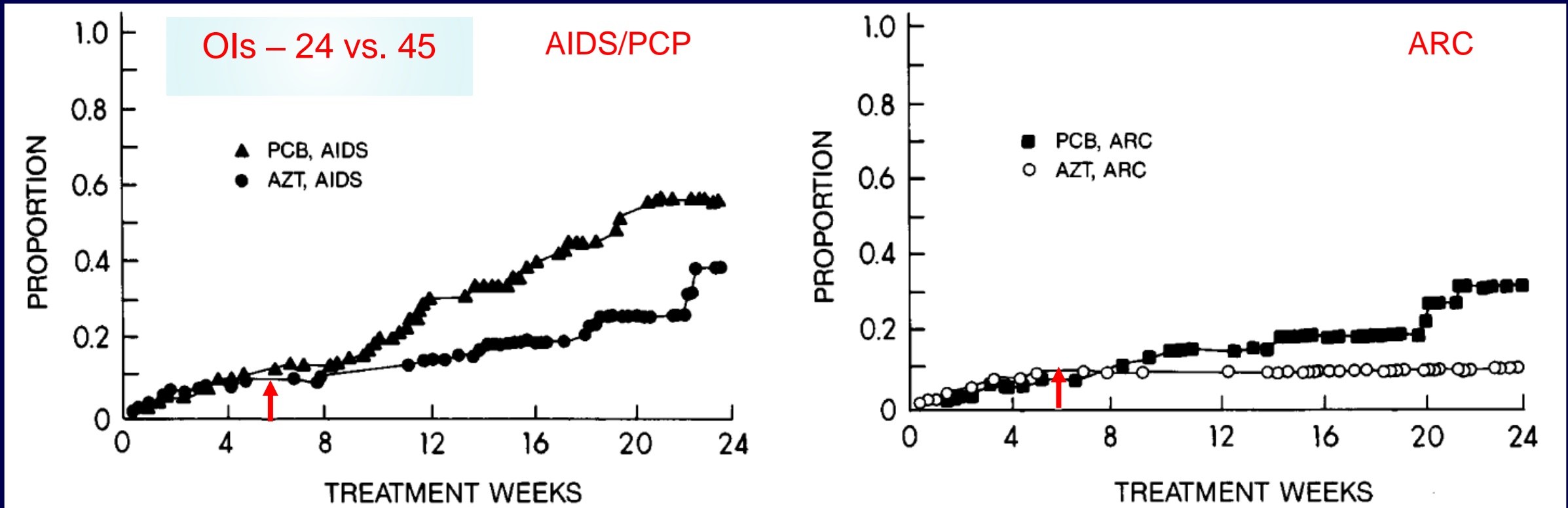


Figure 1. Proportion of Patients in Whom Opportunistic Infections Developed during the Study (Kaplan–Meier Product–Limit Method). The left panel shows infection among patients with AIDS who were receiving AZT or placebo (PCB), and the right panel shows infection among those with AIDS-related complex (ARC).

# CD4 response to AZT Monotherapy

Table 4. CD4 Cell Counts, According to Study Week.

	AZT GROUP			PLACEBO GROUP			P VALUE*
	PATIENTS TESTED	MEDIAN COUNT	MEAN COUNT	PATIENTS TESTED	MEDIAN COUNT	MEAN COUNT	
<b>Patients with AIDS</b>							
Base line	85	54.0	65.6	75	49.0	77.0	—
Week 4	69	133.0	151.6	68	38.5	68.8	<0.0001
Week 8	72	96.0	123.4	60	43.1	64.4	<0.0001
Week 12	67	68.0	105.7	56	32.7	55.8	<0.0001
Week 16	44	49.0	81.0	36	29.0	60.2	0.0082
Week 20	25	49.0	64.7	14	32.0	47.3	0.0344
Week 24	8	18.5	36.6	5	20.0	34.0	0.0240
<b>Patients with AIDS-related complex</b>							
Base line	60	190.0	199.3	61	128.0	175.1	—
Week 4	54	251.0	257.9	51	154.0	182.7	0.0002
Week 8	54	204.5	222.4	48	114.5	161.5	0.0028
Week 12	46	277.6	254.0	47	93.0	164.3	0.0002
Week 16	38	209.0	269.7	38	157.6	178.0	0.0005
Week 20	20	340.0	297.0	22	103.0	156.9	0.0012
Week 24	11	217.0	262.6	9	154.0	232.9	0.7369

\*As determined by stratified Wilcoxon rank-sum test, using the mean of each subject's change from base-line value.

Benefit in CD4 lost after 12 weeks →

# Immune recovery: Reactivity to at least One skin test antigen

- Trichophyton
- Tetanus
- Tuberculin
- Candida

Table 5. Frequency of Skin-Test Conversions during the Study.\*

	NO. POSITIVE/NO. TESTED	P VALUE†
<b>By treatment</b>		
AZT	37/129	<0.001
Placebo	11/117	
<b>By diagnosis</b>		
AIDS		
AZT	20/74	<0.001
Placebo	3/66	
AIDS-related complex		
AZT	17/55	0.074
Placebo	8/51	
<b>By CD4 cell count</b>		
≤100		
AZT	16/80	0.001
Placebo	3/76	
101–499		
AZT	21/49	0.018
Placebo	8/41	

\*A result was considered positive if induration was 10 mm or more.

# Virologic Studies

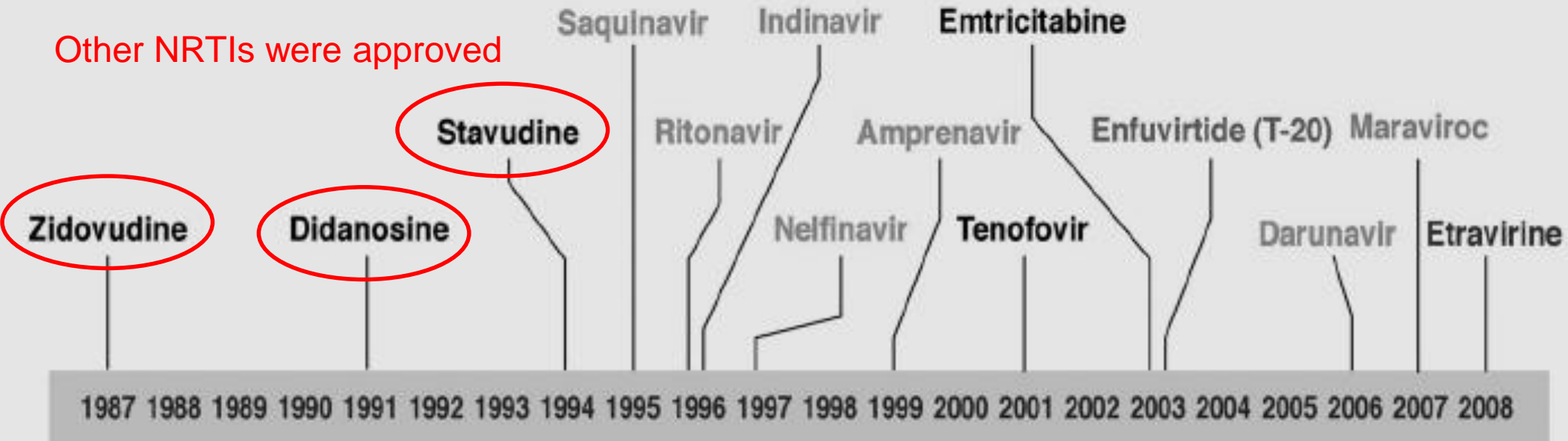
- Qualitative test to detect virus – poor sensitivity
- Quantitation of P24 Ag – as surrogate for virologic response.

AZT decreases OIs and mortality in patients with AIDS and ARC from 8-24 weeks

## Virologic Data

HIV was isolated at entry in 57 percent of the AZT group and 58 percent of the placebo group. No statistically significant differences in isolation rates were noted between the two groups during the study. However, 17 of 33 AZT recipients tested had negative cultures at week 20, as compared with 5 of 19 placebo recipients ( $P = 0.056$ ). There were too few subjects at week 24 of the study to allow statistically valid conclusions about an antiviral effect.

# 30 FDA-Approved antiretroviral drugs



- NRTIs (8)
- NNRTIs (4)
- Protease Inhibitors (10)
- Fusion Inhibitor (1)
- Integrase Inhibitor (1)
- Entry Inhibitor (1)
- Combinations (5) - not shown

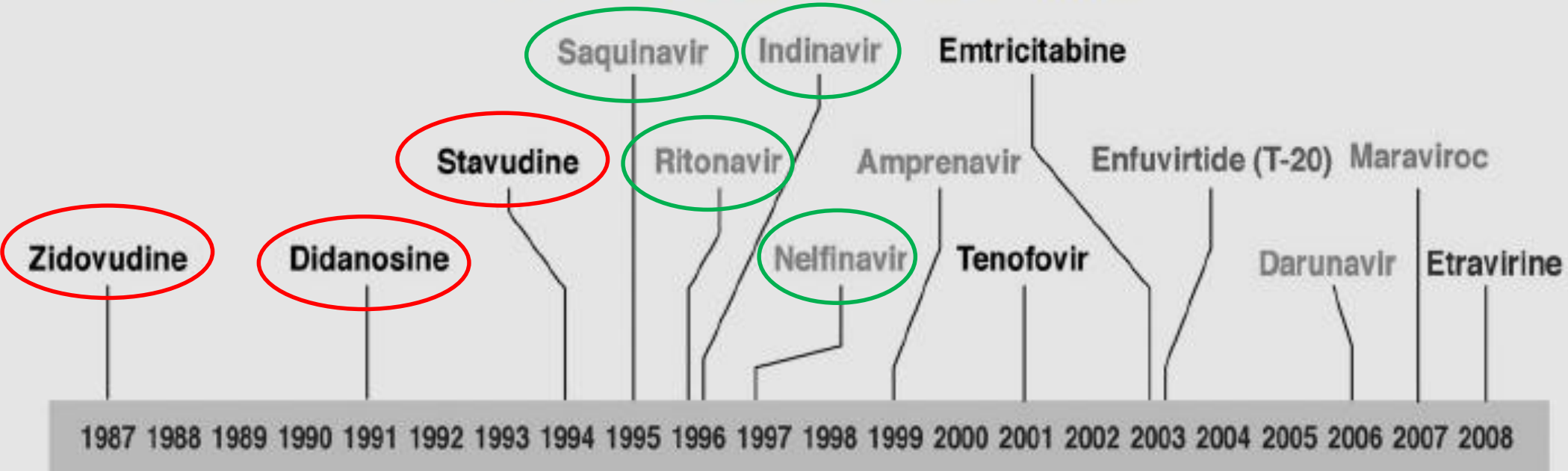
# Using NRTIs for therapy

- Single agent treatment  $\Rightarrow$  Ineffective
- Alternate and intermittent regimens  $\Rightarrow$  ineffective

# Combination NRTI therapy

- Combination of ZDV with ddC or ddI:
  - Limited clinical benefit
  - Poor durability
  - Poor tolerability
- Dose dependent inhibition of DNA polymerase  $\gamma$  - major toxicity
- Development of 3TC turning point
  - Rapid resistance with monotherapy:
  - Well tolerated
  - Synergistic with other NRTIs

# 30 FDA-Approved antiretroviral drugs



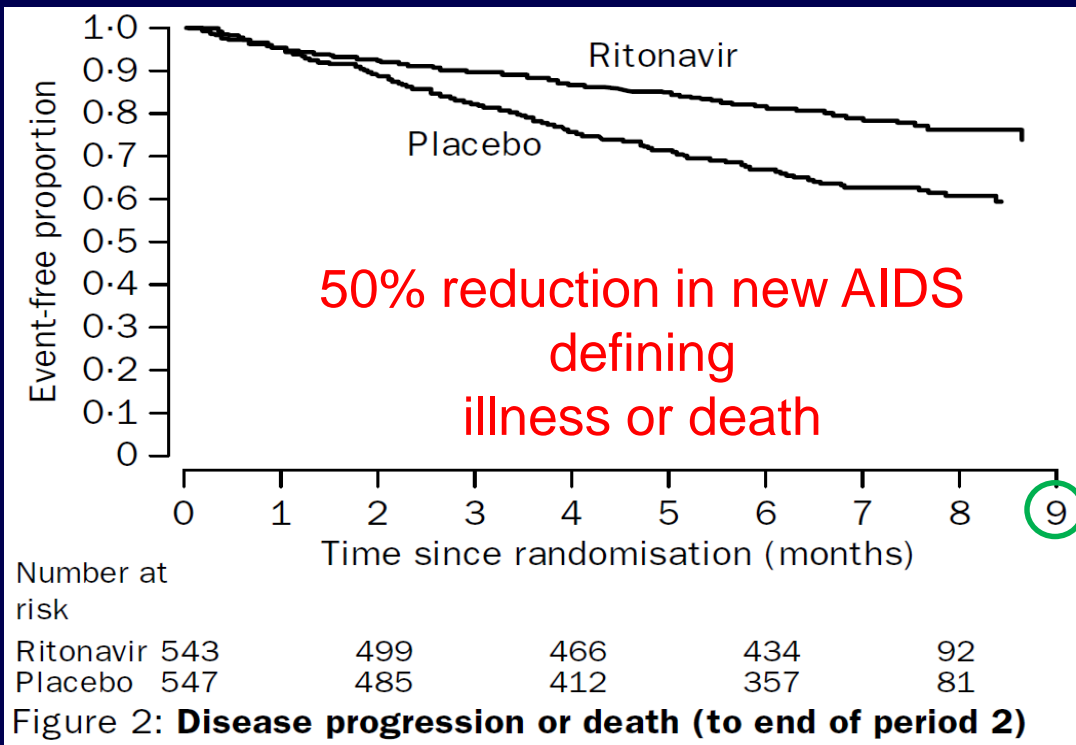
1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008

- NRTIs (8)
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- Combinations (5) - not shown



# Effect of RTV as add on to 2 NRTI Treatment

- RTV 600 mg bid + 2 NRTIs (n=543) or placebo + 2 NRTIs (n=547)
- **Advance disease** - Baseline median CD4 ~ 20,



Symptom	Ritonavir (n=541)		Placebo (n=545)	
	Number with symptom	Number withdrawn*	Number with symptom	Number withdrawn*
Nausea	284 (52%)	56 (10.4%)	143 (26%)	6 (1.1%)
Vomiting	156 (29%)	26 (4.8%)	40 (7%)	5 (0.9%)
Diarrhoea	269 (50%)	23 (4.3%)	116 (21%)	5 (0.9%)
Weakness	134 (25%)	15 (2.8%)	72 (13%)	5 (0.9%)
Altered taste	66 (12%)	9 (1.7%)	22 (4%)	2 (0.4%)
Circumoral paraesthesia	151 (28%)	9 (1.7%)	23 (4%)	0 (0)
<b>Total withdrawn</b>	..	114 (21.1%)	..	45 (8.3%)

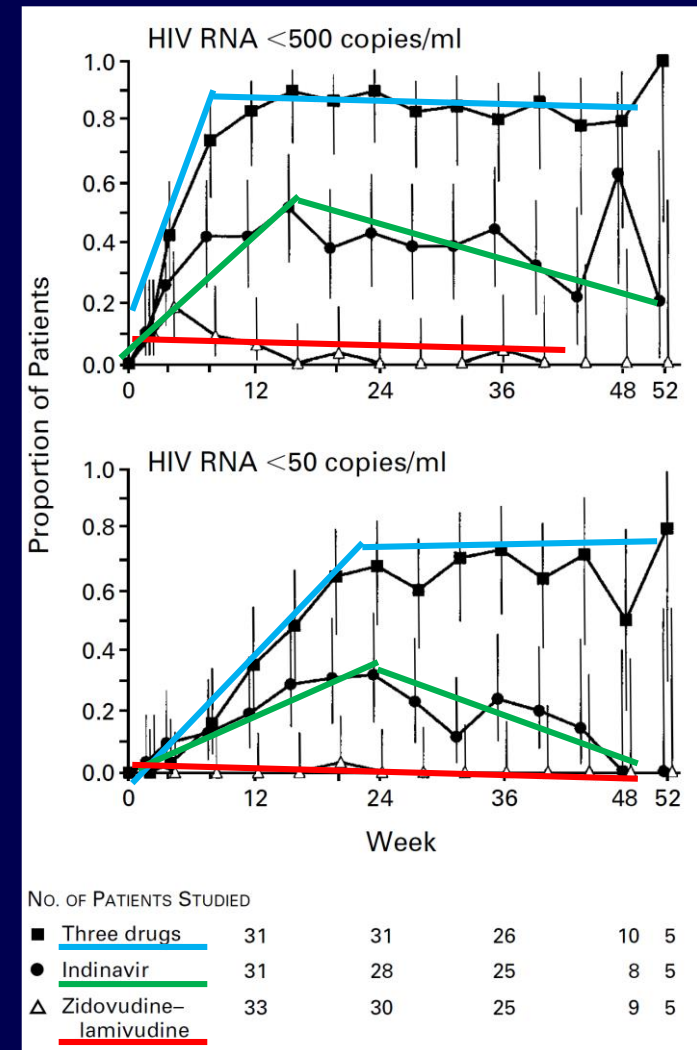
Events of possible, probable, or uncertain relation to study medication.  
\*Some patients had more than one reason for study discontinuation.

Table 4: **Treatment-related adverse events (in >1.5% of participants) and rates of withdrawal from study medication**

# Durable Viral Suppression of IDV, AZT, 3TC

- 3 regimens: IDV (800 mg tds) vs AZT (200 mg TDS) + 3TC (150 mg BID) vs. ALL three drugs
- 3-drug regimen reduced VL < 500 for up to **one year** in > 80%
- All regimens generally well tolerated

**First ART regimen to demonstrate marked, and durable viral suppression.**



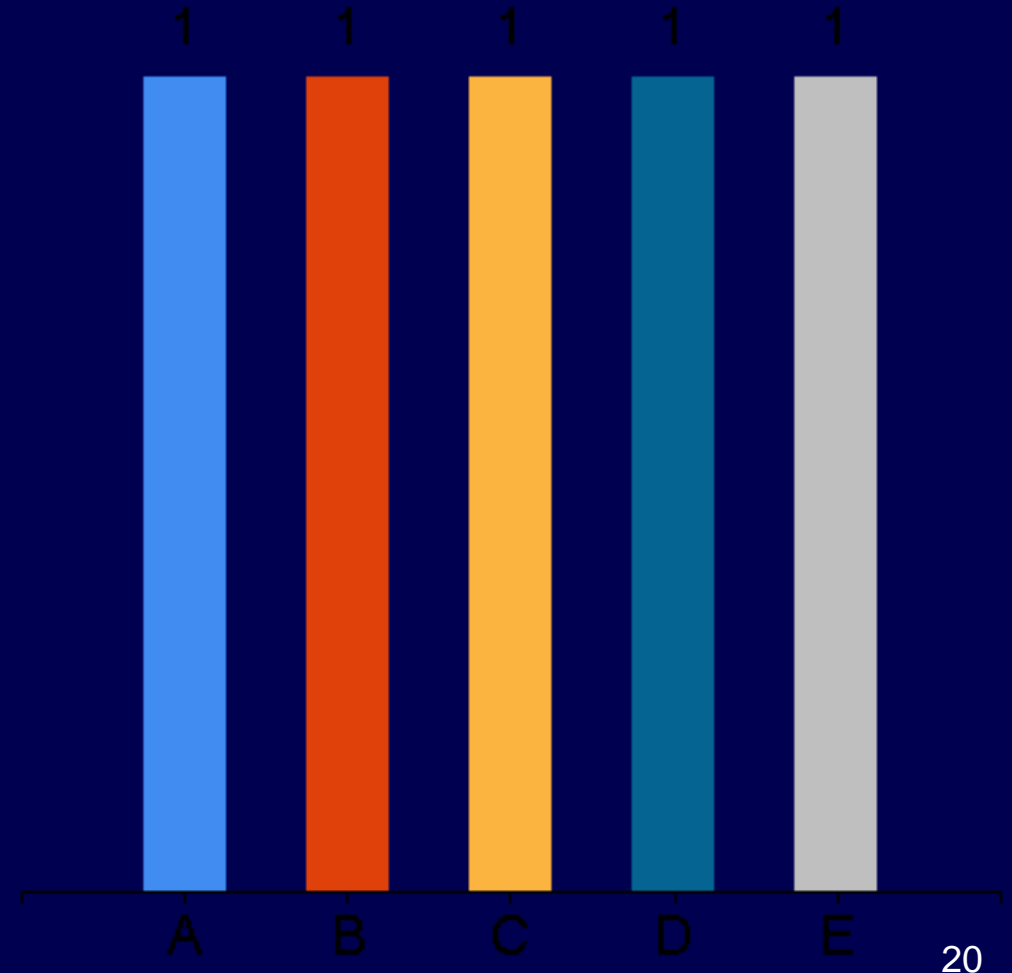
**Figure 2.** Proportion of Patients with Serum HIV RNA Levels of Less Than 500 Copies per Milliliter (Upper Panel) and Less Than 50 Copies per Milliliter (Lower Panel). Bars are 95 percent confidence intervals.

# Fatal Disease turned into a chronic Manageable condition with PI based regimens (HAART)

- Large pill burden
- Frequency of dosing
- Drug –drug interactions
- Interactions with food
- Quality of life
- Short term and long term effects - dysregulation of glucose and lipid metabolism, fat redistribution (the lipodystrophy syndrome)

# Effect of ritonavir on ritonavir boosted PI?

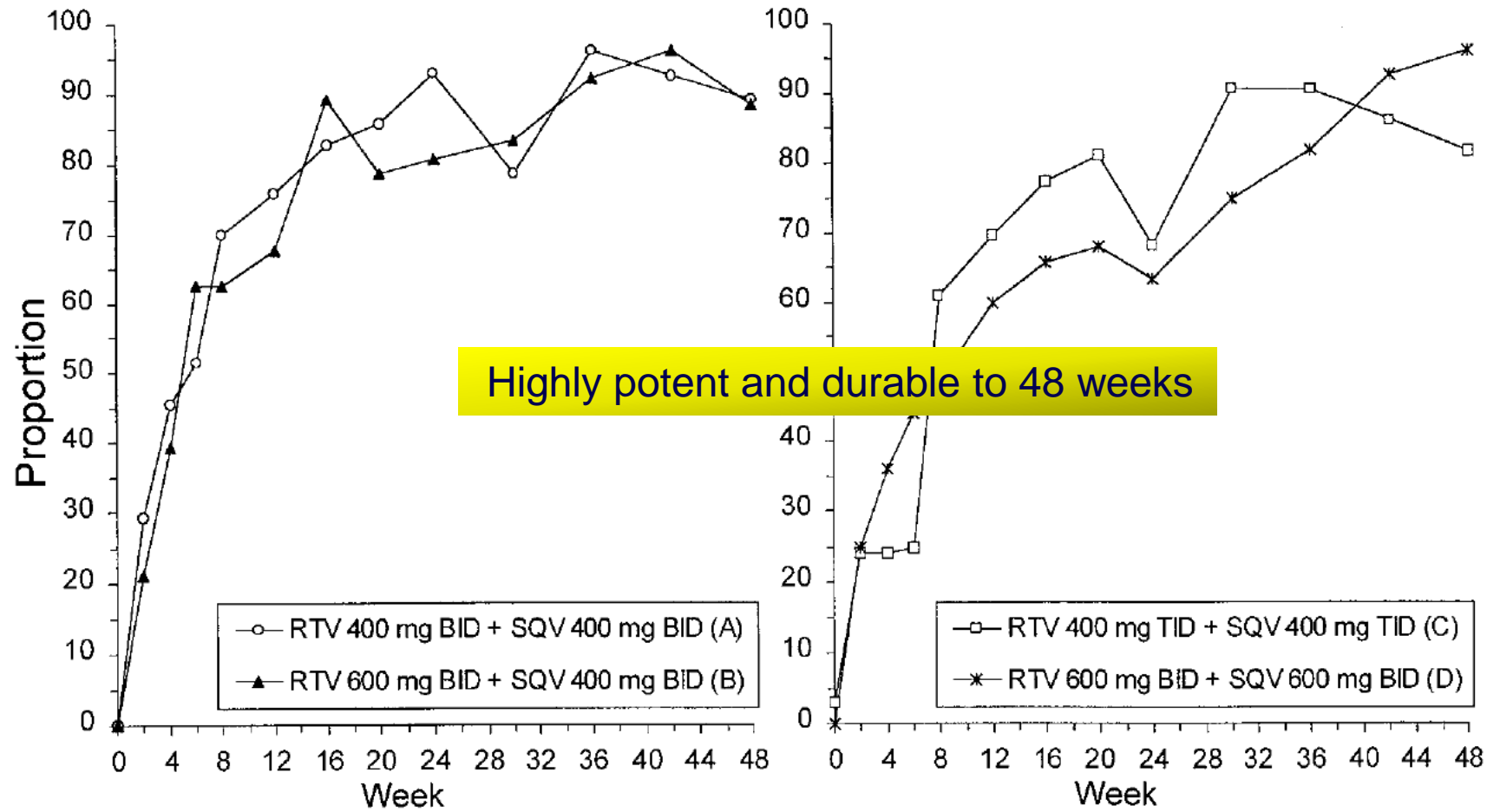
- A. Inhibits metabolism
- B. Improves absorption
- C. Reduces toxicity
- D. Protects the liver from drug induced injury
- E. Adds to the antiviral activity of the companion PI



# PK Boosting of PIs

- Poor bioavailability  $\Rightarrow$  high pill burden, frequent dosing
- Food interactions  $\Rightarrow$  inconvenient dosing schedules
- RTV: potent inhibitor of CYP 450 3A4
  - PK boosting  $\Rightarrow$  increase drug exposure, prolong  $t^{1/2}$
  - Reduces dosing frequency, pill burden and risk of resistance
  - Increased risk of drug-drug interaction and dyslipidemia

# Ritonavir/saquinavir +/- RTI Combination (d4T/3TC)



n = (A) 35	29	29	27	28	(C) 33	23	22	22	22
(B) 34	31	26	26	26	(D) 37	35	30	28	27

Fig. 3. Proportion of patients with plasma HIV RNA levels below the limit of quantitation by week of study. The

# RTV/SQV combination Therapy: Toxicity

**Table 2.** Patients with moderate or severe drug-related events.

Toxicity-related event	Group I		Group II	
	A	B	C	D
At least moderate severity and of possible, probable, or unknown relation to drug(s)*				
Non-site-specific symptoms, n (%)				
Asthenia	2 (5.7)	3 (8.3)	8 (24.2)	10 (27.0)
Gastrointestinal symptoms, n (%)				
Diarrhea	4 (11.4)	11 (30.6)	5 (15.1)	12 (32.4)
Nausea	4 (11.4)	7 (19.4)	4 (12.1)	11 (29.7)
Vomiting	2 (5.7)	2 (5.6)	4 (12.1)	2 (5.4)
Neurologic symptoms, n (%)				
Circumoral paresthesia	1 (2.9)	3 (8.3)	1 (3.0)	4 (10.8)
Depression	1 (2.9)	0 (0.0)	5 (15.1)	4 (10.8)
Dizziness	2 (5.7)	4 (11.1)	3 (9.0)	3 (8.1)
Peripheral parasthesia	1 (2.9)	4 (11.1)	1 (3.0)	2 (5.4)
Grade 3 or 4 toxicity-related laboratory event				
Hepatic transaminase elevation	2 <sup>†</sup>	2	2	8
Triglyceride elevation (> 1500 mg/dl)	3	5	3	5
Discontinuation because of adverse events	1	6	9	6

Treatment groups divided into four arms: A (n = 35), ritonavir 400 mg twice daily, saquinavir 400 mg twice daily; B (n = 36), ritonavir 600 mg twice daily, saquinavir 400 mg twice daily; C (n = 33), ritonavir 400 mg three times daily, saquinavir 400 mg three times daily; D (n = 37), ritonavir 600 mg twice daily, saquinavir 600 mg twice daily. \*At least 5% among all the patients in the study. <sup>†</sup>Includes one patient

# XI International AIDS Conference Vancouver

**One World, One Hope: Vancouver 1996**



**1996 - 1998**

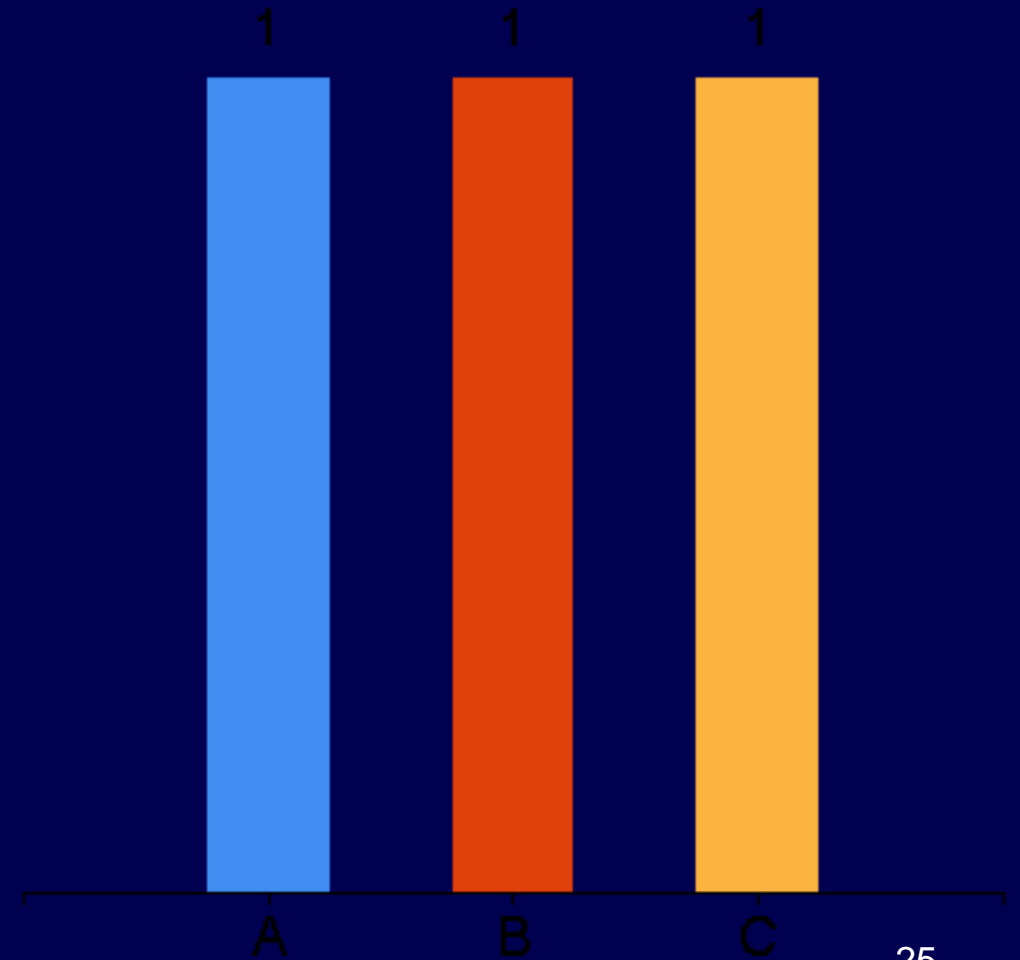
**The Treatment Revolution**

# Who attended the XI International AIDS Conference in Vancouver (1996)?

A. Yes

B. No

C. Would have liked to but needed a “sugar daddy” or a “big mama” 😞



# Vancouver AIDS Conference: A turning point

- Success of triple therapy due to new drugs from different classes first presented
- Understanding of HIV as a disease characterized by high viral turnover with continuous viral replication
- Concentration of HIV (viral load) predicts disease progression  
⇒ effective biomarker for treatment response
- Understanding of drug resistance (molecular, functional & clinical impact)
- Critical need to fully suppress viral replication ⇒ stop mutation

## 20 Years of the International AIDS Society

HIV Professionals Working Together to Fight AIDS

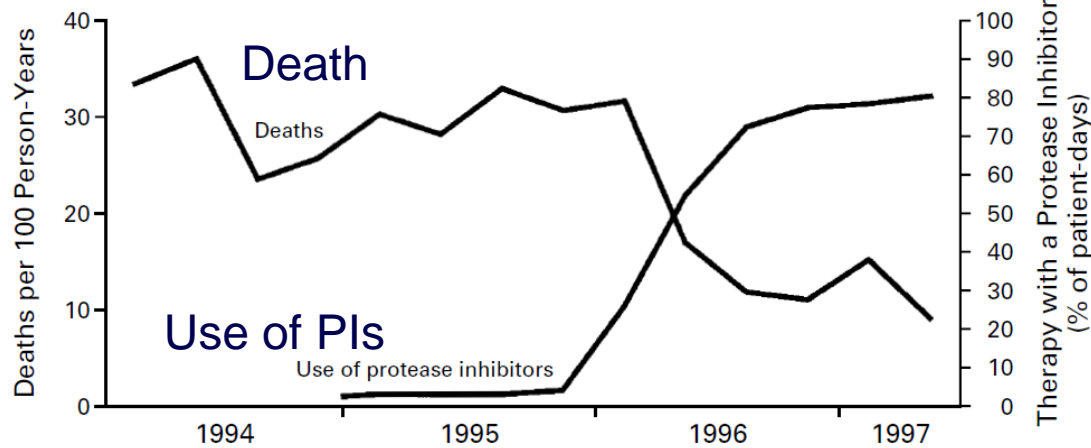


Four Canadian physicians and scientists co-chaired a conference that was finally able to report a significant treatment breakthrough. Clinical researchers reported that using a combination of antiretrovirals – nucleoside reverse transcriptase inhibitors and protease inhibitors or non-nucleoside reverse transcriptase inhibitors – had achieved remarkable clinical results. Highly active antiretroviral therapy (HAART) reduced viral load in peripheral blood to undetectable levels; allowed CD4+ cells, key markers of immune function, to increase; and, most importantly, saw mortality and morbidity among patients drop dramatically. After so many years of disappointing clinical results and bleak prospects, the atmosphere in session halls was electric. HAART revolutionized HIV treatment and care, and for most patients in high-income countries, the prognosis for HIV disease shifted from almost certain fatality to a chronic, manageable illness. The “Lazarus Syndrome” was coined to refer to patients who had returned from the brink of death to good health, and David Ho, one of the lead

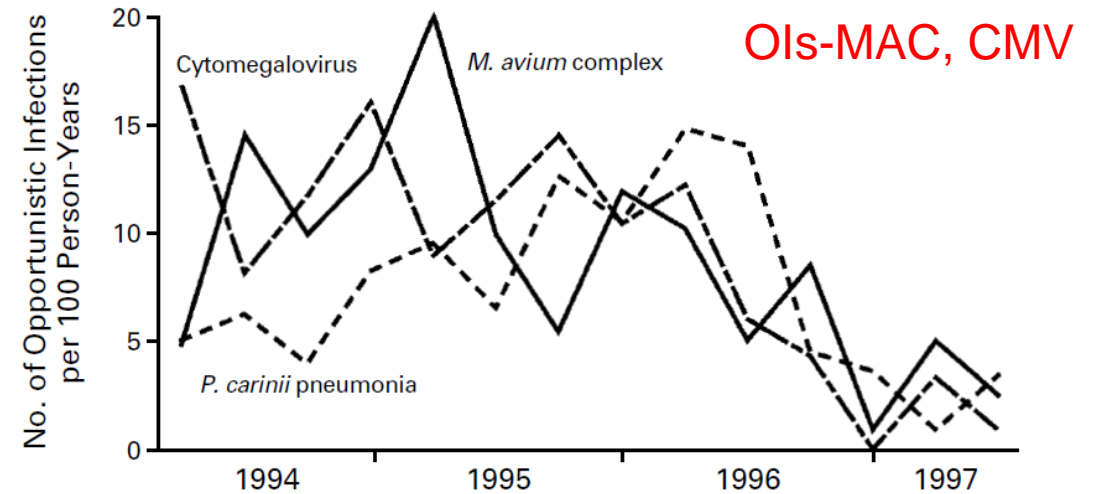
However, it quickly became clear that the complex and expensive regimens of antiretrovirals at that time, coupled with sophisticated clinical and laboratory monitoring requirements, meant that areas of the world where the epidemic was most devastating seemed unlikely to reap the benefit of these new treatments. The theme of One World, One Hope began to ring increasingly hollow.

# Shift in Prescribing

- ART prescribing changed dramatically for pts with CD4 < 100.
- ART prescription from 72% (1994) to 95% (mid 1997)
- Use of combination regimens from 25% (1994) to 94% (mid 1997)
- PI containing regimens from 2% (mid-1995) to 82% (June 1997)



**Figure 1.** Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.



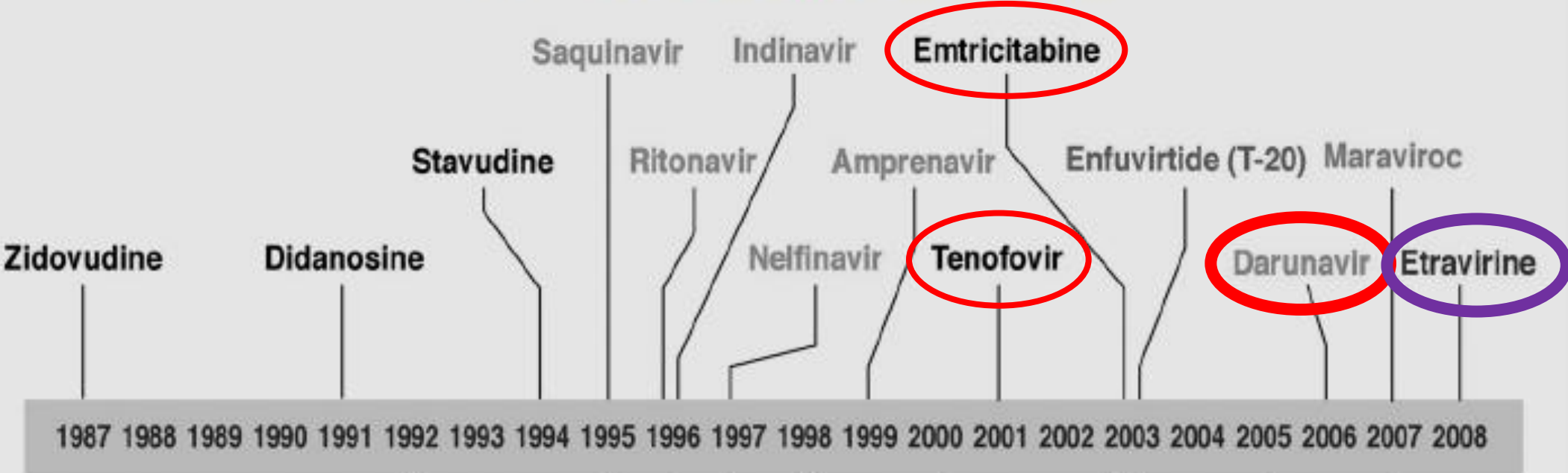
**Figure 2.** Rates of Cytomegalovirus Infection, *Pneumocystis carinii* Pneumonia, and *Mycobacterium avium* Complex Disease among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

# Progress in the new Millennium

## Drug development:

- Safer and more potent drugs belonging to old classes (NRTI, NNRTI, PIs)
- New classes (entry/attachment inhibitors and integrase inhibitors)
- Improved ability to suppress virus in patients with multiple failures and highly resistant virus.

# 30 FDA-Approved antiretroviral drugs



- NRTIs (8)
- NNRTIs (4)
- Protease Inhibitors (10)
- Fusion Inhibitor (1)
- Integrase Inhibitor (1)
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- Combinations (5) - not shown

# Progress in the new Millennium

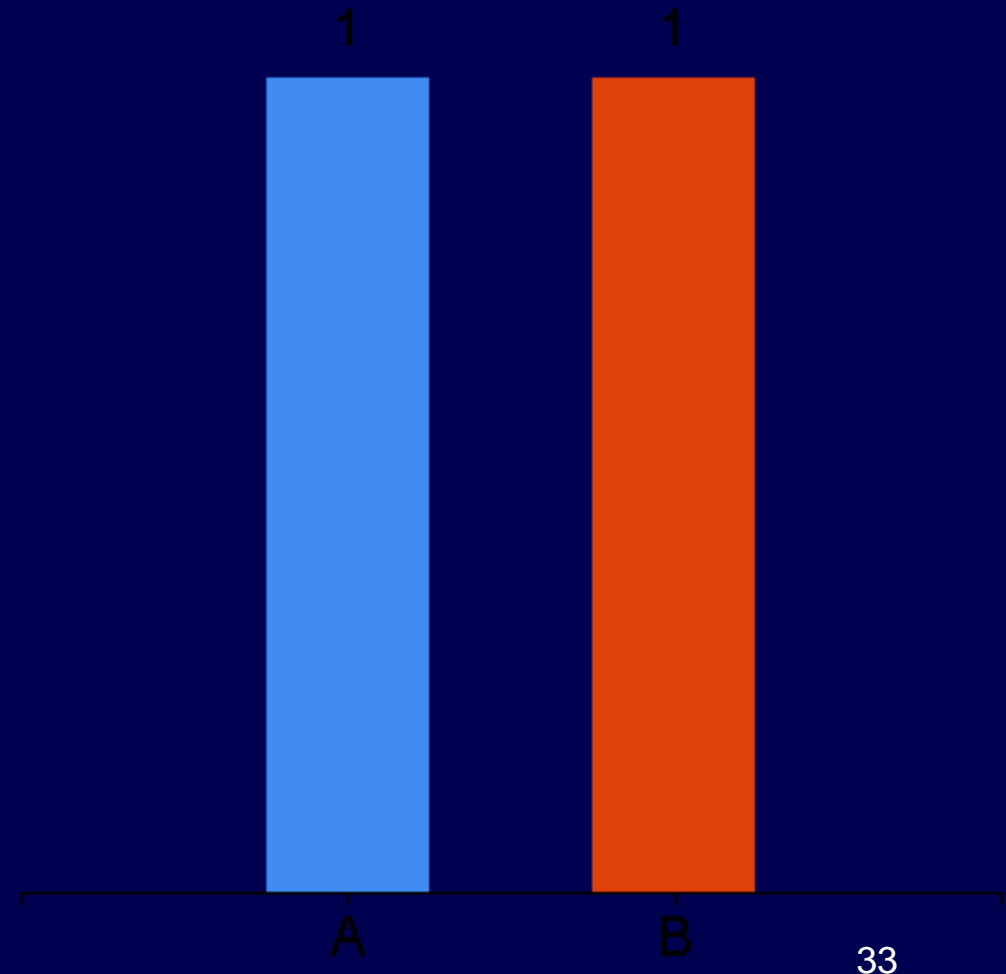
## Approaches to treatment

- Maintain failing treatment – limited options, ↓ fitness
- Strategic Treatment Interruptions – reduce burden of drug toxicities
- Timing of treatment- <200, <350, <500, TAT
- Simplification strategies – reduce pill burden/frequency/toxicity/cost
- Class sparing options – reduce toxicity
- Single drug regimens / Monotherapy reduce drug burden/toxicity/cost
- Fixed Drug Combinations – improved adherence

# Potency of PIs vs. NNRTIs

A. EFV more potent than PIs

B. PIs more potent than EFV

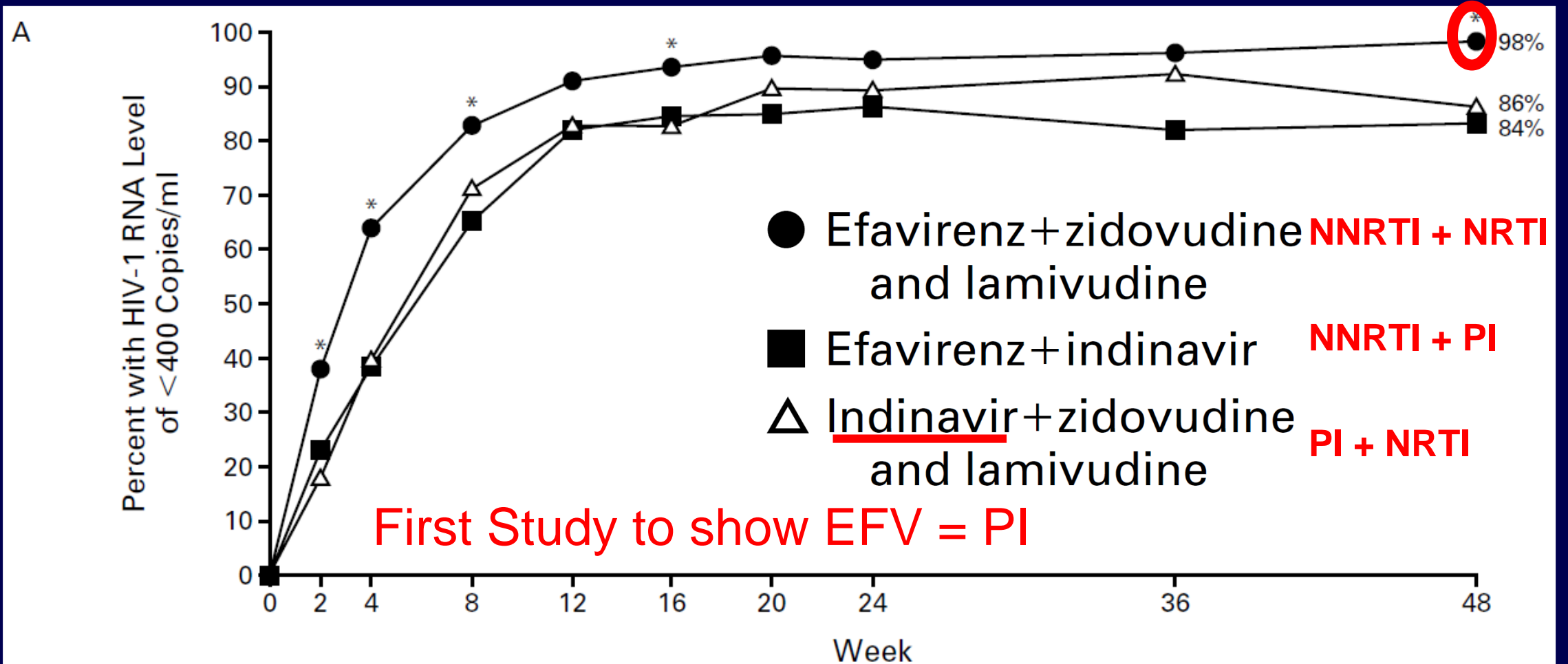


# Can NNRTIs substitute for PIs in HAART?

? Potency

? Toxicity

# NNRTIs effective substitute for unboosted PI



## No. AT RISK

● Efavirenz+zidovudine and lamivudine	134	140	130	121	123	123	115	108	103
■ Efavirenz+indinavir	131	132	124	116	116	115	110	95	91
△ Indinavir+zidovudine and lamivudine	122	131	115	106	105	96	93	79	81

# EFV (plus two NRTIs) vs. LPV/r (plus two NRTIs)

3TC and AZT/d4T/TDF

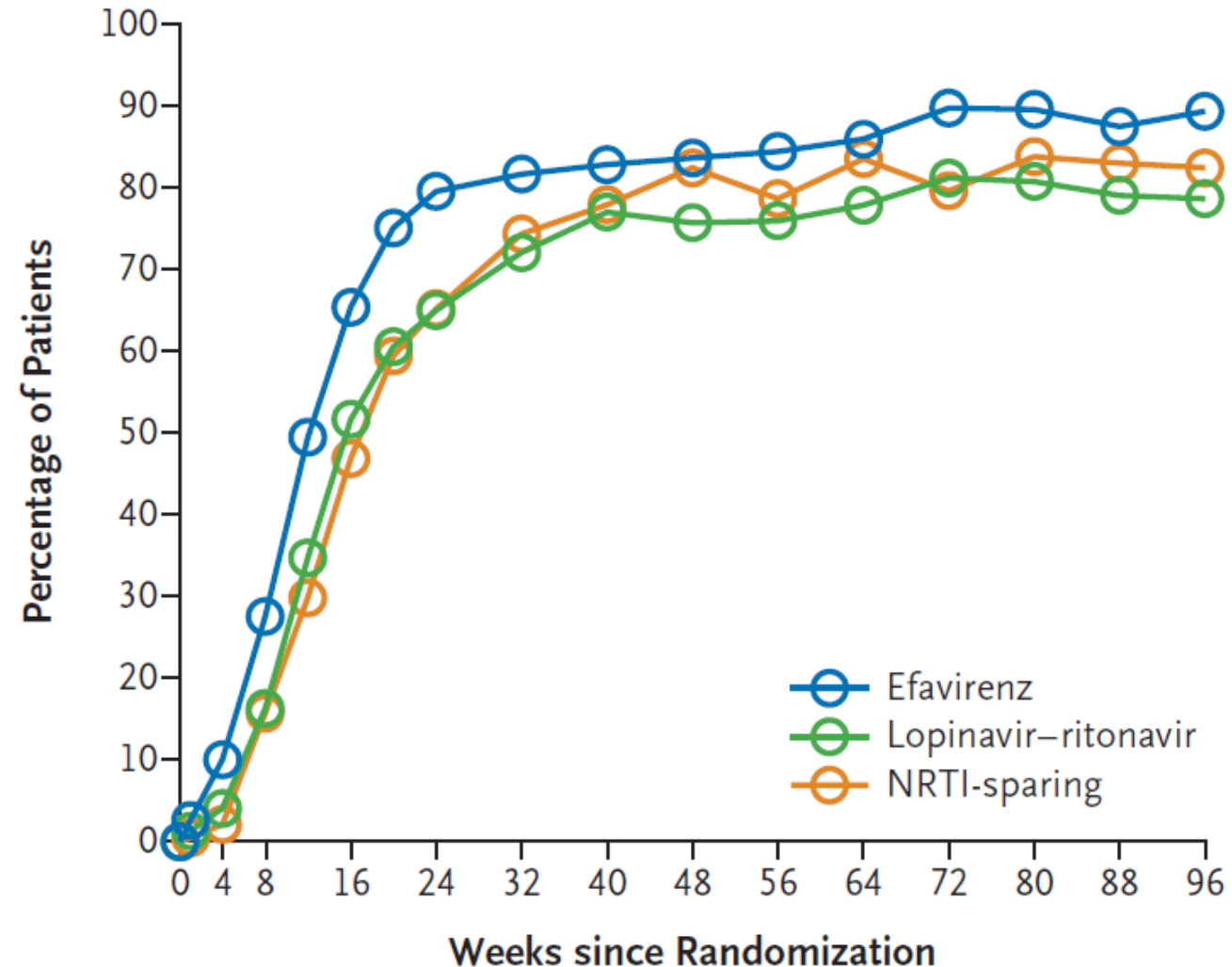
VL < 50 at 96 weeks

- EFV group: 89%
- LPV/r group: 77%

P = 0.003

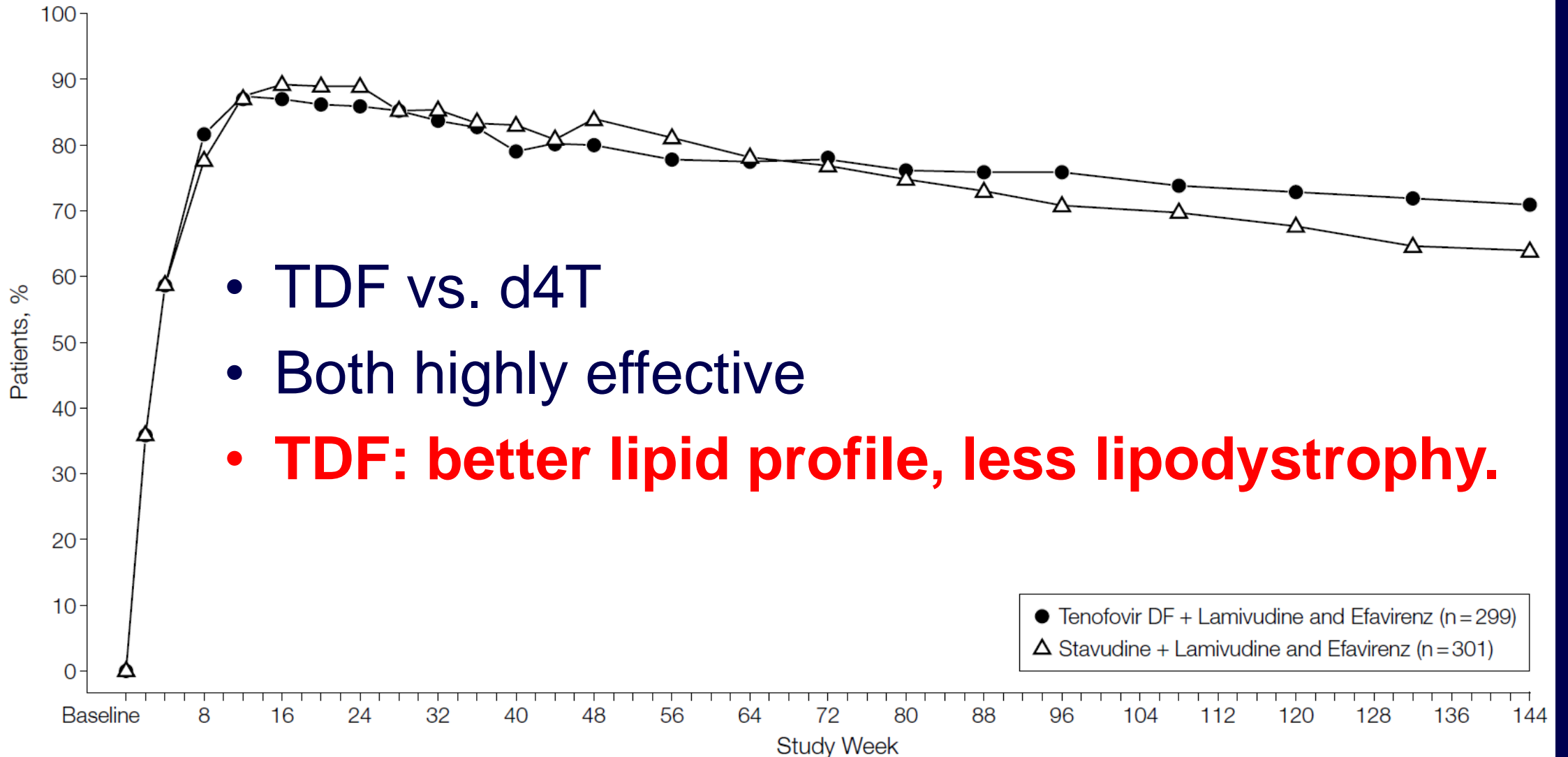
EFV + 2 NRTIs greater overall virologic efficacy

**B** HIV-1 RNA <50 Copies



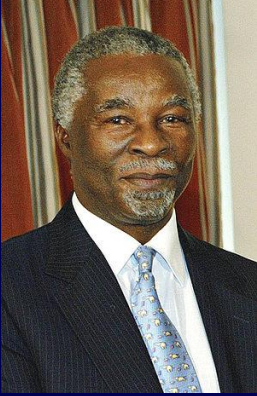
# TDF/3TC/EFV vs d4T/3TC/EFV in ART-Naive

**Figure 2.** Percentage of Patients With HIV RNA Levels of Less Than 400 Copies/mL Using Intent-to-Treat Analysis





# South Africa Situation



- HIV/AIDS denialism –Thabo Mbeki (1999 to 2008)
- Questioned the scientific consensus that HIV causes AIDS
- Instituted policies denying ART to AIDS patients- "poisons"
- MoH- Manto Tshabalala-Msimang promoted herbal remedies  
- ubhejane, garlic, beetroot and lemon juice- "Dr. Beetroot"
- Responsible ~ 350000 preventable deaths

# X111 International AIDS Conference Durban

## Breaking the Silence: Durban 2000



The 2000 conference in Durban was enormously important in building momentum to change the approach to global public health. It was the first International AIDS Conference to be held in a developing country and, more importantly, in a country which had one of the highest HIV-prevalence rates in the world. The theme of the conference was Break the Silence, and the unprecedented media presence in Durban broadcast the staggering impact of the epidemic in sub-Saharan Africa to a world that had yet to fully grasp or respond to the scope of the region's problem. In the first Jonathan Mann

# South Africa

- 1 April 2004 ARV rollout began at several service points
- Kgalema Motlanthe succeeded Mbeki in 2008
- Barbara Hogan - MoH - ended the era of denialism
- Current Situation:
  - Largest number of people on ART in the world.
  - Declining annual incidence - national incidence rate at its lowest
  - Increase life expectancy by about 10 years
- Credit to civil society movements, brave health officials, politicians and clinicians working in a hostile system to bring about change.





# SA Treatment Programme

<b>Initial Regimen: 2004</b>	<b>d4T + 3TC + EFV/NVP</b> <b>AZT + ddl + LPV/r</b>
<b>Current Regimens</b>	<b><u>First Line Regimen</u></b> <b>TDF + 3TC/FTC + EFV/NVP</b> <b>AZT + 3TC/FTC + EFV/NVP</b> <b>ABC + 3TC/FTC + EFV/NVP</b> <b><u>2<sup>nd</sup> Line Regimen</u></b> <b>AZT + 3TC + LPV/r</b> <b>AZT + 3TC + ATV/r</b> <b><u>3<sup>rd</sup> Line Drugs</u></b> <b>DRV/r/INTSI/Etravirine/</b>

# Current Drugs: potent, convenient, well tolerated

- Allowing for flexibility in regimens – individualized treatment
  - Patient characteristics
  - Comorbidities
  - Concomitant medication
  - Disease status
  - Past drug exposure
  - Pre-existing mutations
  - Viral genotype
  - FDC

# Conclusion

- Most severe epidemic of modern times
- Greatest public health challenge in history
- Concerted collaborative effort between researchers, HCWs, pharmaceutical industries, regulators, public health officials and community of patients.
- An inevitably fatal disease converted into a chronic manageable disease.

# Main Challenge!!!!

- Identifying the infected
- Getting the infected onto treatment
- Keeping the infected on treatment

90:90:90

QUESTIONS???