Antiretroviral Therapy
An International Perspective

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Antiretroviral Therapy

- History of therapy
- Therapeutic goals and challenges
  - Developed and developing worlds
- Therapeutic practice
  - Antiretroviral drugs
  - Strategies of therapy
  - Adherence to therapy

History of HIV therapy

1983-95 **Era of therapeutic pessimism**

1996-9 **Era of therapeutic enthusiasm**

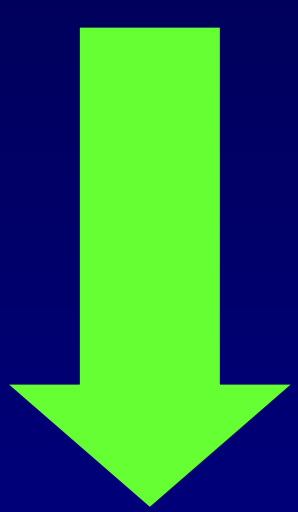
1998-01 **Era of therapeutic balance**

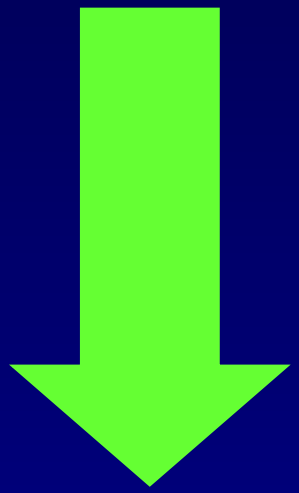
Power and limitations of ARV recognized

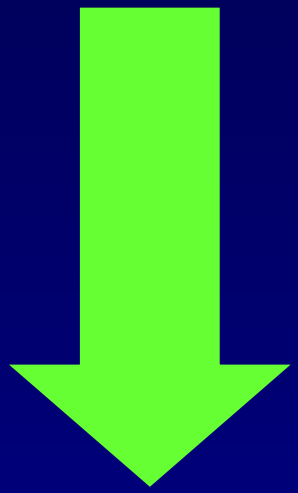
- **Therapeutic gains documented and consolidated for individuals and public health**
- **Short and long term toxicities emerge**
- **Need for additional/simpler treatment options**
- **Need to make treatment available for all with HIV disease**

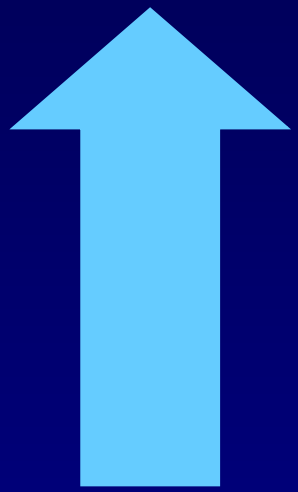
Achievements in HIV therapy

for PLHA and society









matic reduction in mortality

Dramatic reduction in morbidity

Dramatic reduction in health-care utilization

Improvement quality of lif

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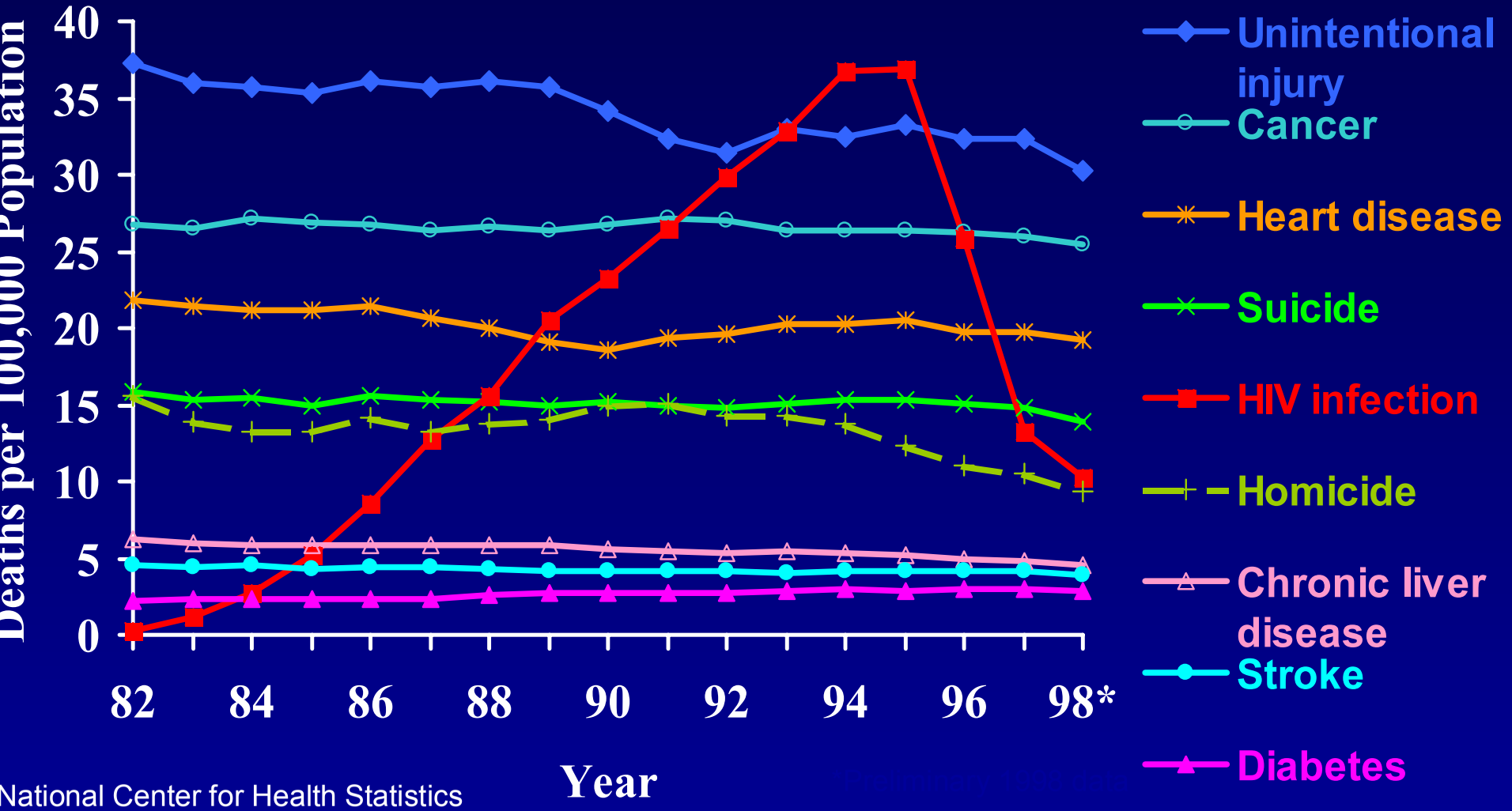
Trends in Annual Rates of Death from Leading Causes of Death Among Persons 25-44 Years Old, USA, 1982-1998



National Center for Health Statistics
National Vital Statistics System

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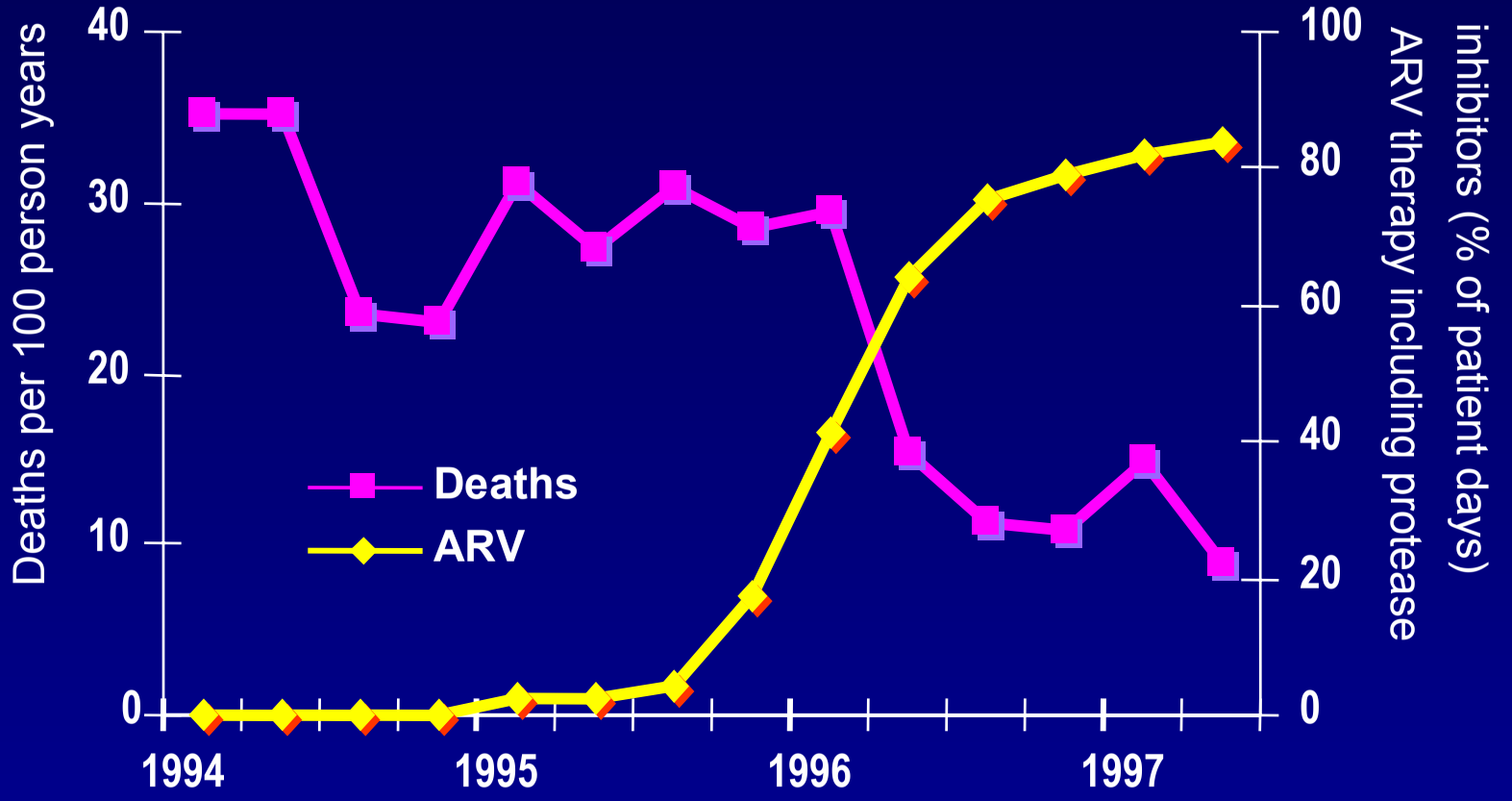
Mortality in patients with CD4<100 on antiretroviral (ARV) therapy USA, 1994–1997



Source: Palella *et al., New England Journal of Medicine,* 1998 Mar, **26:**338–60

98036-E-35 – 15 July 1998

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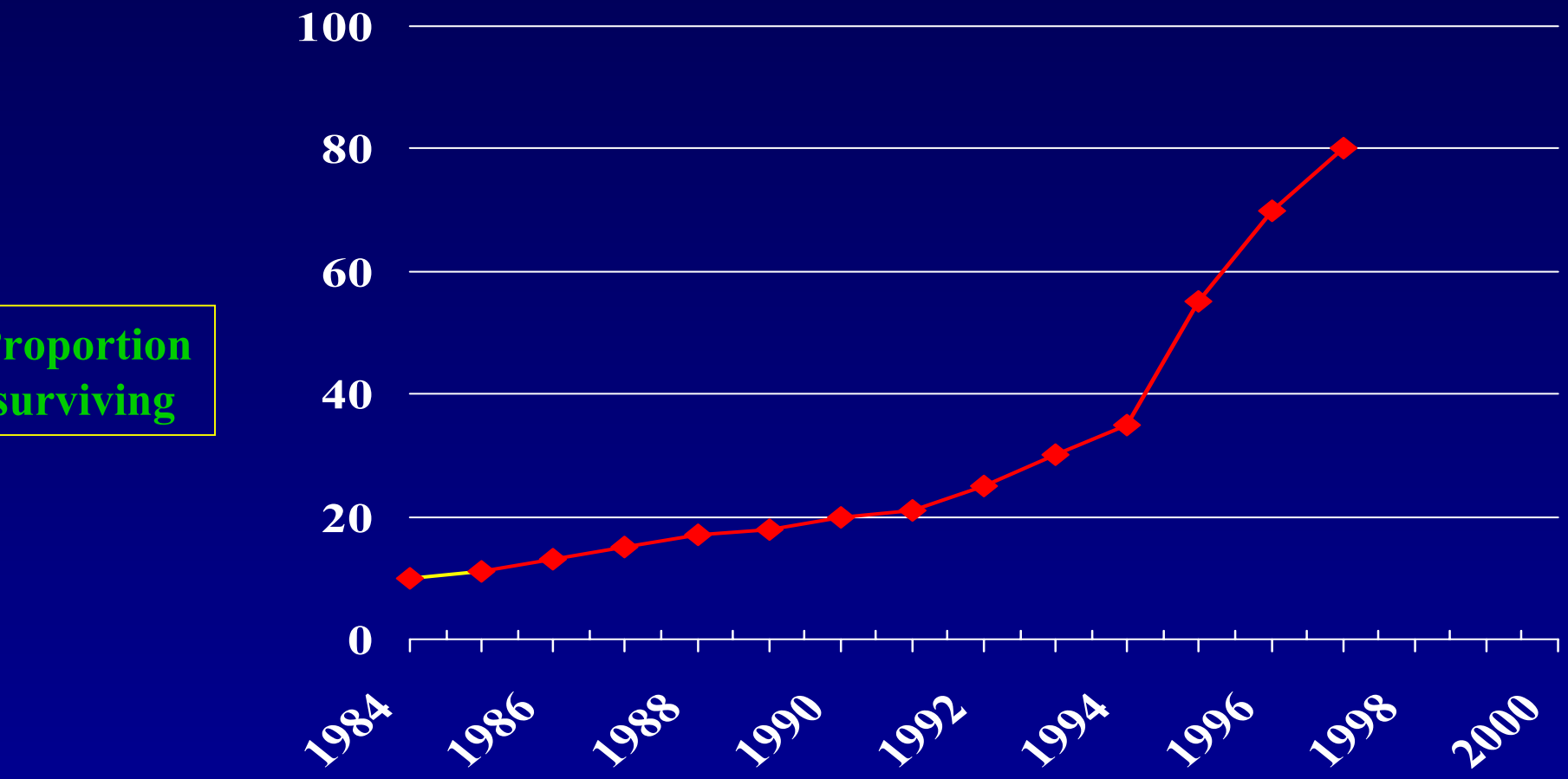
Proportion Surviving 24 mos after AIDS-defining OI diagnosis by year of diagnosis-US, 1984-1997



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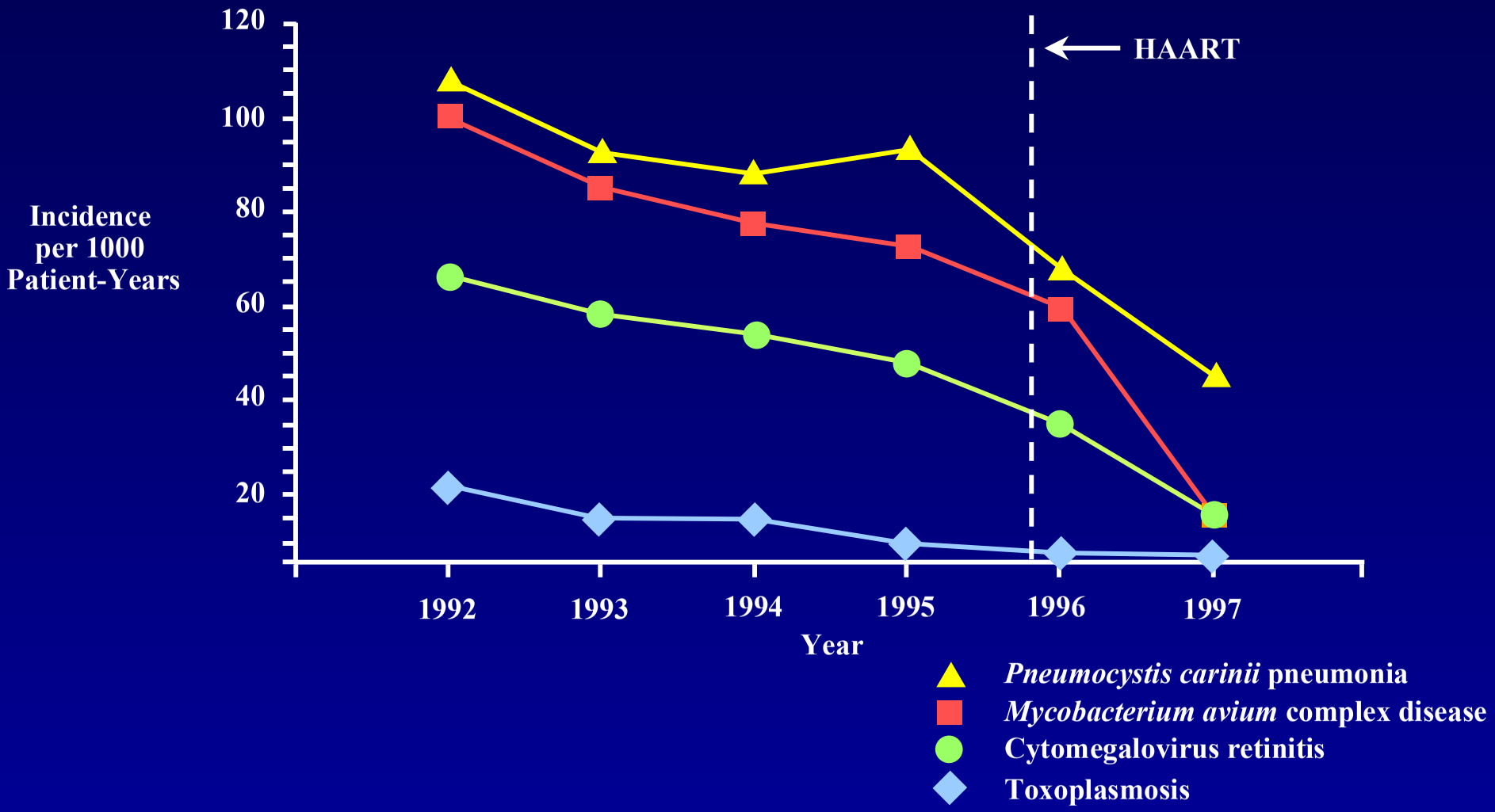
Selected OIs in Patients With HIV Infection, 1992–199

Kovacs JA, et al. N Engl J Med. 2000;342:1416-1429. (Based on CDC data.)



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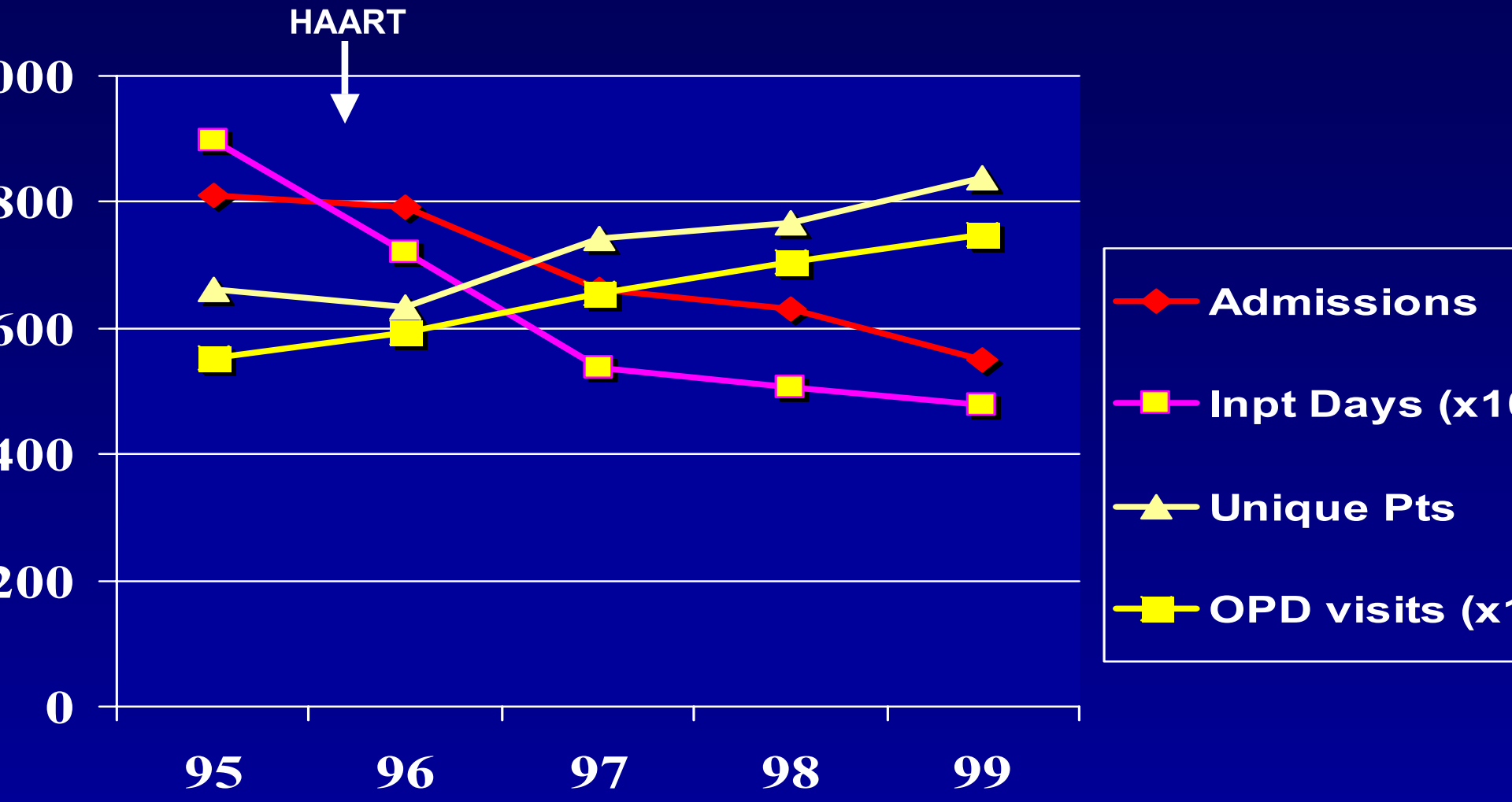
Changes in Inpatient and Outpatient Utilization Over Time



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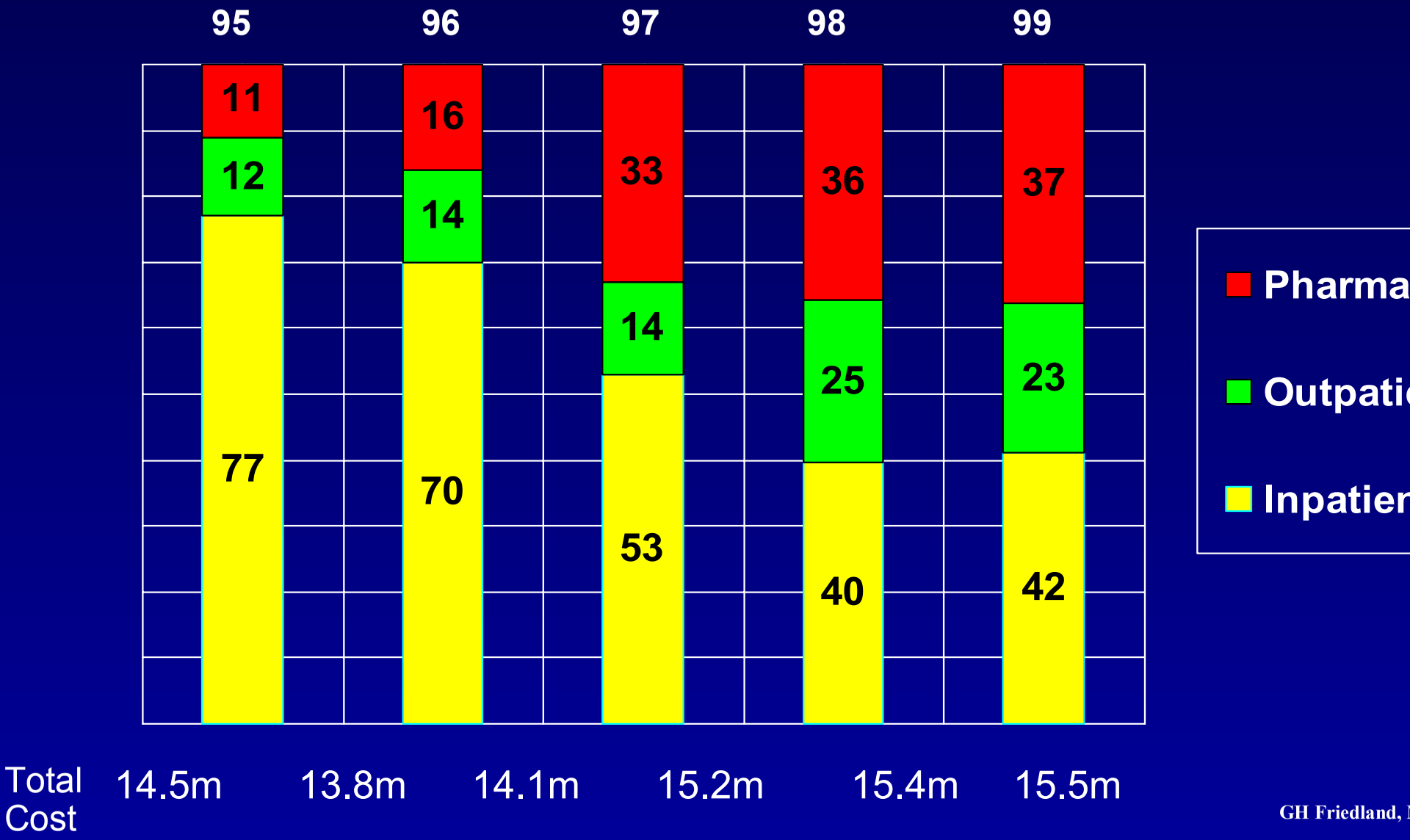
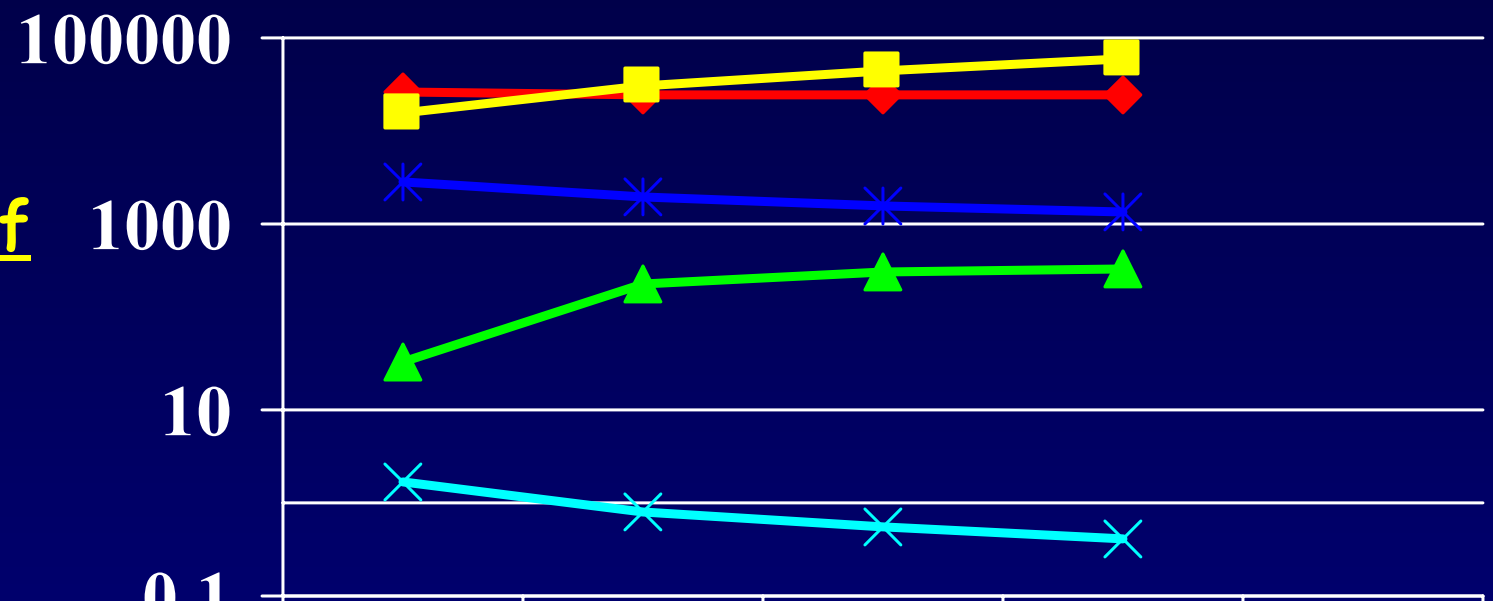
Change in Source of Cost

100% of Cost



COST-BENEFIT of HAART Brazil



	1996	1997	1998	1999	
Hospitalizations	25458	25157	24700	23698	
# Pts assisted	15390	31140	43823	57604	
Deaths (Sao Paulo)	2772	1940	1547	1368	
Drug expenditures (million U$)	34	224	299	336	
Hospitalizations/pt (mean)	1.65	0.81	0.56	0.41	

1997-1999:
Hospitalizations avoided:146,000
Savings: $472 million

Ministry of Health, Brazil

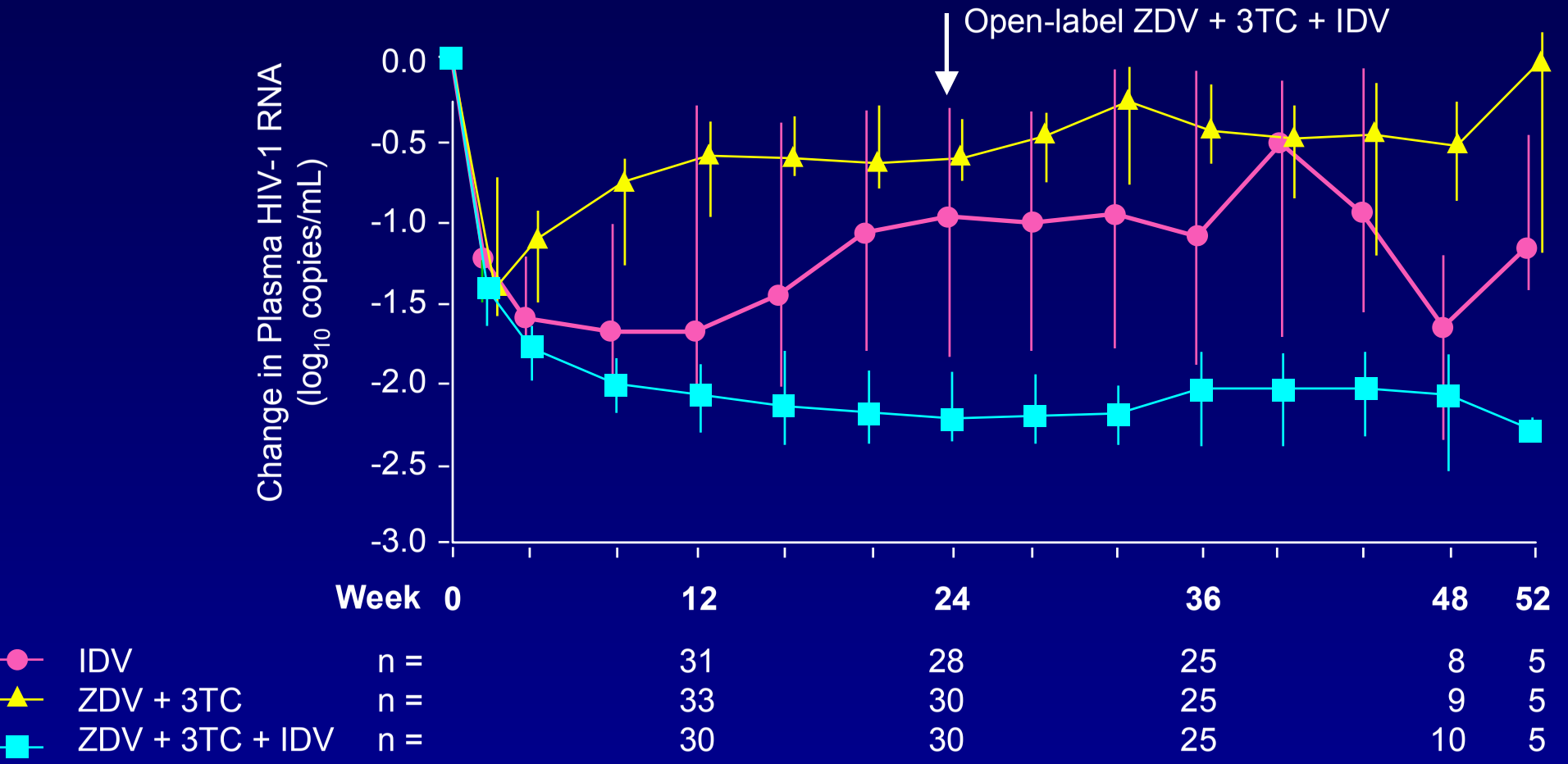
Past "mistakes" in antiretroviral therapy

- Viral eradication possible-cure
- Use of regimens with insufficient potency
  - one drug at a time, two drugs at a time
- Hit hard and hit *too* early
- Regimens too difficult, drugs too toxic
- Insufficient attention to adherence, pharmacology and resistance
- Inadequate attention to development and funding of comprehensive systems of care

One vs Two vs Three drugs

MK 035: IND, AZT+3TC, IND+AZT+3TC

Mean Plasma HIV-1 RNA Change From Baseline



V = Indinavir.

ource: Gulick et al. *N Engl J Med.* 1997;337:737.

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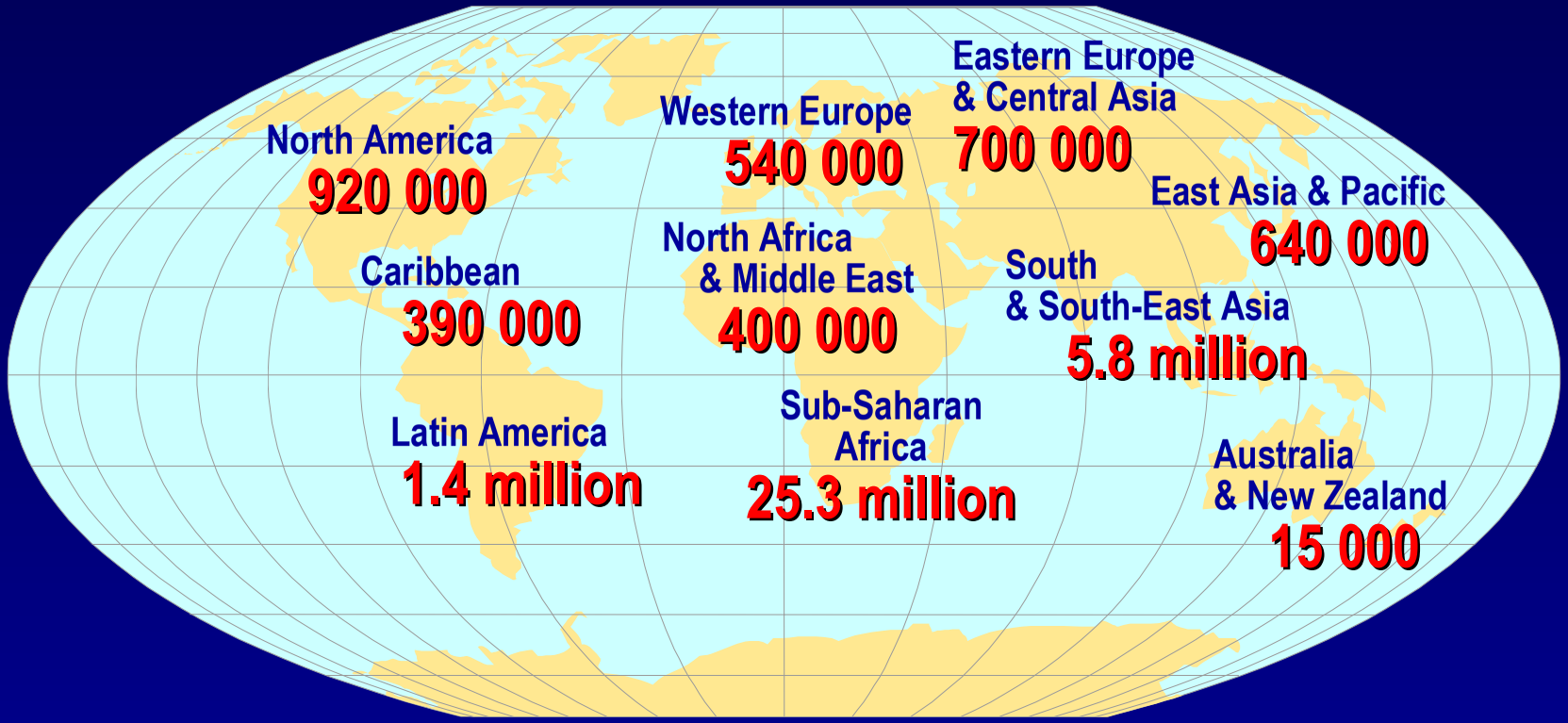
Past "mistakes" in antiretroviral therapy

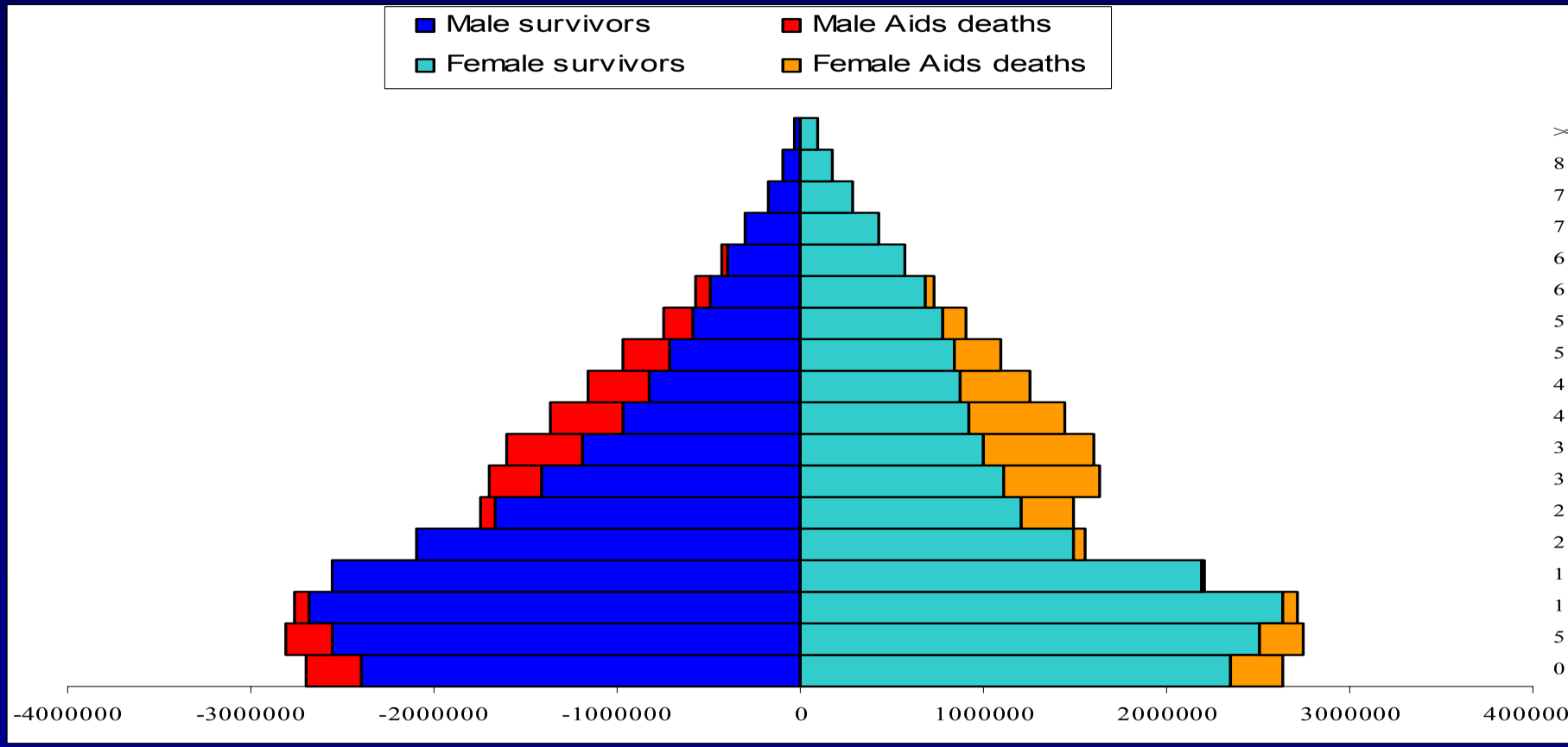
- Thinking too short term
  - Recommendations based upon short term surrogate markers and toxicities
  - Need for long term clinical outcome studies
- Separation of prevention and treatment
- Insufficient attention to operational research and strategic studies
- Generalizing from insufficient data
  - Potent regimens must include PI
  - PIs solely responsible for lipodystrophy
  - You only have one chance with a PI

Adults and children estimated to be living with HIV/AIDS as of end 2000

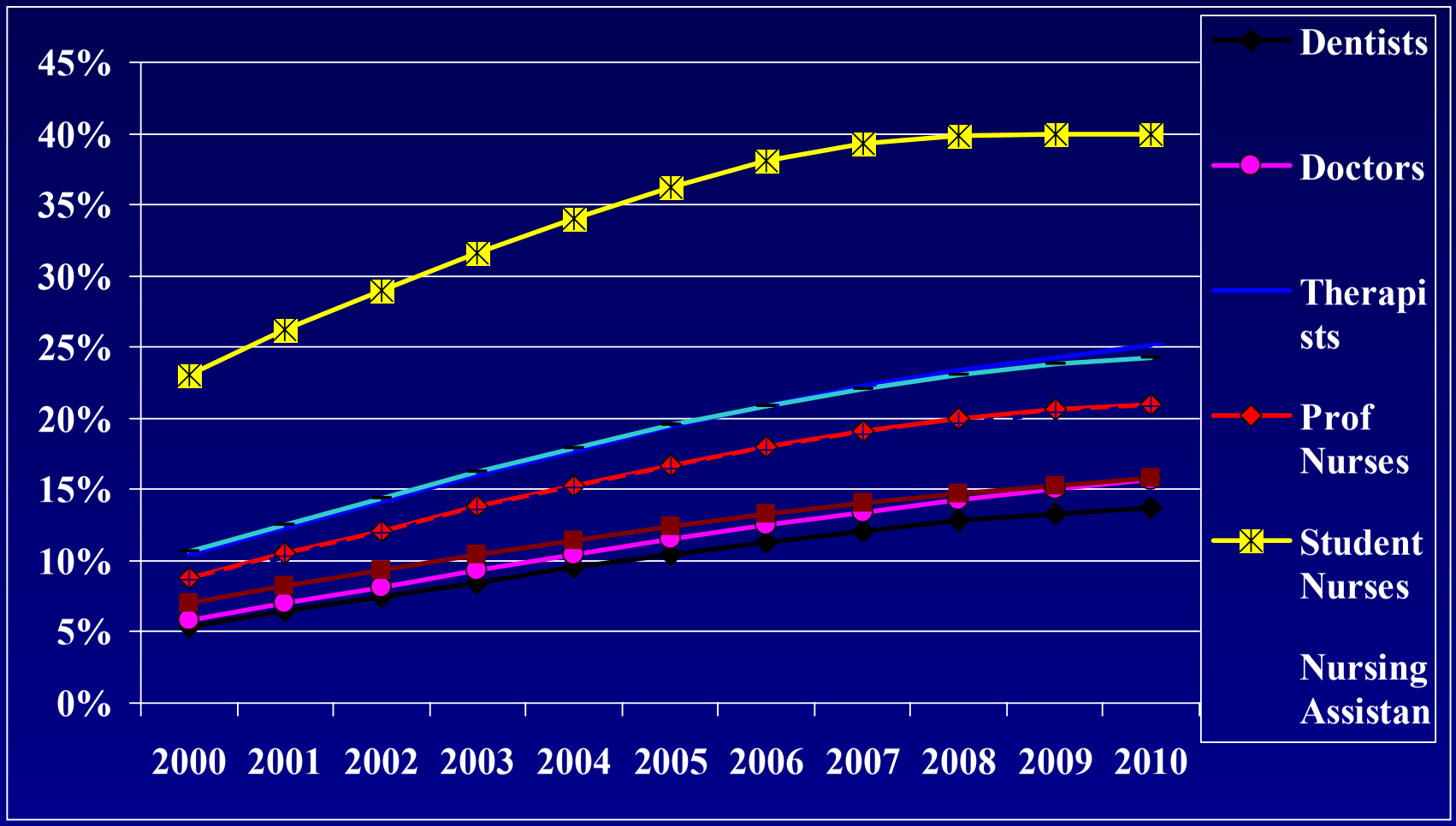


Total: 36.1 million

HIV/AIDS and MORTALITY
SA POPULATION STRUCTURE for 2009



Projected HIV infection levels in the Health Sector by Job Category



Antiretroviral Therapy

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  - Developed and developing worlds
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  - Strategies of therapy
  - Adherence to therapy

Goals of HIV Therapy

- Maximal and durable suppression of viral replication
- Restoration and/or preservation of immune function
- Reduction of HIV-related morbidity and mortality
- Improvement of quality of life -conversion of HIV to a "chronic disease"
- Reduction of HIV transmission

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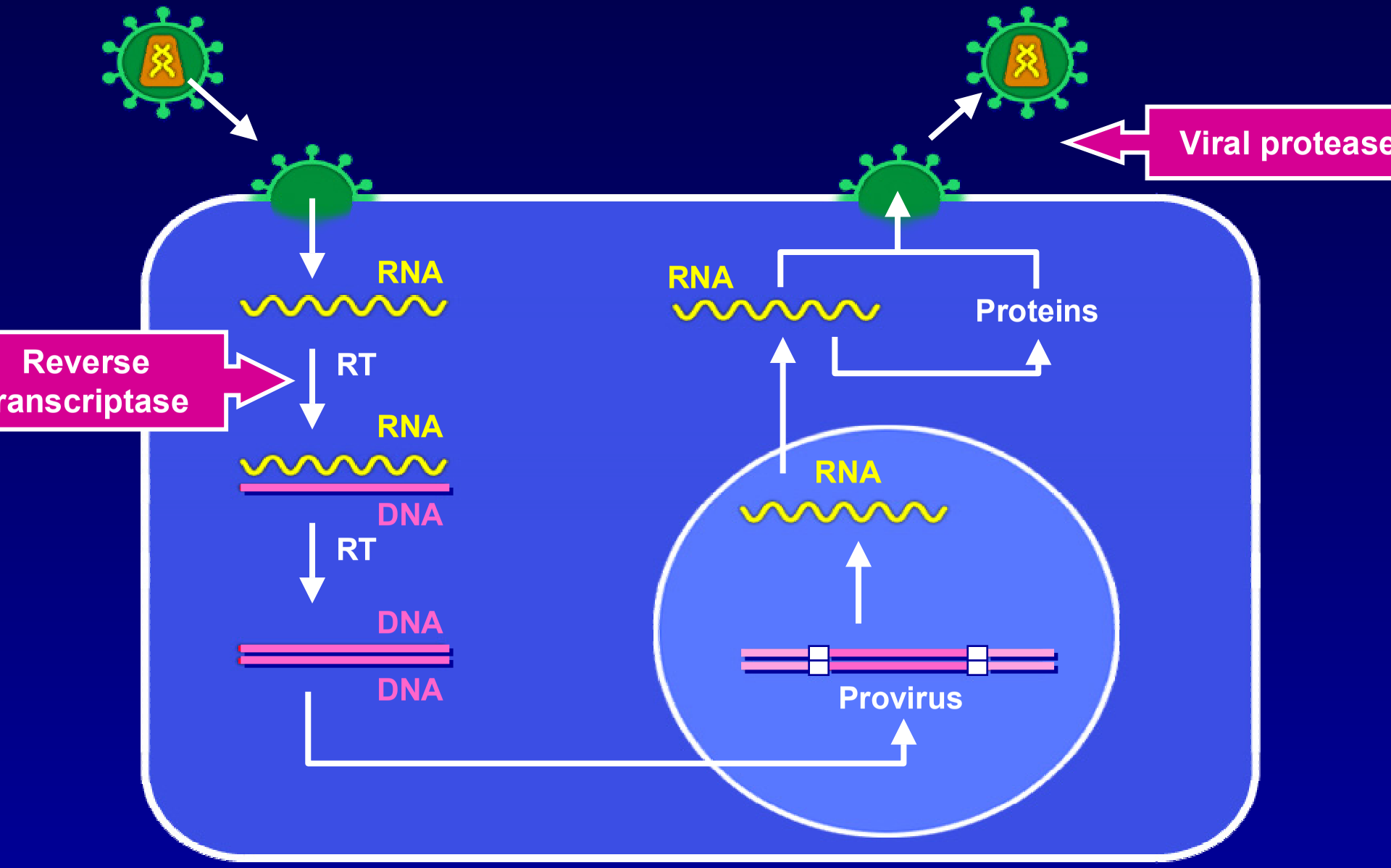

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Antiretroviral Agents-2001

NRTIs	NNRTIs	PIs
AZT	nevirapine	saquinavir
ddI	delavirdine	ritonavir
ddC	efavirenz	indinavir
d4T		nelfinavir
3TC		amprenavir
ABV		lopinavir/rit

Others: hydroxurea, tenofovir

ARVs are easier to take

- Reduced dose
  - AZT
- Fewer side effects
  - ddI, AZT, ritonavir
- Reduced frequency
  - once a day-ddI, 3TC, d4T, nevirapine, efavirenz
  - twice a day-AZT, protease inhibitors

Long term Toxicities

- Long term
  - metabolic/mitochondrial
    - lipodystrophy
    - lipoatrophy/hyperlipedemia/
    - glucose intolerence/lactic acidosis
    - bone and mineral metabolism
      - ? cardiovascular

Short term Toxicities

- Short term
  - gastrointestinal side effects/hepatitis
  - hematologic
  - neurologic
  - rash

Strategic Questions

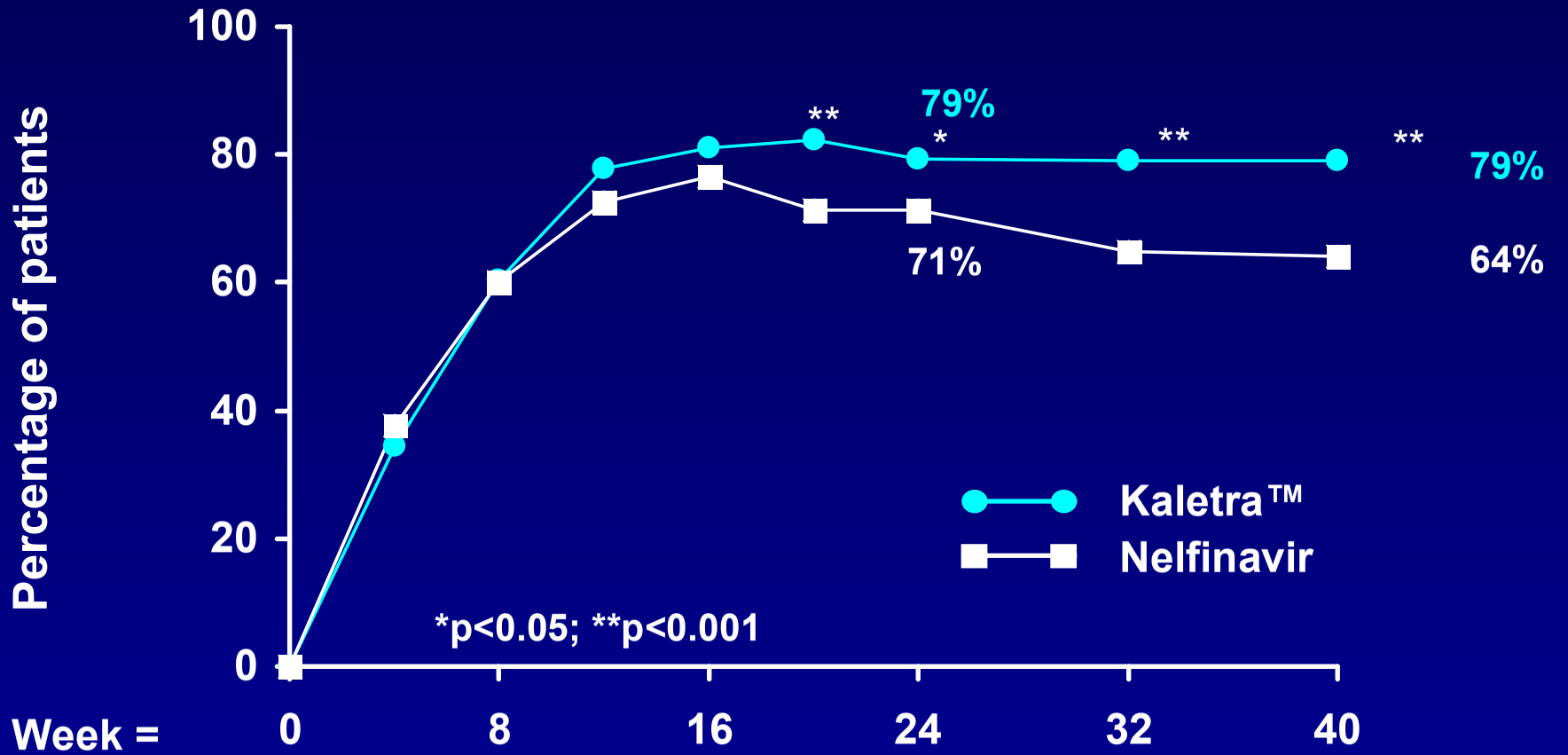
- ✓ When to start?-"the golden moment"
- ✓ What to start with?
- ✓ Where to start?
- ✓ When to switch?-"the silver moment"
- ✓ What to switch to?
- ✓ When to stop?-"the bronze moment"
- ✓ How to monitor for benefit and toxicity?

Choice of initial regimen sufficiently potent

- Possible regimens for initial therapy:
  - 2 Nucleoside RTI + 1-2 Protease Inhibitors
  - 2 Nucleoside RTI + 1 NonNucleoside RTI
  - 3 Nucleoside RTI
  - all 3 classes

Two protease based regimens

HIV RNA <400 copies/mL (ITT M=F)



etra™, n = 326
inavir, n = 327

40th ICAAC, September 2000 – M98-863 Week 40 resul

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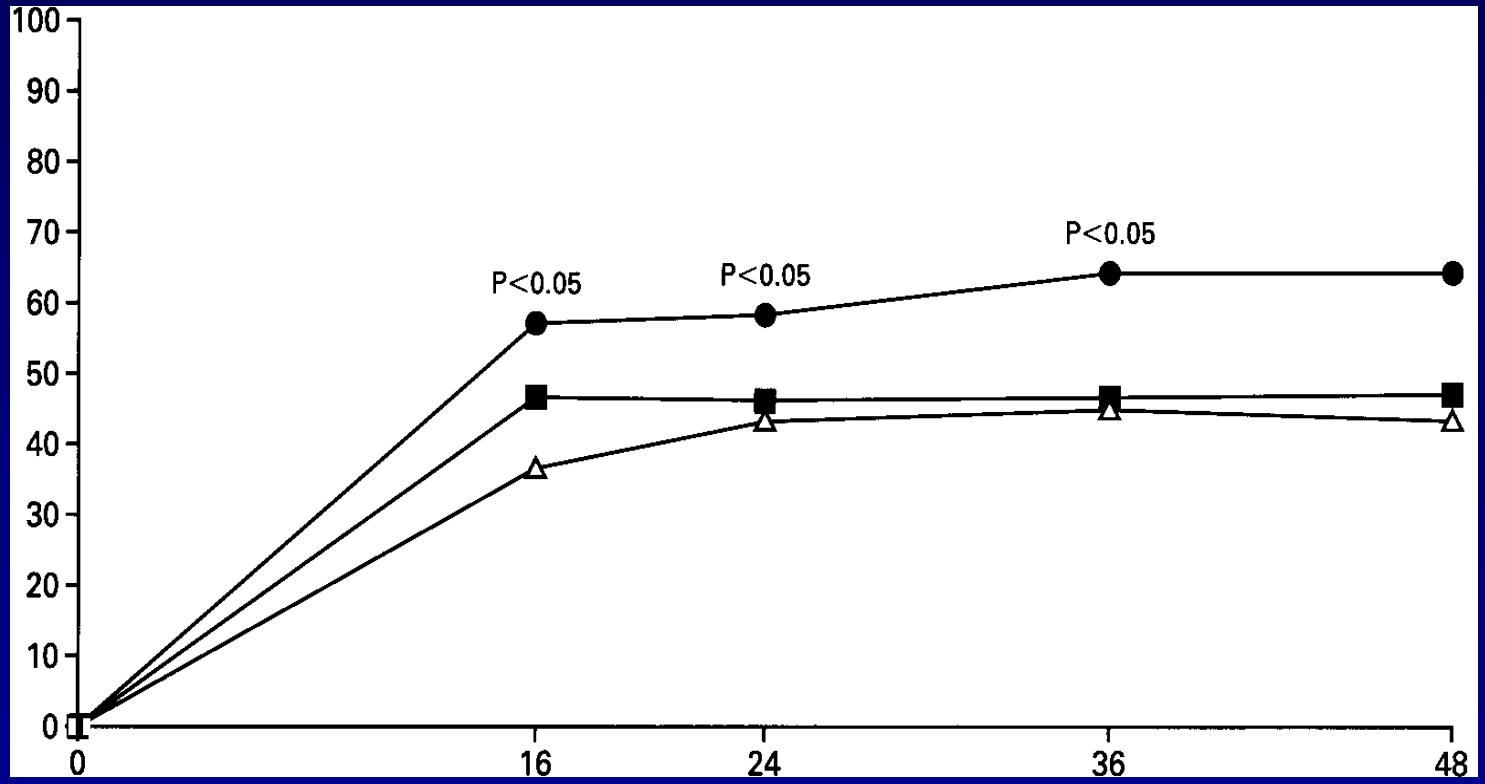
NNRTI vs Protease
AZT+3TC+IND vs. AZT+3TC+EFV
Percent of Patients with HIV RNA Below Assay Detection

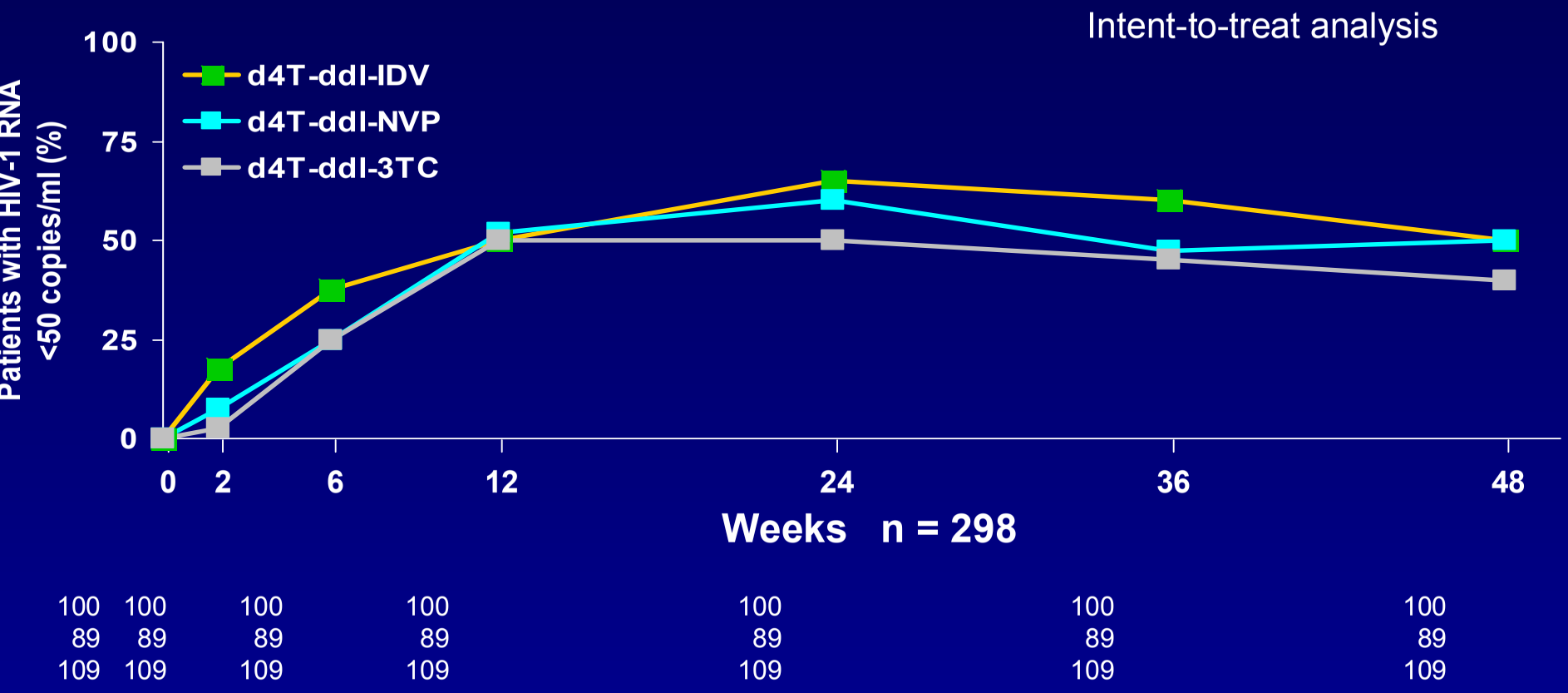


EFV/3TC

EFV/IND
IND/ZDV

dapted from Staszewski et al. *NEJM*. 1999.

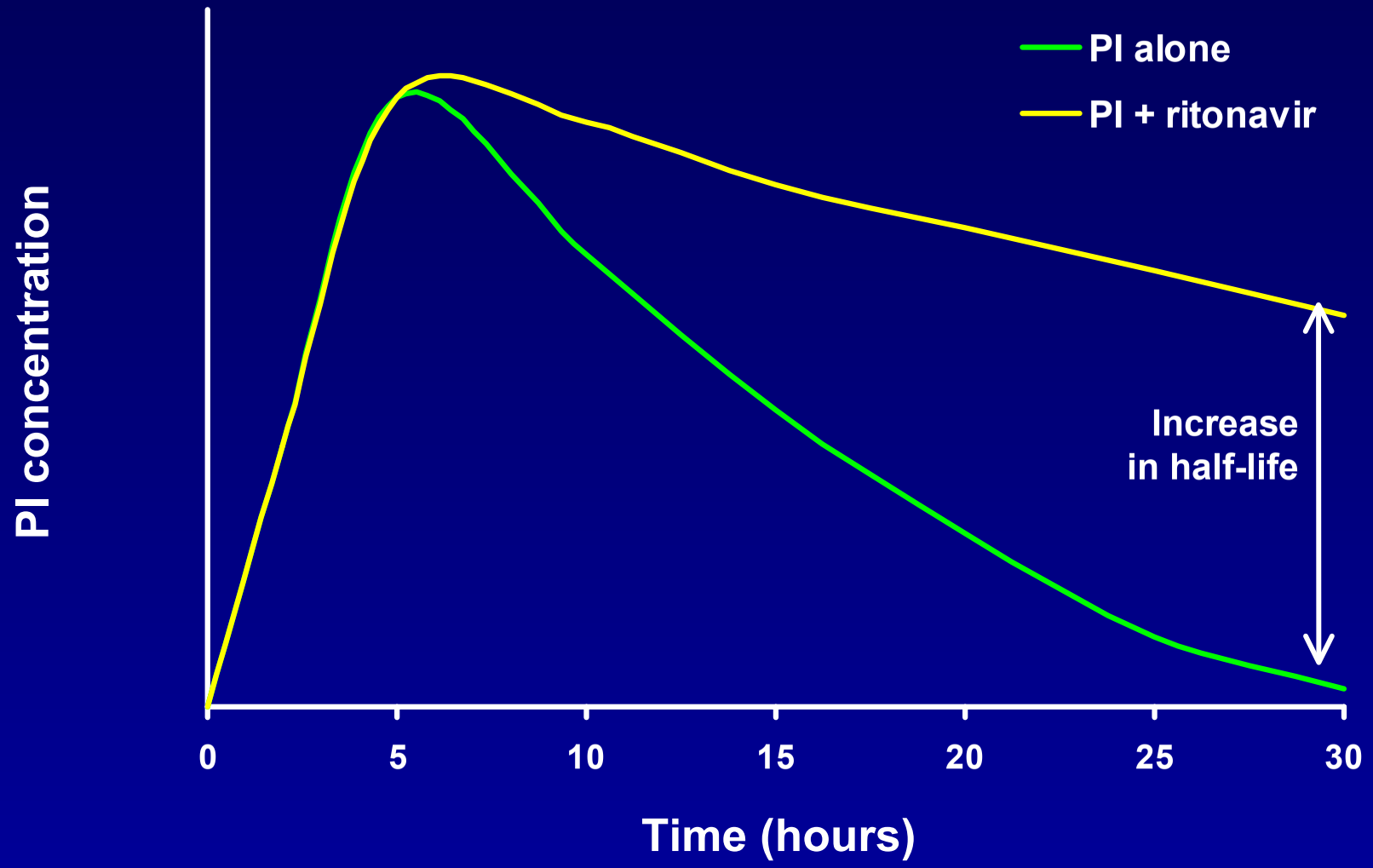
Atlantic trial – 48 weeks follow-up



Baseline viral load 4.25 $\log_{10}$ copies/ml, CD4 cell count 406/µl

uires K, *et al*. XIII IAC, Durban 2000. Abstract Lb46

Effect of ritonavir on saquinair, indinavir, lopinavir Half-life/Trough boosting



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Initial Therapy Regimens
Strategic Questions

- What to start with?
  - There are many good options
  - Individualise
  - Cost
- When to start?
  - More problematic- more controversial

Initiation of Antiretroviral Therapy: When to Start "The Golden Moment"

- Symptomatic established infection
  - AIDS or HIV related disease
- Primary infection?
- Asymptomatic infection?

Table 1

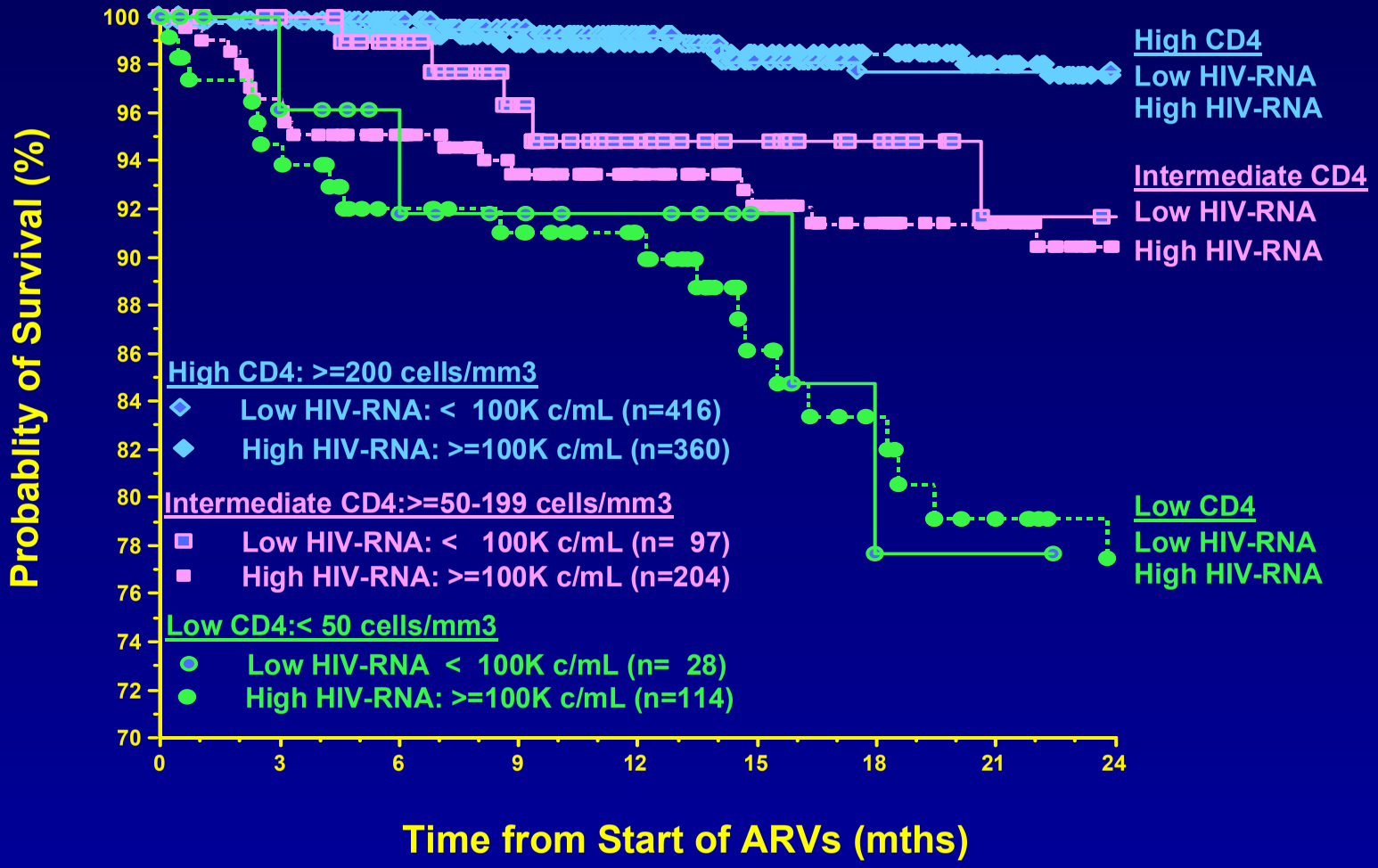
Relative Risk of Disease Progression or Death According to Proximal CD4+ Cell Count Tertile

CD4+ Tertile (cell/mm^3)	Unadjusted		Adjusted for proximal HIV RNA	
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
1 (<80)	12.8	6.2 to 26.6	7.0	3.3 to 15.0
2 (80-190)	3.2	1.4 to 7.0	2.4	1.1 to 5.3
3 (>190)	1.0	(ref. group)	1.0	(ref. group)
	Coeff* (SE): -.0131 (.0015)		Coeff* (SE): -.0104 (.0016)	

*coefficient corresponding to proximal CD4 (cells/mm^3)

Outcome in B.C. Cohort Using Combined CD4 & Viral Load Groups

Montaner et al 2000



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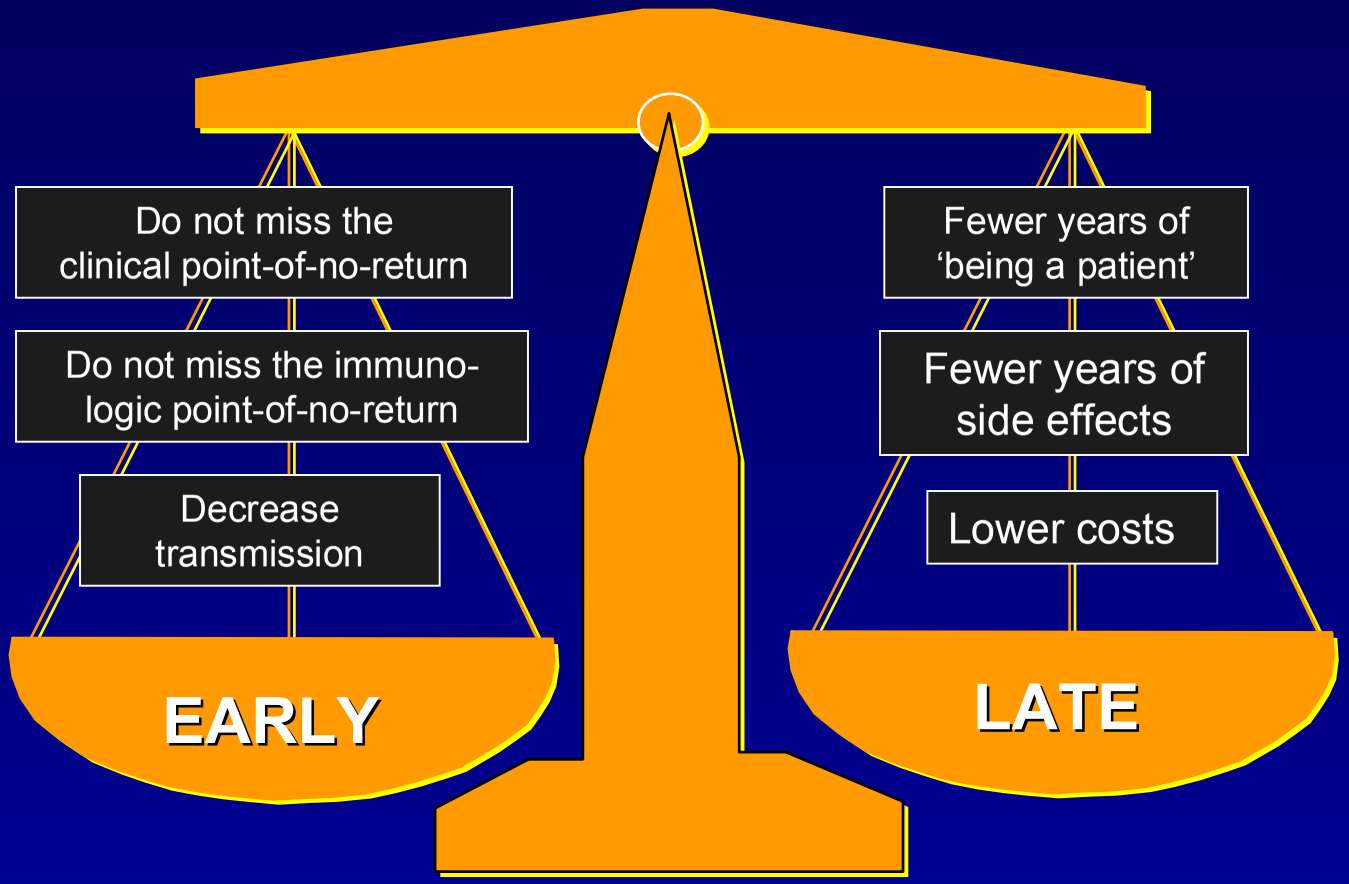
Indications for ART in the HIV-Infected ***Asymptomatic*** Patient

- **Clinical benefit has been demonstrated for patients**
  - **» w/ CD4 <200 mm^3**
- **– Most experts would *offer* therapy at a**
  - **» CD4 <350 mm^3 -(vl >30,000)**

Striking a balance:
When to start in the asymptomatic patient?



Treatment Failure
When to switch
"The silver moment"

- Clinical progression
- Unable to achieve virologic suppression
- Virologic rebound
- Toxicity/Adverse events

Treatment Failure

- Early
  - first or second failure
  - assess reason for failure
  - multiple options
  - goal still viral suppression
- Late
  - multiple failures
  - assess reason for failure
  - multi-drug resistance
  - few options
  - goal is maintain CD4 and clinical function

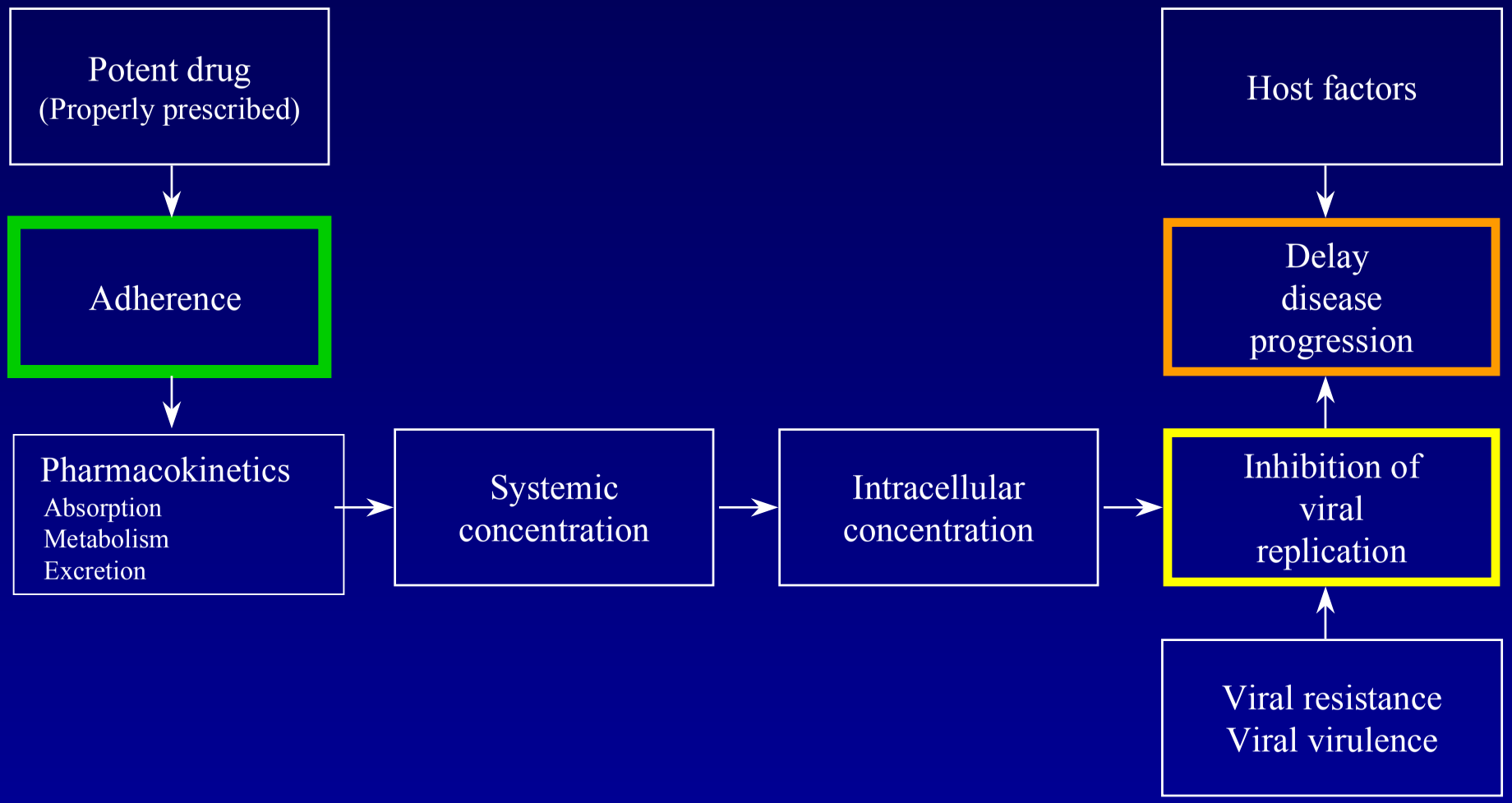
When to stop?
The "bronze moment"

- treatment interruption and cessation
- Early and often
- use clinical and life-event indicators
- toxicity should result in discontinuation
- increasing evidence for the sustained benefit even of "failed regimens"?

Adherence

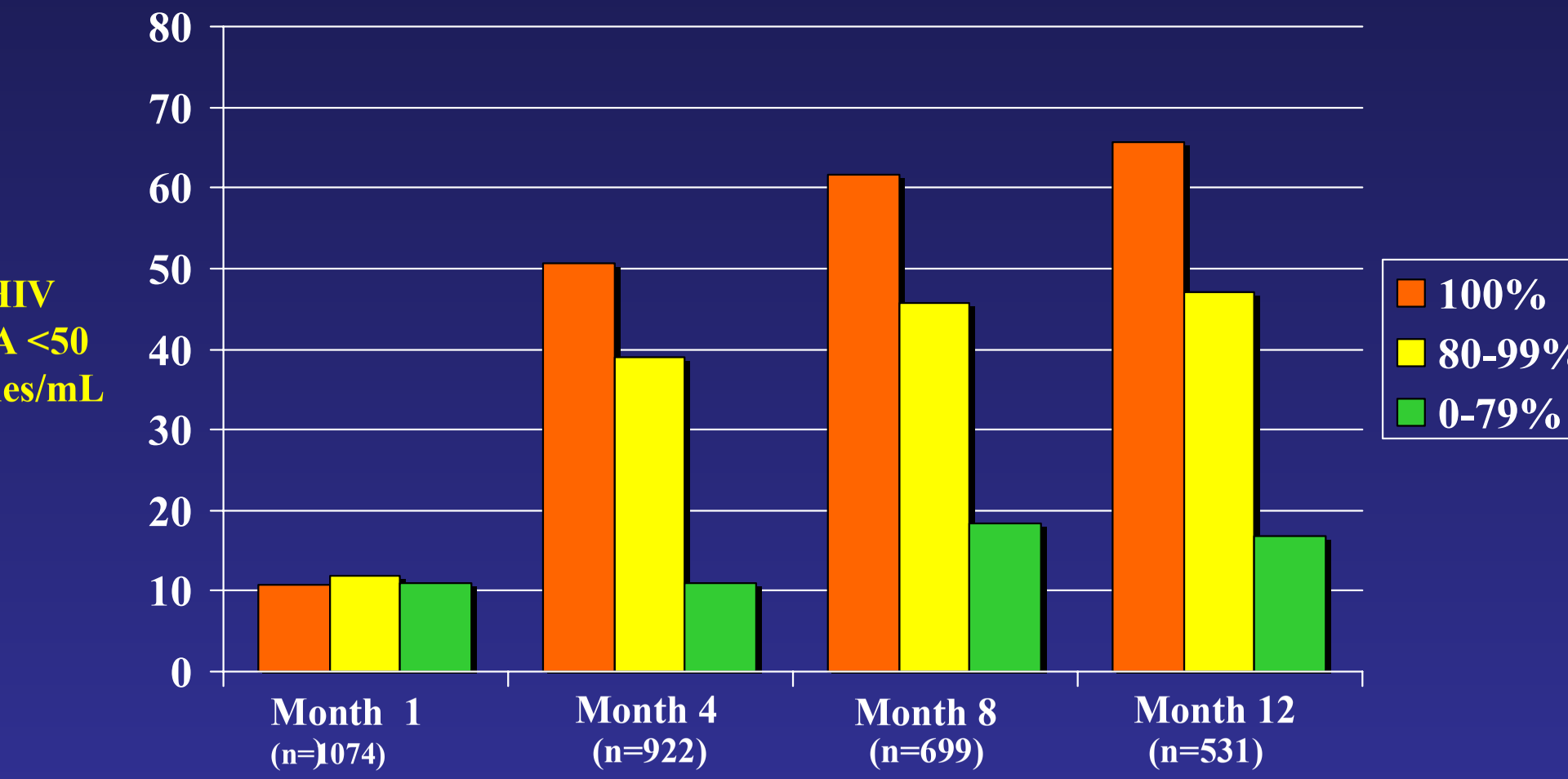
The Achilles heel of antiretroviral therapy

HIV Therapeutics
Drug Efficacy



Virologic Outcomes by Adherence Level

% HIV RNA <50 copies/ml



P<.005 at months 4,8,12

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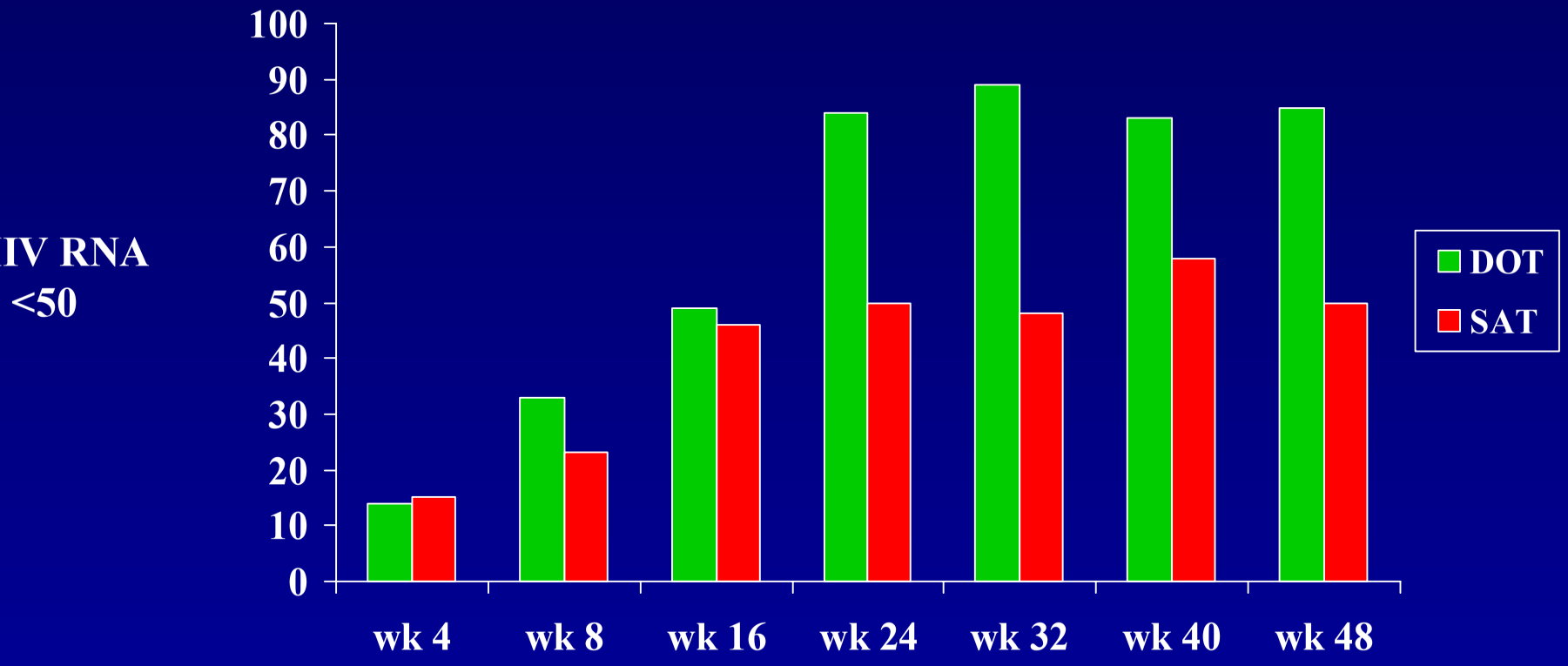
Directly Observed Therapy and RNA Decline

Fischl et al 7th CROI 2000

- Prisoners in 4 clinical trials by DOT or self administration (SAT)
- Proportion declines in HIV RNA($p<0.01$)



How to improve adherence?

Improving Adherence

- A trusting provider-patient relationship
- Education, Motivation
  - Social support network
  - Depression and substance abuse
- Development of treatment plan with patient
  - No antiretroviral emergencies
  - Simplest effective regimen
  - Provide medication taking skills


HAS SET THE REC
A LITTLE TOO ST

The future

- Provision of therapy more widely throughout SA
  - a practical and moral imperative
  - finding creative ways to begin and sustain
  - keep the pressure on
- Cheaper drugs
- Expanding expertise, building infrastructure and providing adherence support
- Address strategic and operational issues

All predictions are difficult, particularly when they involve the future

Dan Quayle

? George W