Adherence, Pharmacy Data & Survival in HIV-Infected Adults

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Financial Disclosure

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  - NIH/NIAID, DAIDS
    - RO1
    - K23
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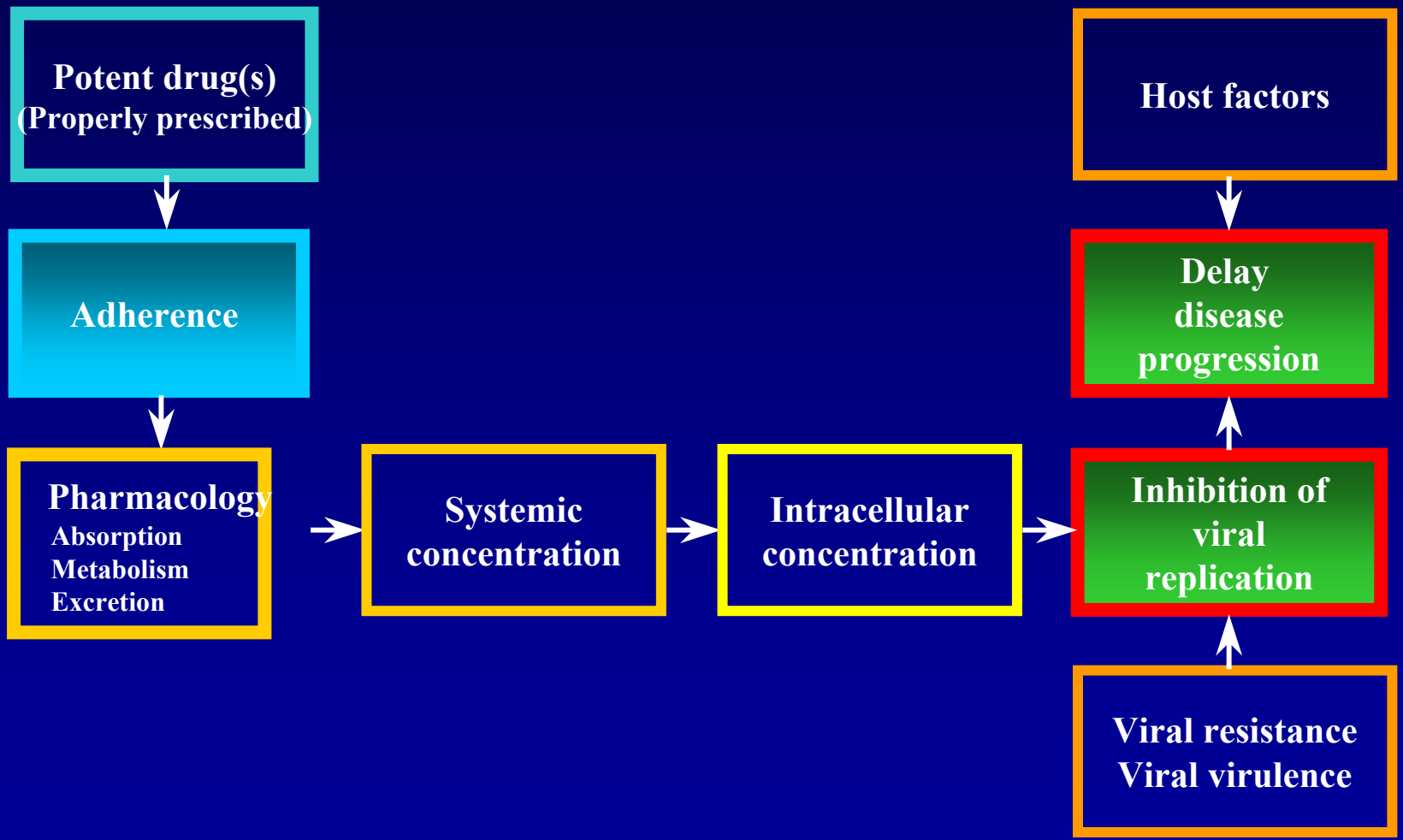
  - Glaxo Smith Kline
  - Bristol Myers Squibb
  - Aspen Pharmaceuticals

Adherence-Intersection of Biology and Behavior

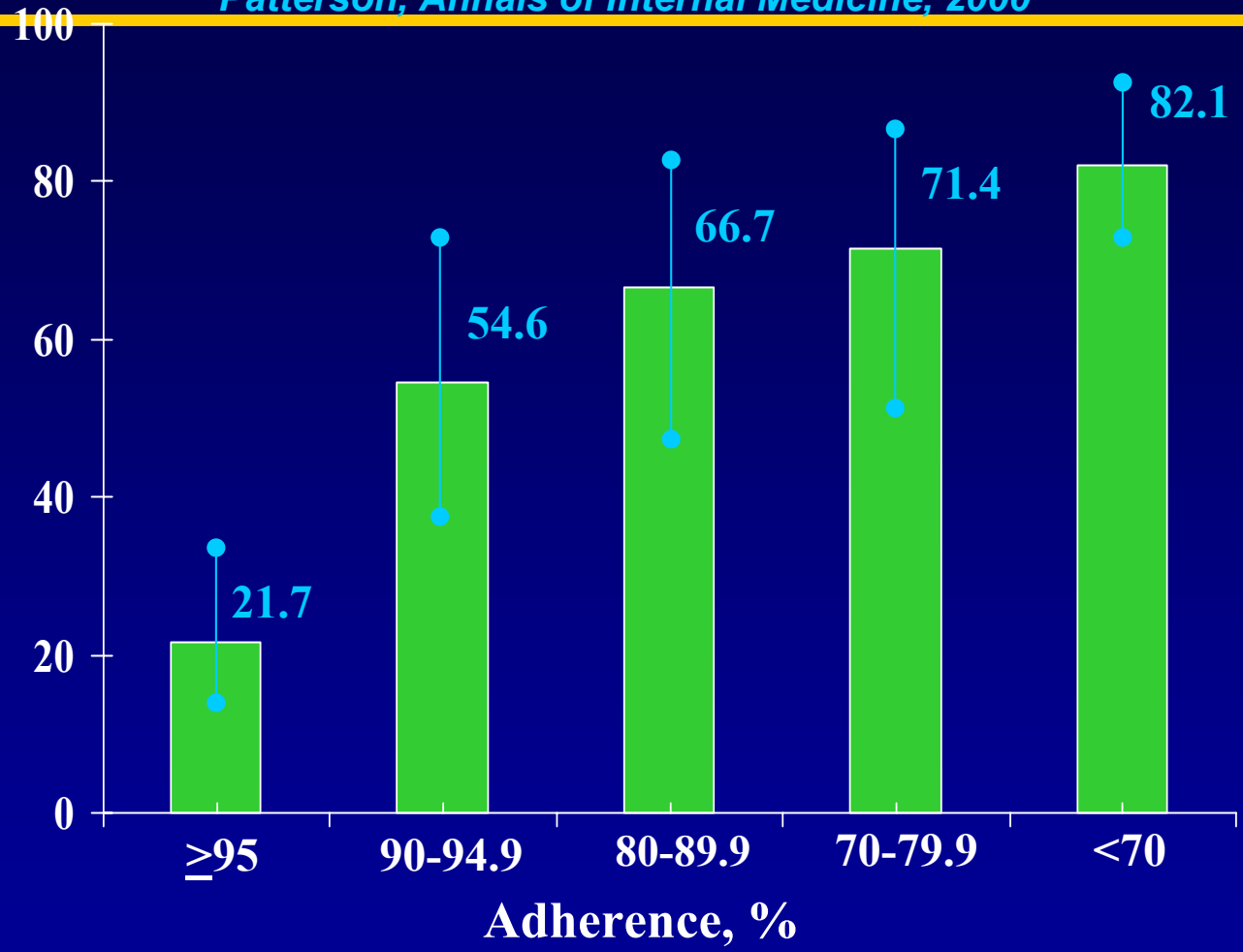
- Medical care- complex synthesis of biologic and behavioral expertise + social context and compassion.
- Medication adherence exemplifies this interaction and the central role that each plays in therapeutic outcome.
- For HIV disease, adherence to HIV medications is a major determinate of biologic, clinical and public health outcomes.

HIV Therapeutics
Determinants of Drug Efficacy



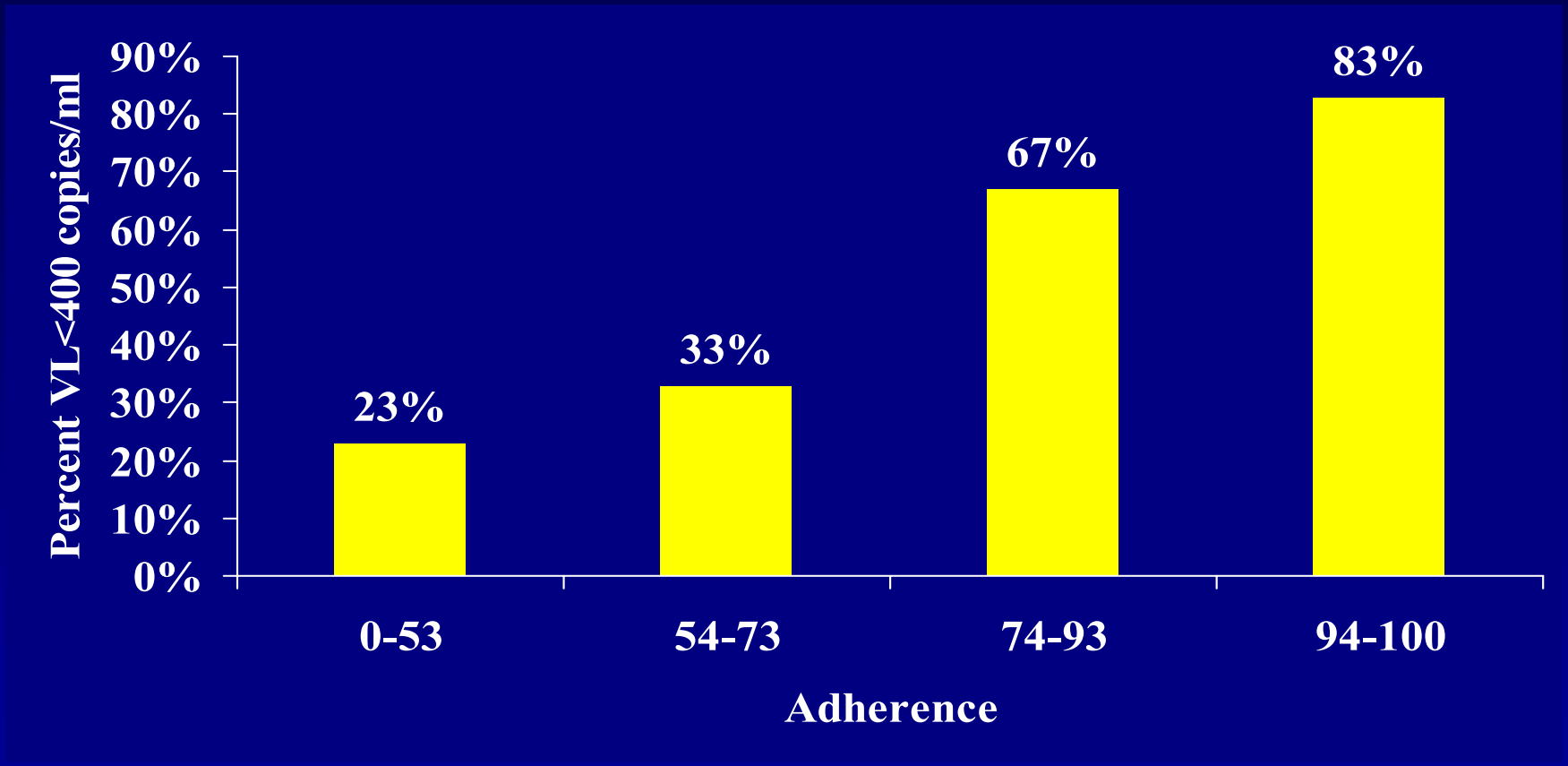
Adherence to antiretroviral therapy and virologic failure

Patterson, Annals of Internal Medicine, 2000



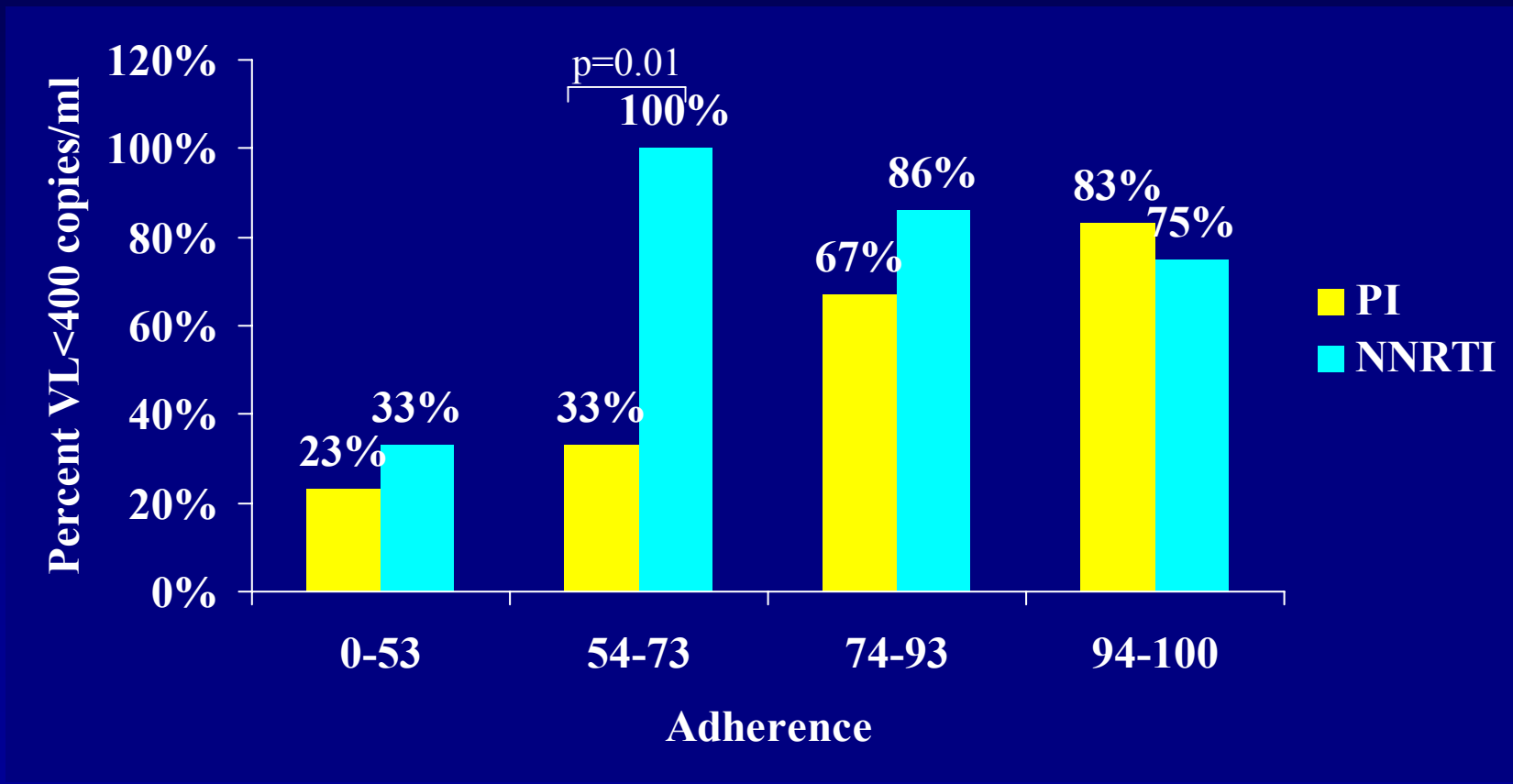
The degree of adherence was asignificantly associated with risk for virologic failure (P<0.001). Adherence of 95% or greater was associated with the lowest incidence of virologic failure.

# Proportion HIV VL <400 copies/ml by electronic medication monitor adherence
n=65



Bangsberg et al 12th CROI 2005 # 616

Proportion HIV VL <400 copies/ml by electronic medication monitor adherence n=65

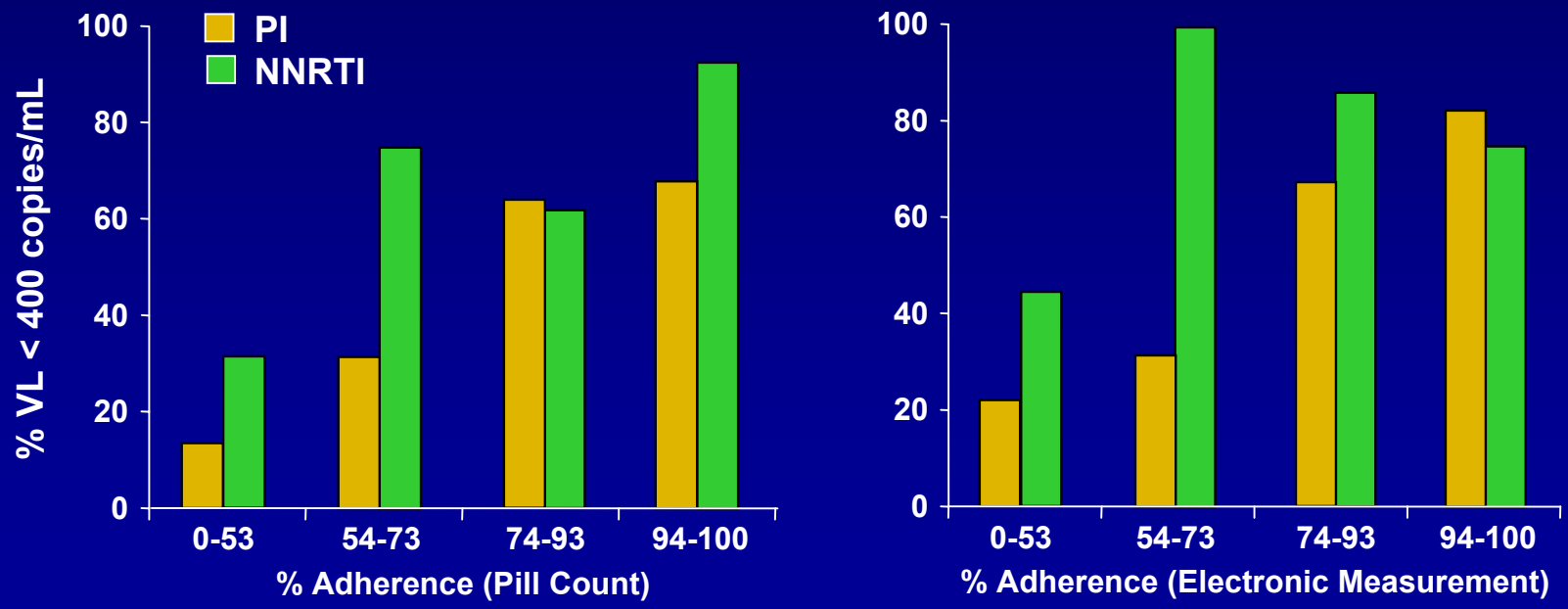


Bangsberg et al 12th CROI 2005 # 616

How Much Adherence is Needed for Viral Suppression?

- 109 indigent patients in San Francisco
  - 56 unboosted PI, 53 NNRTI regimen

- VL < 400 reliably seen with NNRTI if adherence > 54%, but with unboosted PI, only with very high adherence

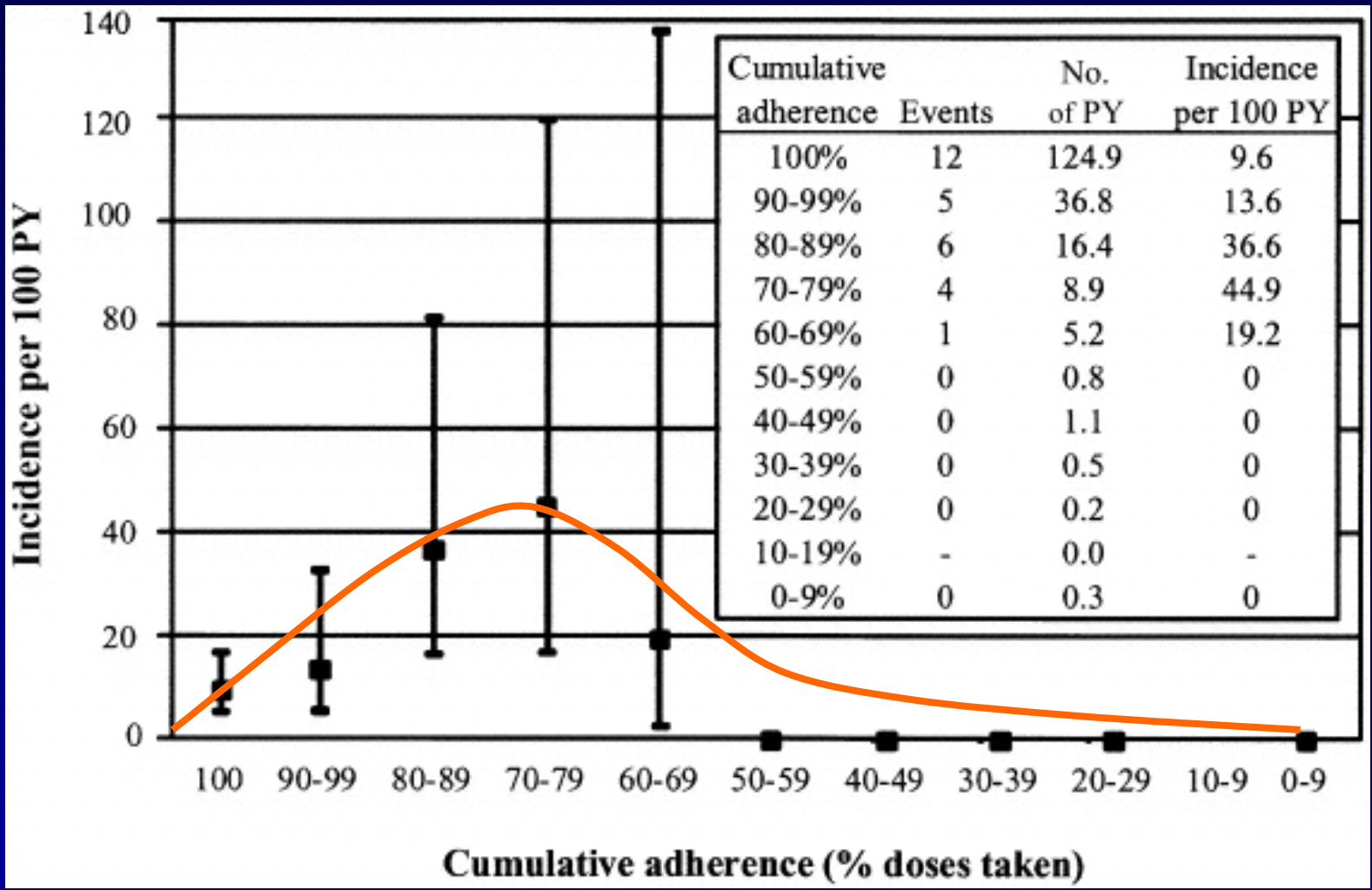


Bangsberg DR et al. CROI 2005

Adherence and resistance

- The relationship between adherence and resistance is evolving
- High levels adherence associated with more viral suppression
- For individuals with remaining detectable VL, resistance increases with increasing levels of adherence
- Different drugs (and drug combinations) may have different adherence/resistance dynamics
- High levels of adherence reduce progression of HIV but may contribute to increase in population based rates of resistance.
-

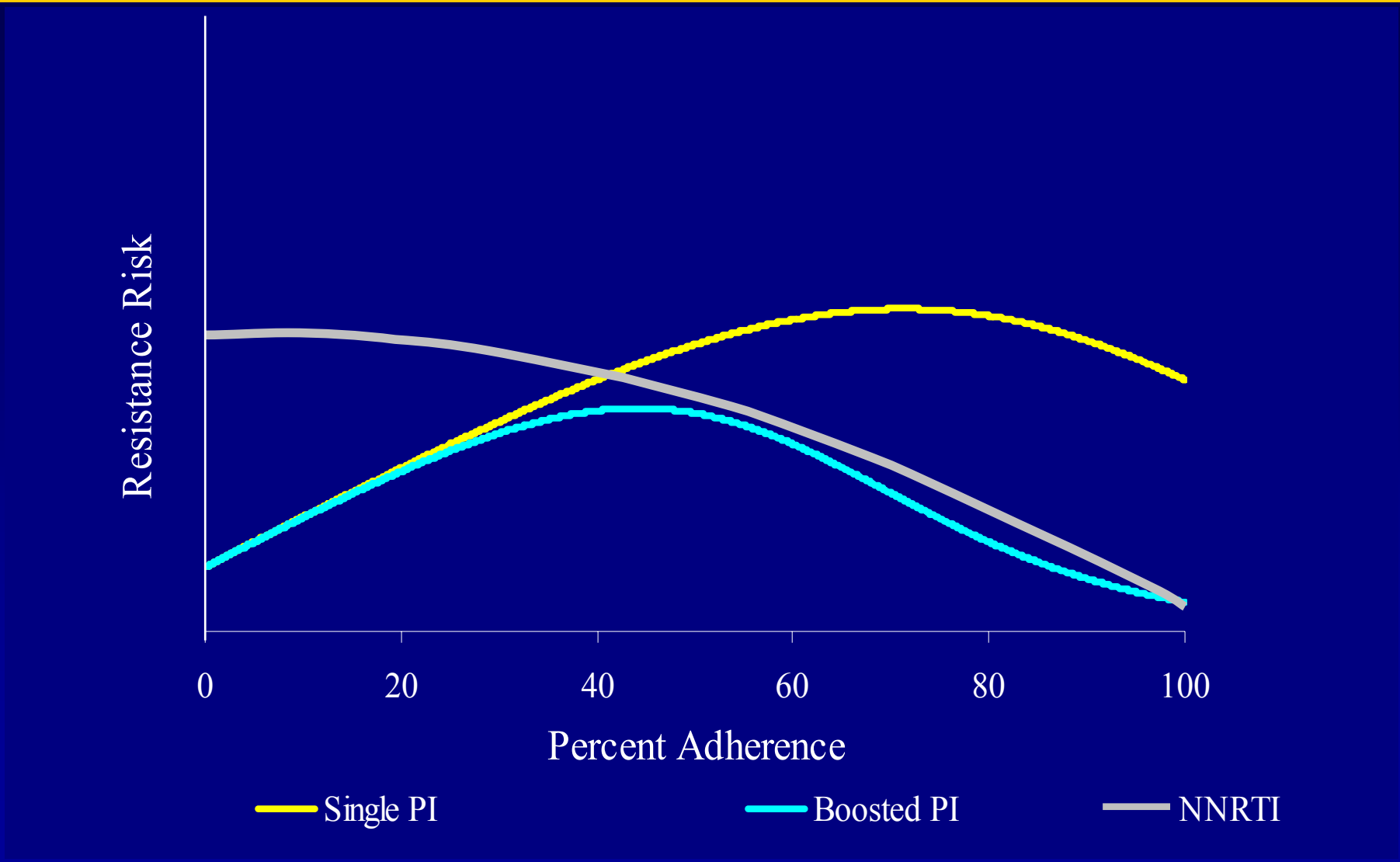
Adherence and risk of viral rebound with new drug resistance



Cumulative adherence	Events	No. of PY	Incidence per 100 PY
100%	12	124.9	9.6
90-99%	5	36.8	13.6
80-89%	6	16.4	36.6
70-79%	4	8.9	44.9
60-69%	1	5.2	19.2
50-59%	0	0.8	0
40-49%	0	1.1	0
30-39%	0	0.5	0
20-29%	0	0.2	0
10-19%	-	0.0	-
0-9%	0	0.3	0

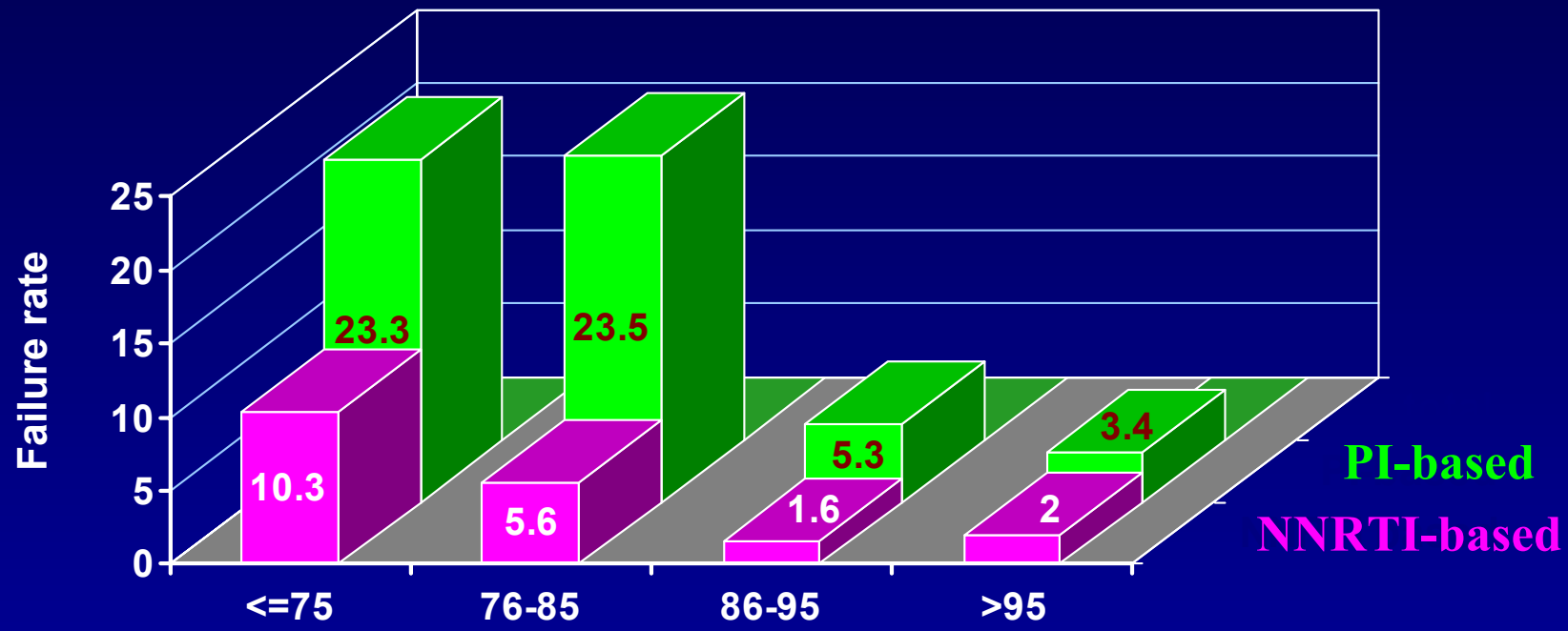
Sethi et al. Clin Infect Dis 2003; 37: 112

Resistance Risk by Adherence and Regimen Class



Bangsberg et al J. Antimicrob Chem; 2002 53(5):696-9.

Adherence and virological failure at month 6



Adherence: Patient report of % daily doses taken at the right time

Maggiolo F et al. CID 2005;40:158–163.

Classes of Antiretroviral Agents

Entry Inhibitors	NRTIs	Integrase Inhibitors	NNRTIs	PIs
T-20	Zidovudine	MK058	Nevirapine	Indinavir
CCR5	Didanosine		Efavirenz	Saquinavir
	Zalcitabine		Delavirdine	Ritonavir
	Lamivudine			Nelfinavir
	Stavudine			Amprenavir Fosamprenavir
	Abacavir			Lopinavir/rtv
	Tenofovir			Atazanavir
	Emtricitabine			Tipranavir

The Move Toward Simpler Regimens
3-drug regimens: 1996 and 2004

1996:

ddI + d4T + SQV

- -24 pills per day:
- -SQV: 6 q8h with food
- -ddI: 2 bid ½ hr ac or 2 hrs pc
- -d4T: 1 pill bid
- -significant long-term toxicity

2004:

TDF/FTC or ABC/3TC + EFV

- -2 pills qd
- -no food restrictions
- -no long-term toxicity anticipated

Levels of adherence found to be disappointingly low

- San Francisco
  - Bangsberg AIDS 2000 **67%**
- Pittsburgh
  - Paterson An Int Med 2000 74%
- Los Angeles
  - Liu Annals Int Med 2001 63%
- New York City
  - Arnsten CID 2001 57%
- Baltimore
  - Lucas JAIDS 2001 73%
- Philadelphia
  - Gross AIDS 2001 79%

Reported HAART Adherence Across Sub-Saharan Sites

Study	N	Duration	Method	Adherence Rate
Orrell et al. AIDS 2003	289	12 Mos	Pill count	93.5%
Weiser et al. JAIDS 2003	109	6Mos	Self-Report	74%
Laniece et al. AIDS 2003	158	36Mos	Self-Report	91%
Nachega et al. AIDS Res Hum Retr 2004	66	18Mos	Self-Report	88%

Reasons for Missing Doses of Antiretroviral Therapy

US

Chesney

- Simply forgot
- Slept through dose
- Away from home
- Change in routine
- Busy with other things
- Too sick
- Depressed

Africa

Weidle, Orrell, Nachega, Brown,

- Forgot
- Away from home
- Schedule difficulties
- Ran out of pills
- Cost
- Home language
- Fear of stigmatization by sexual partner

HAART Adherence in sub-Saharan Africa

- Rates of adherence are better-than in developed countries.
  - Africans are better medication adherers
  - Maybe too early to tell
    - Precious resource
    - Highly selected populations
    - Short term studies
    - Starting with better regimens
    - Positive results reported
  - Early good results are encouraging but not a reason for complacency

Measurement Options

- Direct observation
- MEMS Caps (Electronic diaries)
- Pharmacy Refill data
- Pill counts
- Self-reports
- Drug levels
- Provider assessment

DOT: PROS ☺!

- Direct observation therapy
  - Definitively externally verify a dose taken
  - Can be performed by variety of individuals
  - Especially easy in care facilities

Pharmacy Data

- Advantages
  - Only choice for retrospective studies
  - Can assess short or long-term behavior
- Disadvantages
  - No intra-interval information
  - Removed from actual drug taking
  - May not capture prescriptions from other sources
  - If automatic refills, data useless

DOT: CONS ☹…

- "Fool's gold" standard
  - Packaged as an intervention so not useful for observational studies
  - Not generalizable for behavioral studies
  - Need other measure for control group
  - Stigma/confidentiality issues

Electronic Diaries

- Advantages
  - Full variability of pill taking
  - Less sensitive to overestimates
  - Short and long term behavior
- Disadvantages
  - Inconvenience
  - May suffer from underestimation
  - Cost

Pharmacy Data

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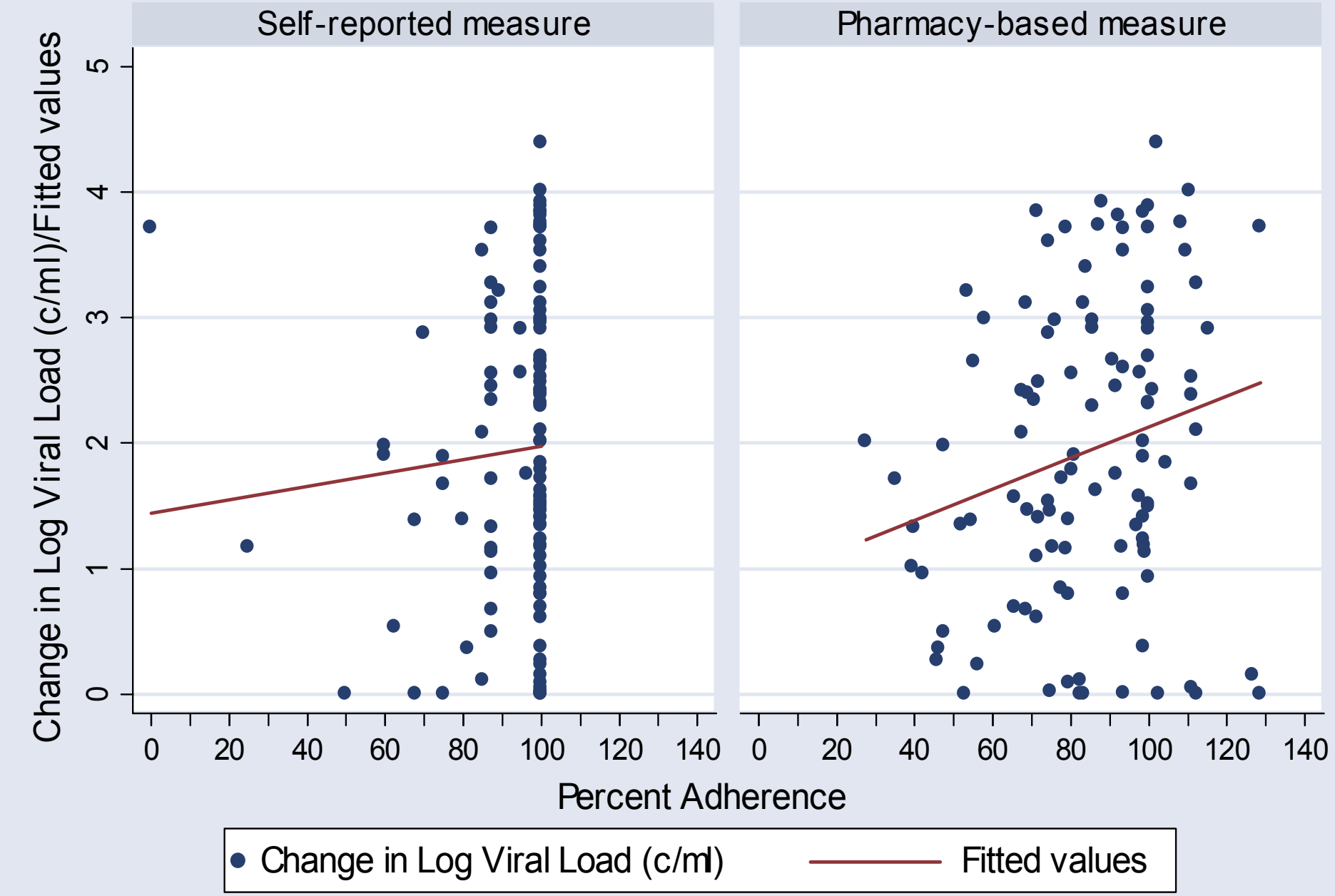
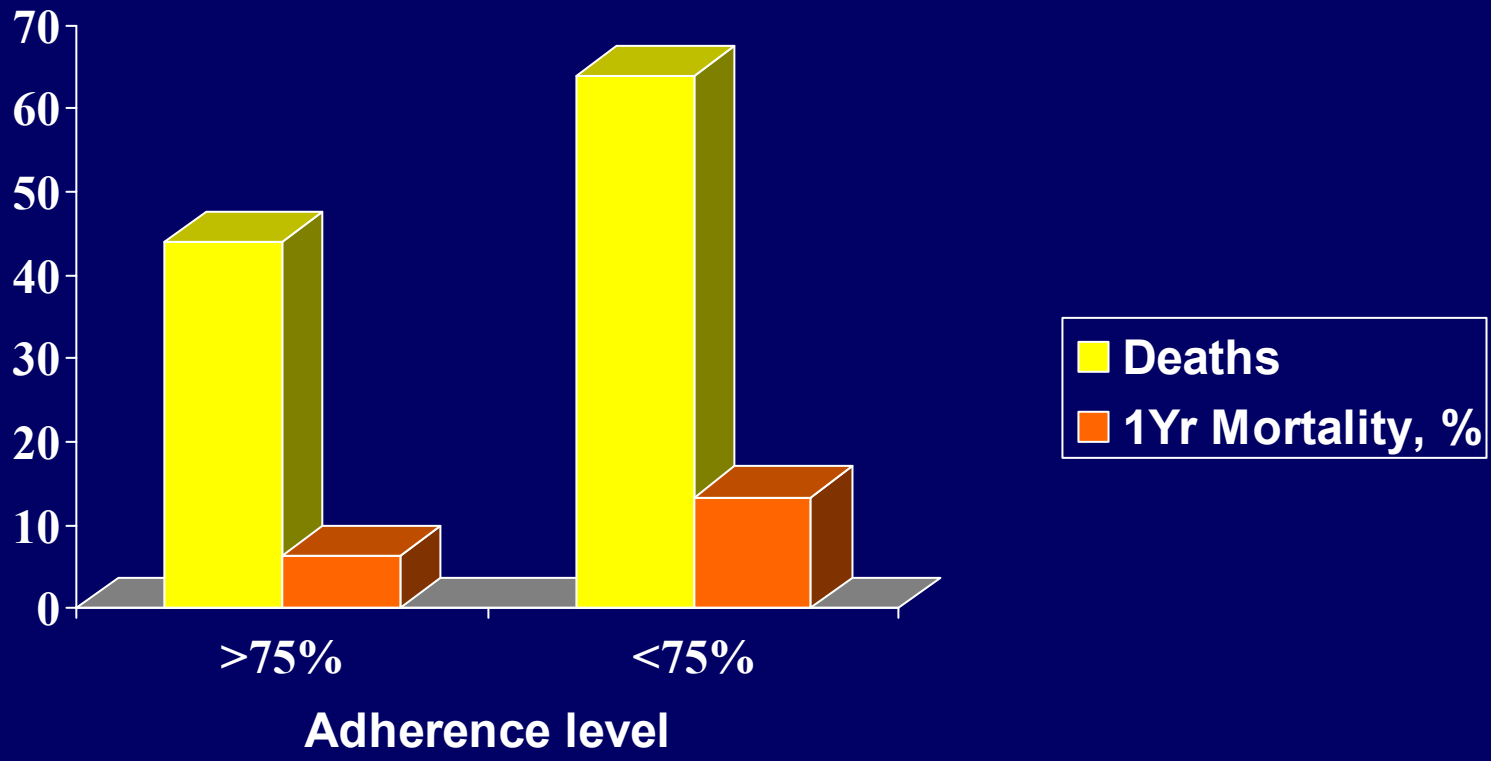


Entire cohort, N=110

Pharmacy Refill Adherence and Subsequent Mortality in Patients Starting HAART (N=1280)

p<0.001



Hogg et al. AIDS 2002, 16: 1051-58

Self-reports

- Advantages
  - Easy to obtain
  - Minimal cost
- Disadvantages
  - Overestimate true adherence
    - Even if non-adherence reported
      (Wagner GJ, AIDS Care 2000)
  - Only short-term exposure accurate
  - Limited variability over time

Self-Reports Measures

- Haubrich/CCG
  - Classification by centile over 4 weeks
- Chesney/ACTG
  - Missed doses over prior 4 days
- Walsh
  - VAS over prior month
- Variations

Drug levels

- Advantages
  - No assumptions about behavior
  - “Hard” data for skeptics
- Disadvantages
  - If short half-life: data re: last dose only
  - Variability in drug taking not assessed
  - Cost

Validity of Drug Levels

- Untimed measures of serum PIs/NNRTIs levels
  - Poor sensitivity/fair specificity (Liechty CA et al., AIDS 2004)
  - Additive to pharmacy refill data (Harrigan PR et al., JID 2005)
- Indinavir in hair (Bernard L et al. AIM 2002)
  - Routine access not available

Drug levels

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RECAP

- DOT is gold standard
  - limited utility
- Other methods have strengths and weaknesses depending on setting
  - MEMS most sensitive to non-adherence
  - Self-reports most specific
  - Pharmacy data useful for large populations or retrospective studies
- Challenges still exist
  - lumping of drugs, populations
  - relevant outcome: adherence, suppression, resistance, survival

HAART Adherence Assessed by Pharmacy Claims Predict Survival in HIV-infected South African Adults

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Hypothesis

Our hypothesis was that a high rate of consistently filled pharmacy claims would be predictive of better survival rates in HIV-infected South African adults.

Nachega J, Hislop M, Dowdy D. et al., CROI 2005, Ab#25, Boston, MA

Methods I

- Evaluation of records from HIV-infected enrollees in Aid for AIDS (AfA) between Jan 1999 and Mar 2003.
- AfA is a disease management program available to beneficiaries and employees of contracted medical insurance funds and companies in Southern Africa.
- Inclusion criteria: age >18; HAART naïve; minimum HAART duration: 6 months.
- Adherence expressed as % (number of months with claims submitted, divided by number of complete months since submitting the first claim for HAART).

Methods I

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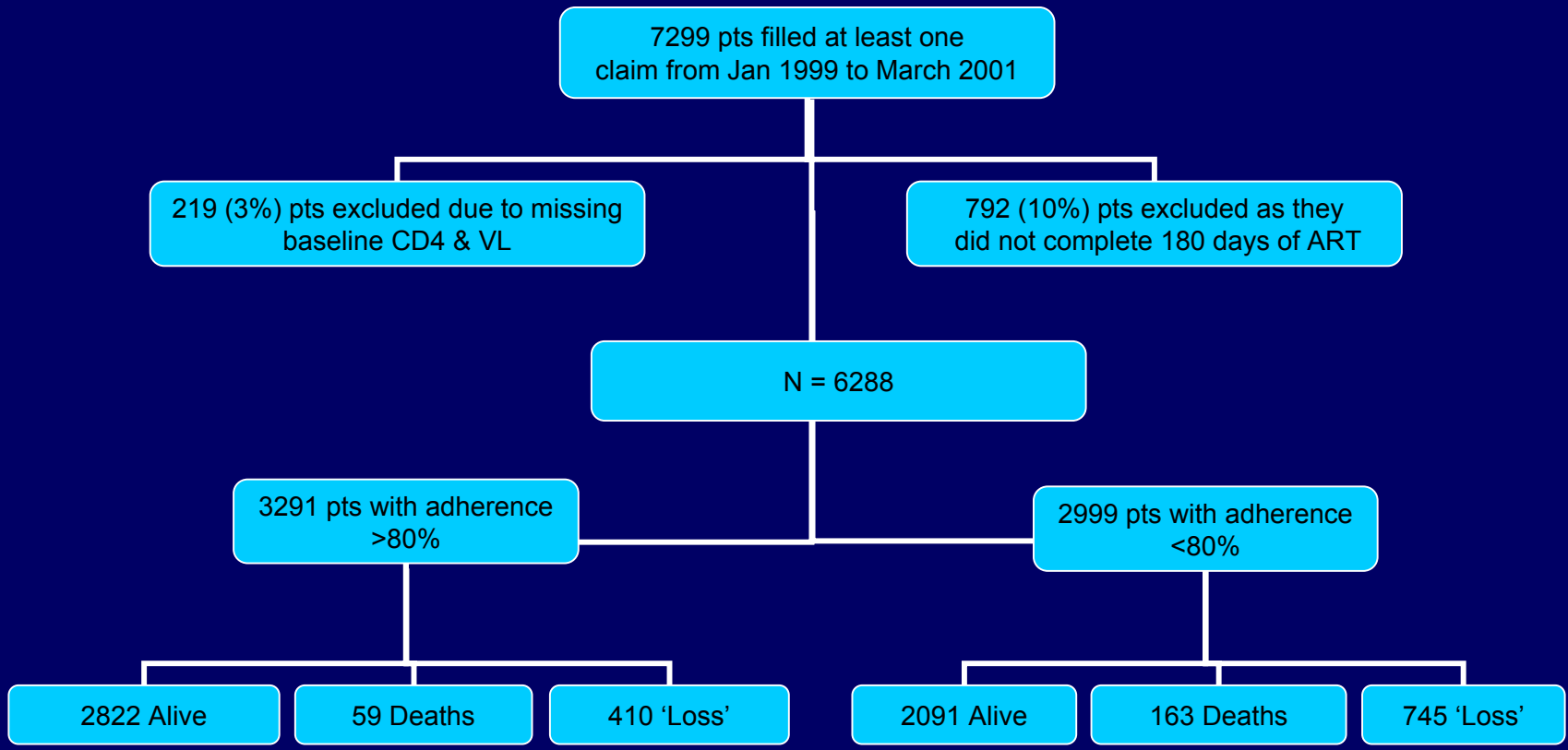
Methods III

- Analysis was restricted to patients with at least 6 Months of follow up after their initial pharmacy claim.
- Chi-Square Statistics and Univariate Logistic regression were used to identify predictors of viral suppression
- Adherence rates were compared against the reference stratum (>95% adherence) using Chi-square statistics for trend.
- Multivariate Logistic Regression was used to model the individual and simultaneous effects of baseline variables and HAART adherence on viral suppression.

Study Profile & Outcomes



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Baseline Characteristics by Adherence at HAART Initiation (N=6288)

	Adherence <80% N=2990 (47.6%)	*Adherence >80% N=3298(52.4%)*	*P-Value*
Median (IQR) Age	**35.8 (31.1-41.4)**	**36.3 (31.6-42.0)**	**0.01**
Gender			**0.001**
▪ **Male, %**	**42.0**	**37.2**	
▪ **Female, %**	**58.0**	**62.8**	
Race			**0.7**
▪ **Black, %**	**97.1**	**96.8**	
▪ **White, %**	**1.7**	**2.0**	
▪ **Other, %**	**1.2**	**1.2**	
Median (IQR) CD4+ (cell/mm^3)	**149 (66-228)**	**148 (64-227)**	**0.67**
Median (IQR) Log_{10}V L (c/ml)	**5.17 (4.6-5.6)**	**5.15 (4.6-5.6)**	**0.56**

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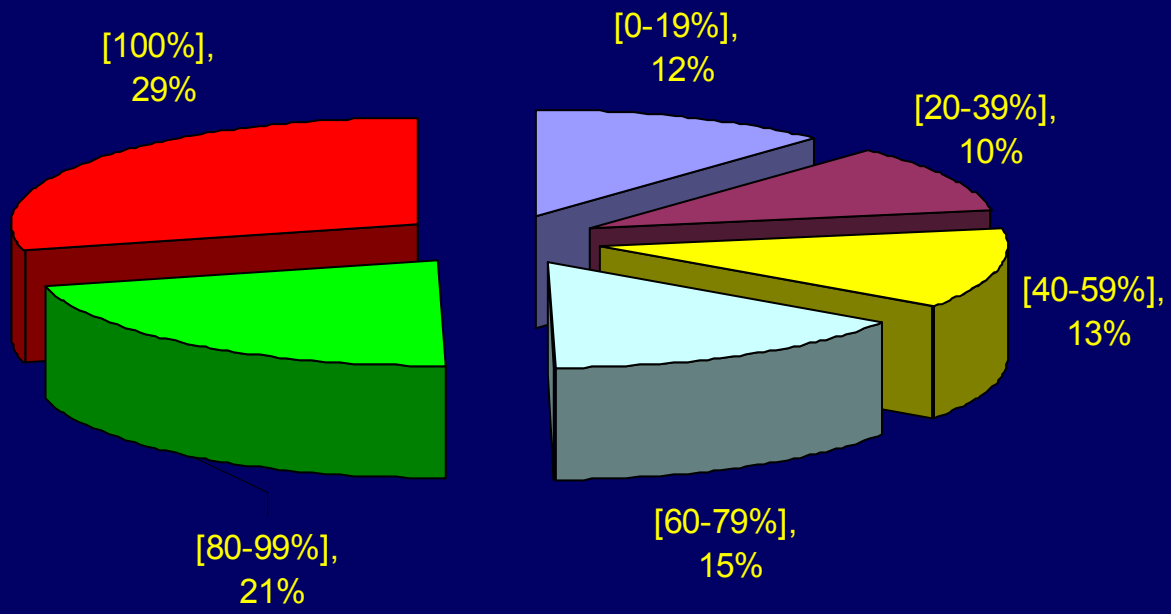
Patient % by Adherence Stratum
N= 6288



Nachega J, Hislop M, Dowdy D. et al., CROI 2005, Ab#25, Boston, MA

Bivariate & Multivariate Analysis of the Baseline Factors Associated with Survival (N=6288)

Variable	*Crude RH(95% CI)*	*Adjusted RH(95% CI)*
Adherence		
▪ <80%	3.01 (2.24-4.06)*	3.23 (2.37-4.39)*
▪ >80%	1.00	1.00
Gender		
▪ Female	1.00	1.00
▪ Male	1.50(1.15-1.95)*	1.22(0.39-1.59)
Race		
▪ Black	1.00	
▪ White	1.34 (0.59-3.03)	
▪ Other	1.23(0.39-3.85)	
Age (yrs)		
▪ 18-34	1.00	1.00
▪ 35-44	1.21(0.91-1.61)	1.13(0.84-1.51)
▪ 45-54	1.06(0.68-1.64)	1.02(0.66-1.59)
▪ >55	2.03(0.98-4.18)	2.00(0.96-1.95)
CD4+ (cell/mm^3)		
▪ <50	6.00(4.03-8.92)*	5.13(3.42-7.72)*
▪ 51-200	2.15(1.45-3.22)*	1.86 (1.23-2.80)*
▪ >200	1.00	1.00
Log_{10}V L (c/ml)		
▪ <4	1.00	1.00
▪ 4-4.99	1.57(0.74-3.31)	1.37(0.65-2.90)
▪ >5	2.93(1.44-5.95)*	2.93(0.98-4.11)

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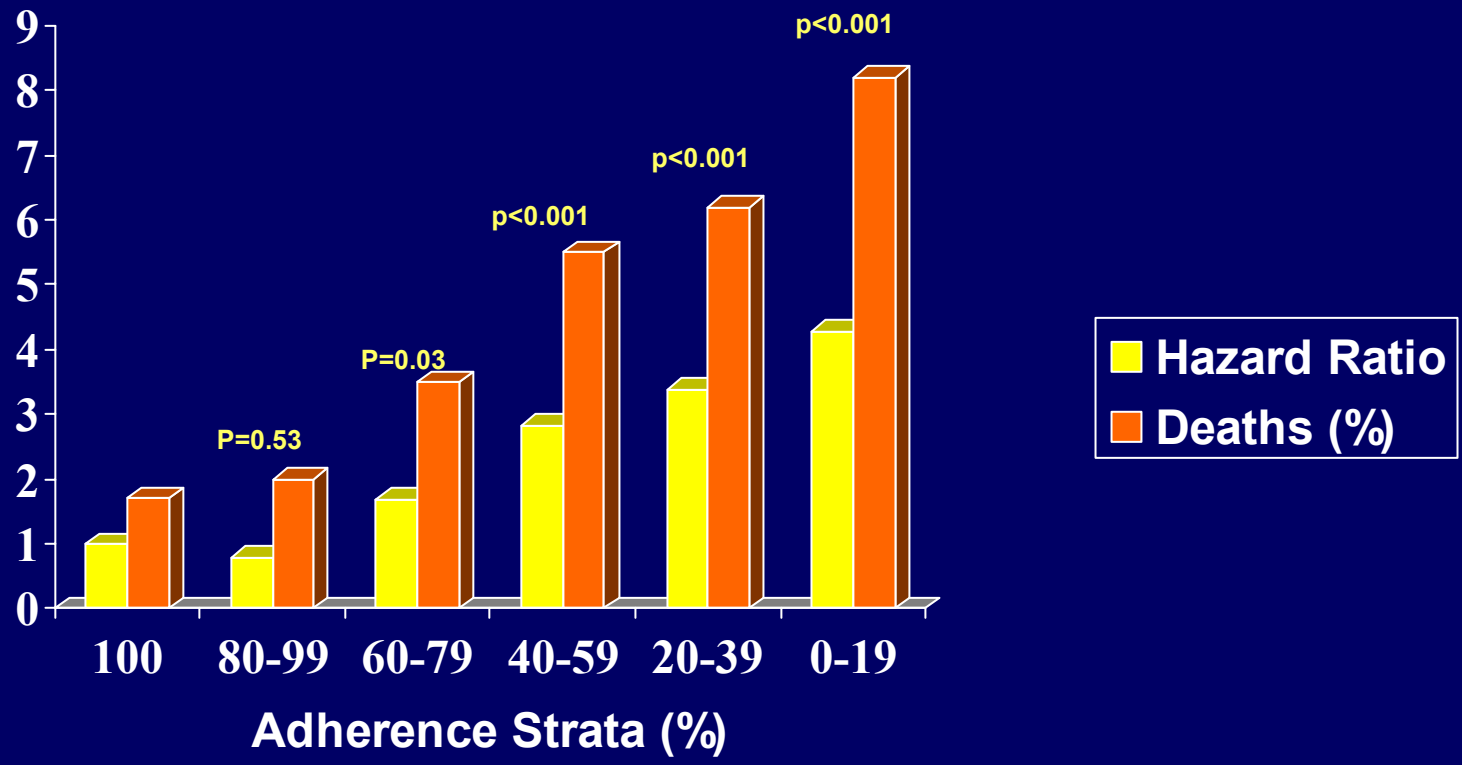
Cox's Proportional Hazard Analysis by Level of Adherence I



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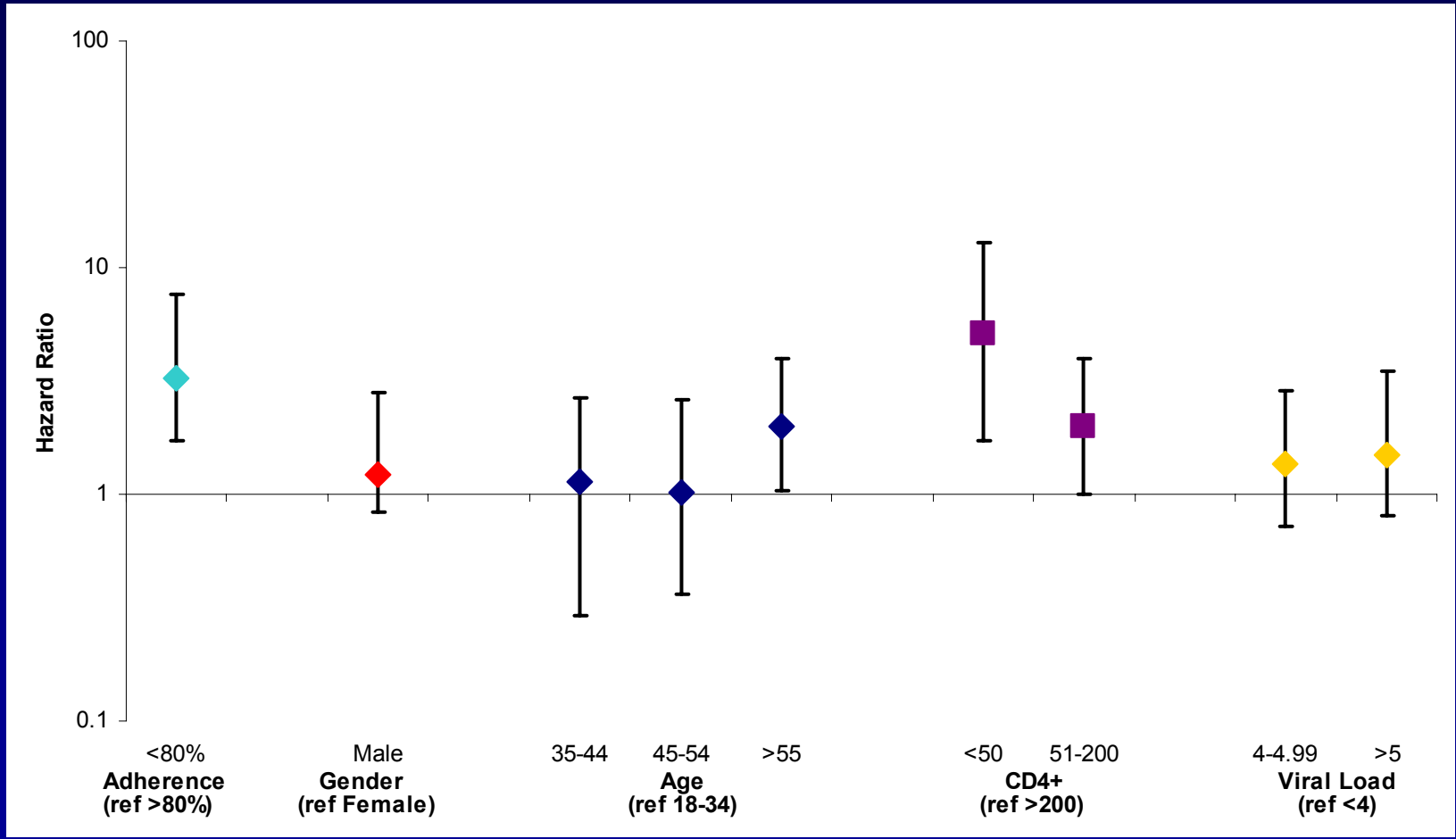
Multivariate Analysis of the Baseline Factors Associated with Survival (N=6288)



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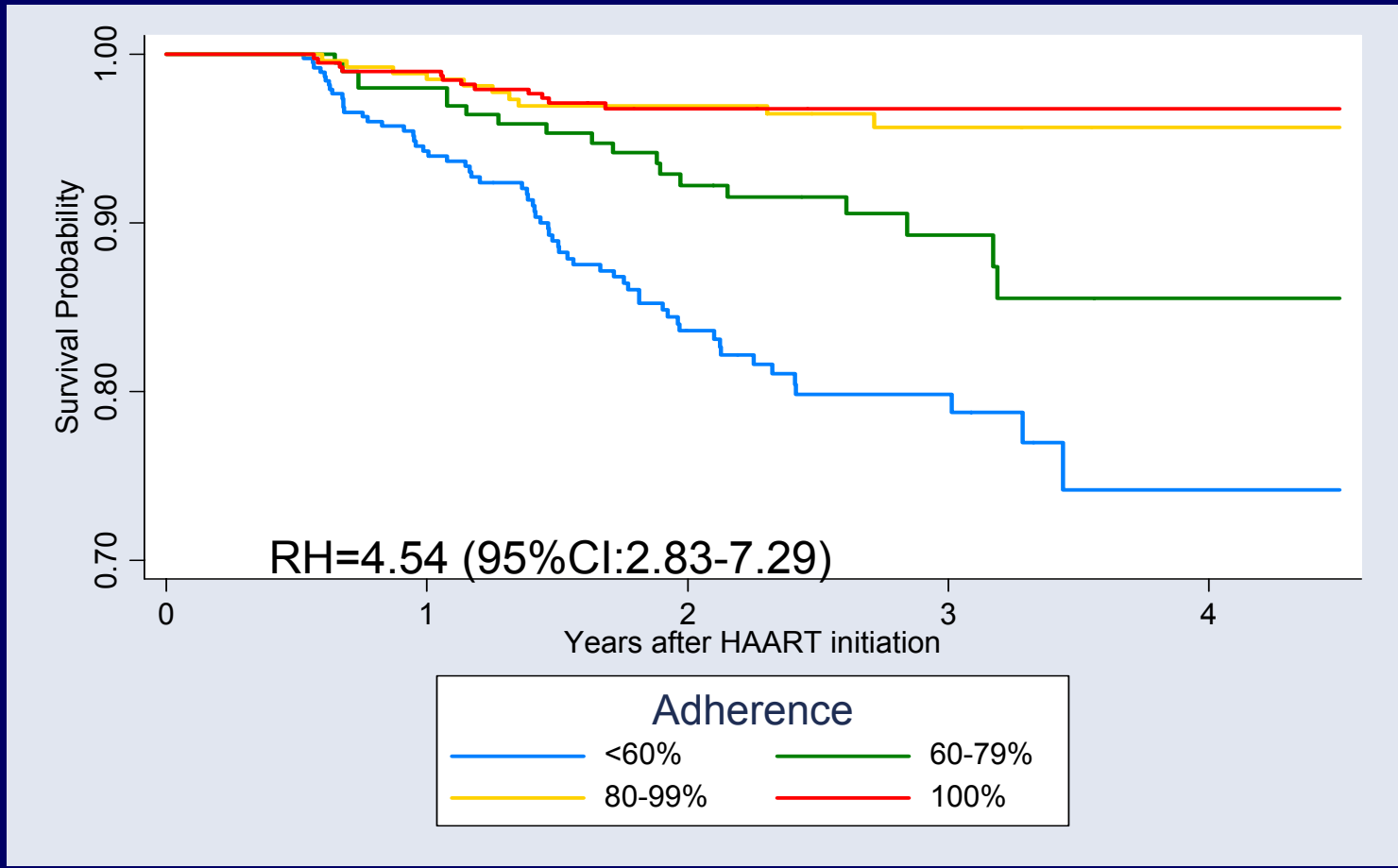
Cox's Proportional Hazard Analysis by Level of Adherence II

Adherence	*Hazard Ratio* (95%CI)	P-Value
>80%	1.00	
<80%	3.01 (2.24-4.06)	<0.001

Nachega J, Hislop M, Dowdy D. et al., CROI 2005, Ab#25, Boston, MA

Survival by Adherence Level
CD4 counts < 50



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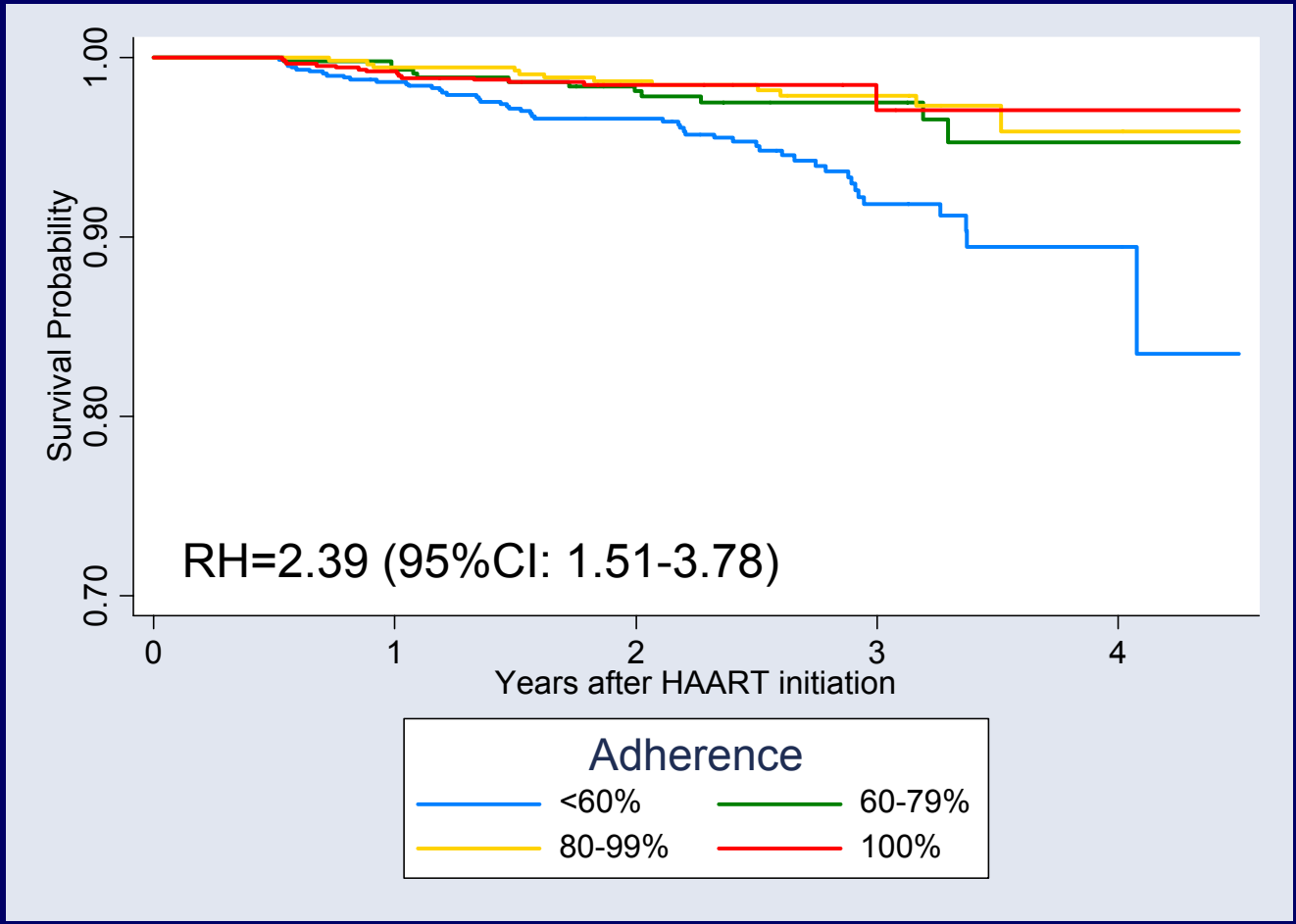
Survival by Adherence Level
CD4 = 50-200



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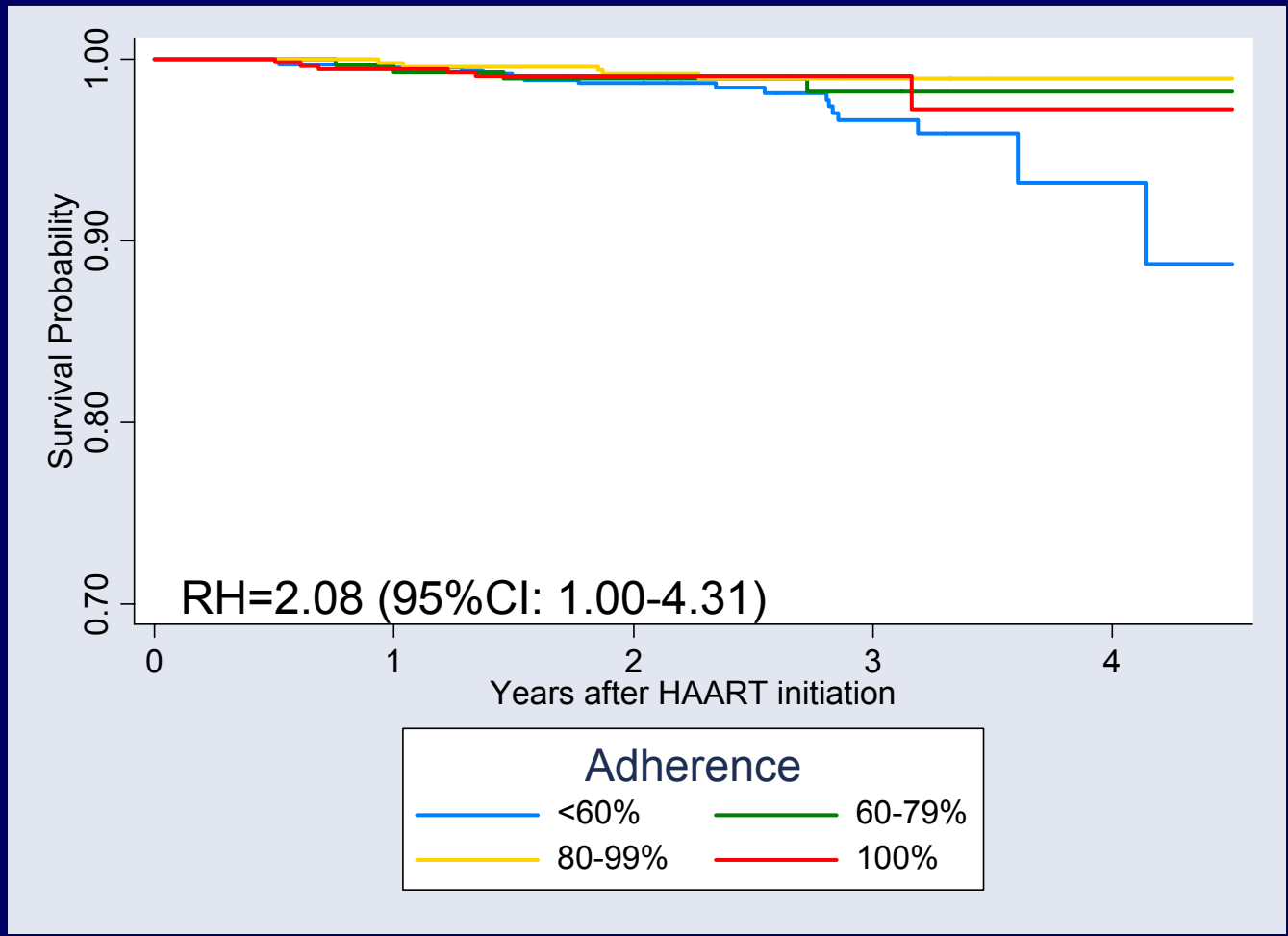
Survival by Adherence Level
CD4 > 200



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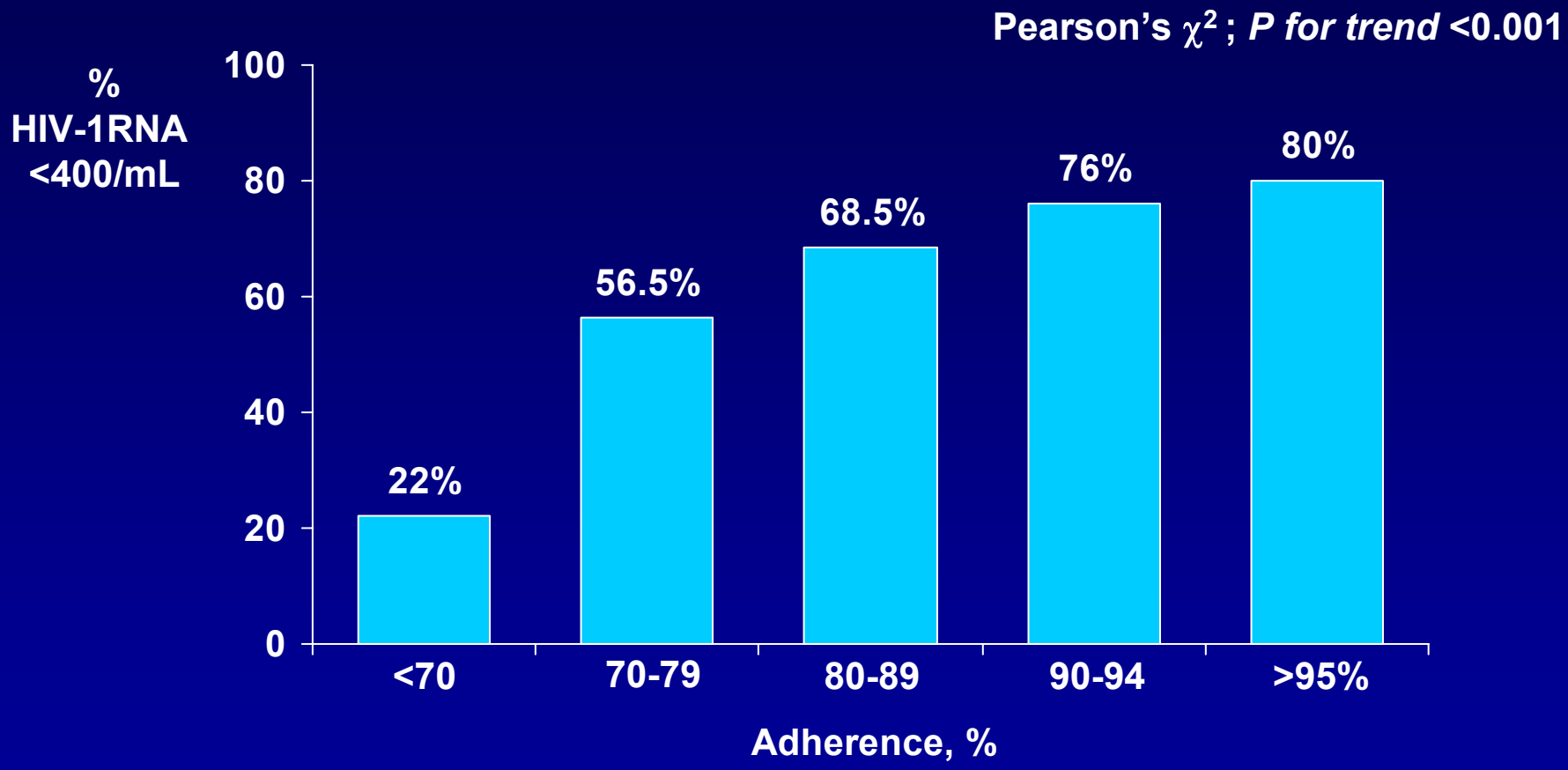
Adherence to NNRTI-Based HAART & Virologic Outcomes in South Africa

Aim: To Assess whether high level of adherence is consistently required for virologic suppression for patients on NNRTI-based HAART as First Line

3,325 HIV-infected Adults enrolled in a private-sector HIV/AIDS disease management program were studied.

Primary end point: proportion of patients in whom VL remained <400 copies/mL in 80% of samples.
This is a 28-month median follow-up study

Dose Response Pattern Between NNRTI Adherence & Virologic Suppression (N= 3,325)



Nachega et al 13th CROI 2006, Denver, CO, AbOr# 93

Univariate & Multivariate Analysis of the Baseline Factors Associated with VL Suppression (N=3220)

Variable	*Univariate OR(95% CI)*	*Adjusted RH(95% CI)*
Age (per 10 yrs)	1.13 (1.04-1.23)	1.1 (0.94-1.32)
Gender		
▪ Female	1.23(1.08-1.40)	1.11(0.94-1.32)
▪ Male	1.00	1.00
Race		
▪ Black	1.00	
▪ White	1.38 (0.95-1.99)	
▪ Other	1.23(0.39-3.85)	
Adherence		
▪ <70%	1.00	1.00
▪ 70-79%	3.73(2.89-4.80)*	4.58(3.44-6.10)
▪ 80-89%	6.81(5.46-8.50)*	7.54(5.88-9.67)
▪ 90-94%	9.80(7.60-12.62)*	11.91(8.91-15.9)
▪ >95%	12.06(9.98-14.58)*	15.58 (12.44-19.52)
CD4+ (cell/mm^3)		
▪ <50	1.00	1.00
▪ 51-200	1.19 (1.00-1.41)*	1.09 (0.87-1.36)
▪ >200	1.49(1.25-1.79)*	1.36 (1.07-1.74)*
Log_{10}V L (c/ml)		
▪ <5	1.37(1.20-1.55*)	1.27(1.07-1.50)*
▪ >5	1.00	1.00

Variables Associated with Viral Suppression in Multivariate Logistic Regression Model

MLR
• High ART adherence (OR: 15.6; 95% CI 12.4-19.5) • High baseline CD4 count (OR:1.4; 95% CI 1.1-1.7) • Baseline viral load $<10^5$ copies/ml (OR: 1.3; 95% CI 1.1-1.5)

Study Limitations

- Filling a pharmacy claim does not necessarily mean that the patient is correctly taking the claimed medication.
- Study population included patients enrolled in a private managed insurance program.
- Therefore, the utility of pharmacy refill as a measure of adherence needs to be evaluated in the public sector.

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Summary I

- When used appropriately in the setting of ‘fully suppressive’ triple-drug therapy, NNRTIs are highly effective against HIV-1 with durable viral suppression[1-3]
- High levels of adherence, as assessed by pharmacy claim data, in private-sector management program, strongly predict VL suppression on NNRTI-based ART
- Pharmacy records are a simple and valid program-level adherence monitoring tool

Summary II

- Pharmacy claim records provide a valid tool of evaluating HAART adherence.
- Each 20% decrease in adherence, as measured by pharmacy claims, is associated with decreased survival.
- Pharmacy claims (or refills in public sector) may be a simple and low cost adherence monitoring tool in settings where other labor-intensive or expensive methods are not practicable.

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- Gary Maartens, MD, FCP, Univ. Cape Town, South Africa