

# Promoting Adherence to Antiretroviral Therapy

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# Learning Objectives

At the conclusion of this presentation participants should be able to :

1. Communicate the role of medication adherence in obtaining successful outcomes of antiretroviral therapy to individuals with HIV in your practice setting.
2. Utilize interventions to enhance adherence to antiretroviral therapy.

This presentation will  
not discuss any non-  
FDA-approved or  
investigational uses of  
any products/devices.

# ARS Question

# History of Medication Adherence

- 1949: First study of adherence in *JAMA*
  - Recognized non adherence as pervasive and costly
  - ½ patient did not accrue treatment benefits due to non adherence
- 1970: National Heart, Lung and blood Institute funded grants to address non adherence in hypertension
  - No single intervention or optimal assessment strategy emerged
- 1995: Re-emergence of adherence attention with introduction of combination antiretroviral therapy (ART)
  - Initial concerns over transmission of drug resistant HIV strains

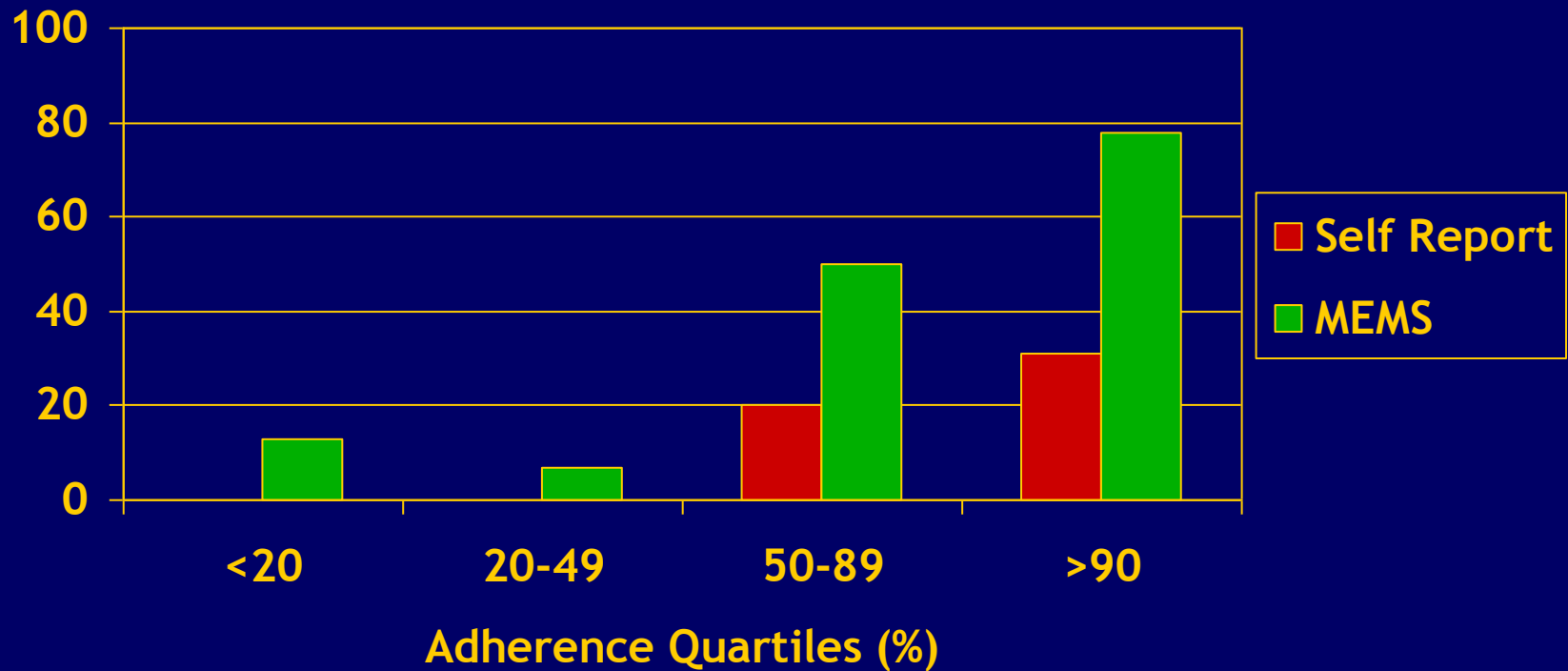
# Adherence to Antiretrovirals (ART)

- Is adherence important ?
  - How much?
- Can adherence be measured ?
  - Are patients adherent?
  - Why not?
- What can be done to improve adherence?

# ARS Question

# Effect of adherence on HIV Viral Load (VL)

% patient with HIV Viral Load undetectable

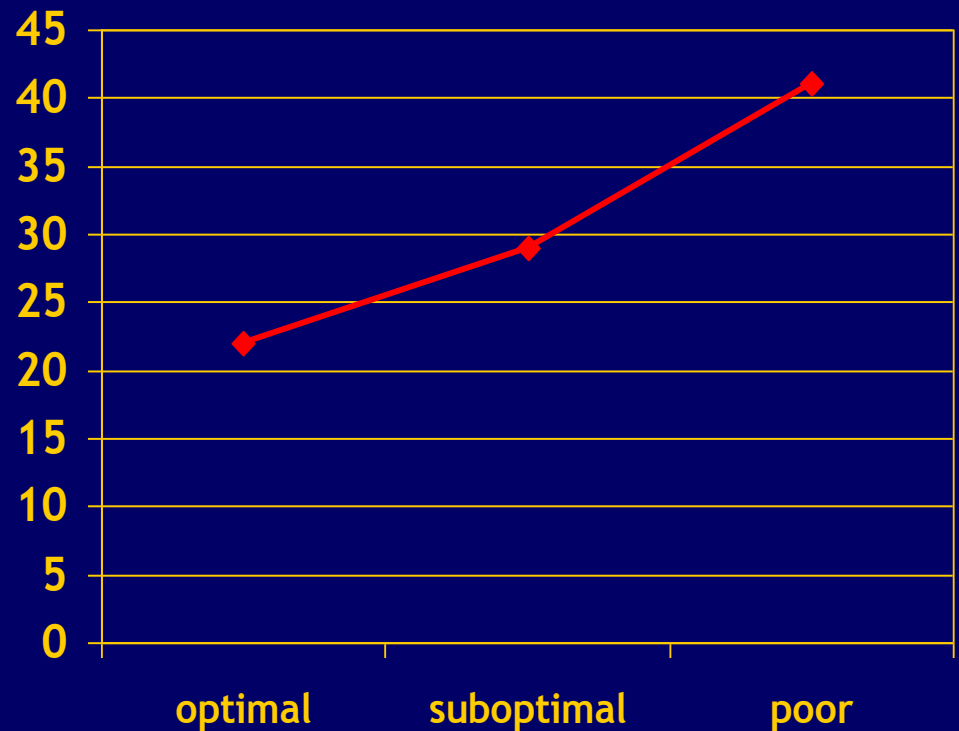




# Effect of adherence on HIV Viral Load (VL)

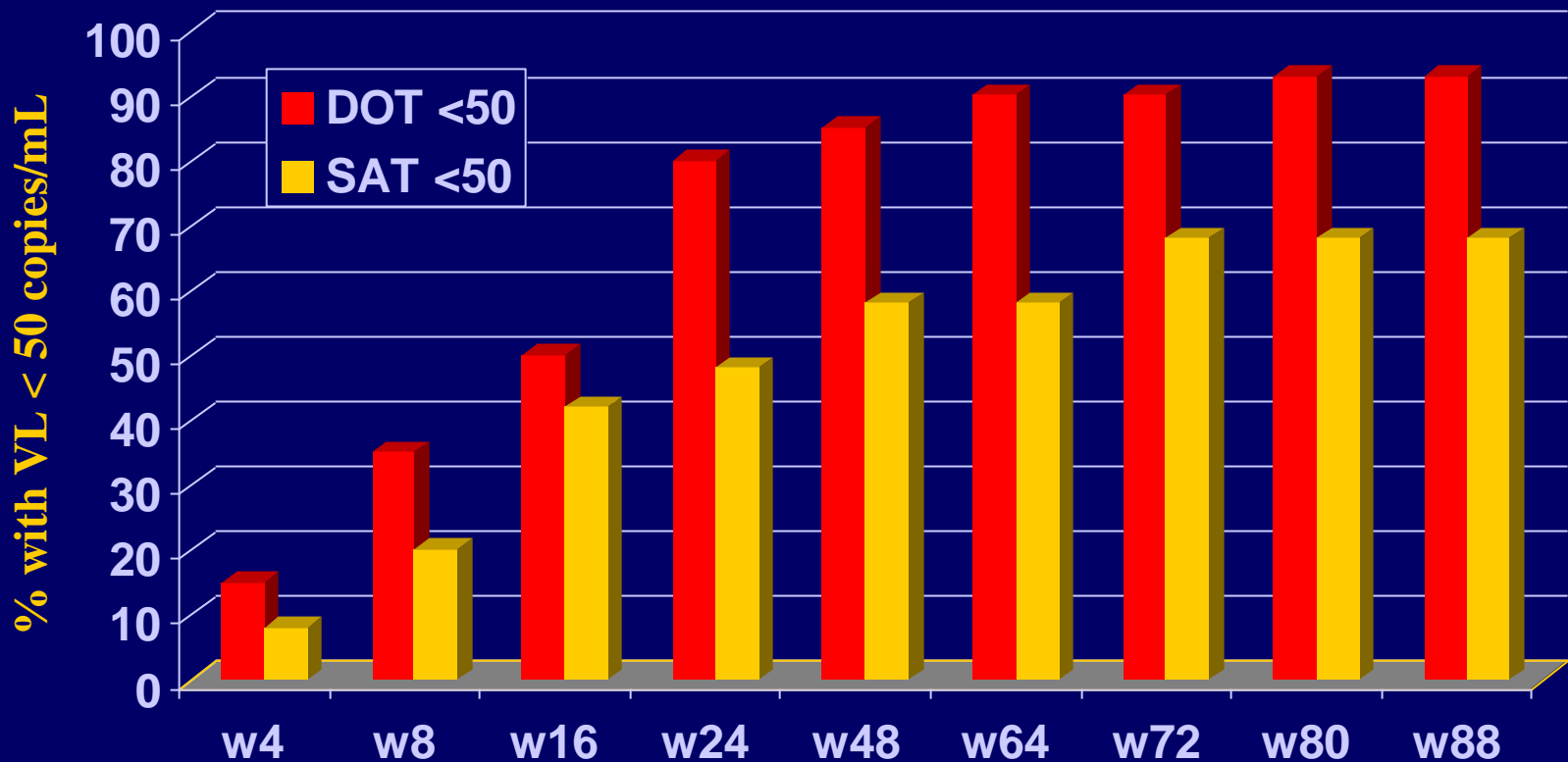
- 931 patients
- Measured adherence by MPR
  - 531 optimal (>95%)
  - 306 suboptimal (80-94%)
  - 76 poor (< 80%)
- Adjusted relative risk for virologic failure:
  - 1.3 Suboptimal
  - 1.7 Poor

% patients with detectable VL



# Self-Administered vs Directly Observed Therapy During Incarceration

N = 50 in each group



$p < 0.01$

# Incidence and Risk of Emergence of Drug-Resistance Mutations in Initial Therapy

- Drug-resistance mutations detected in 25% of subjects
  - Lamivudine resistance: 68.5%
  - NNRTI resistance: 40.3%
  - Other NRTI resistance: 32.9%
  - PI resistance: 22.8%
  - Median time to detection of drug resistance: 8.2 months

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Baseline HIV-1 RNA*	1.85 (1.51-2.26)	< .001	1.59 (1.29-1.96)	< .001
Baseline CD4+ cell count†	1.11 (1.05-1.18)	< .001	1.08 (1.02-1.14)	< .001
Adherence (based on refill %)				
□ 80% - < 90%	-	-	4.15	< .001
□ ≥ 95% + 2 plasma drug conc < steady-state trough conc	-	-	4.57	< .001
Intravenous drug use	1.41 (1.11-1.79)	.005	1.33 (1.04-1.71)	.23

\* HR per log increment † HR per 100 cells/mm<sup>3</sup> decrement

# Incidence and Risk of Emergence of Drug-Resistance Mutations in Initial Therapy

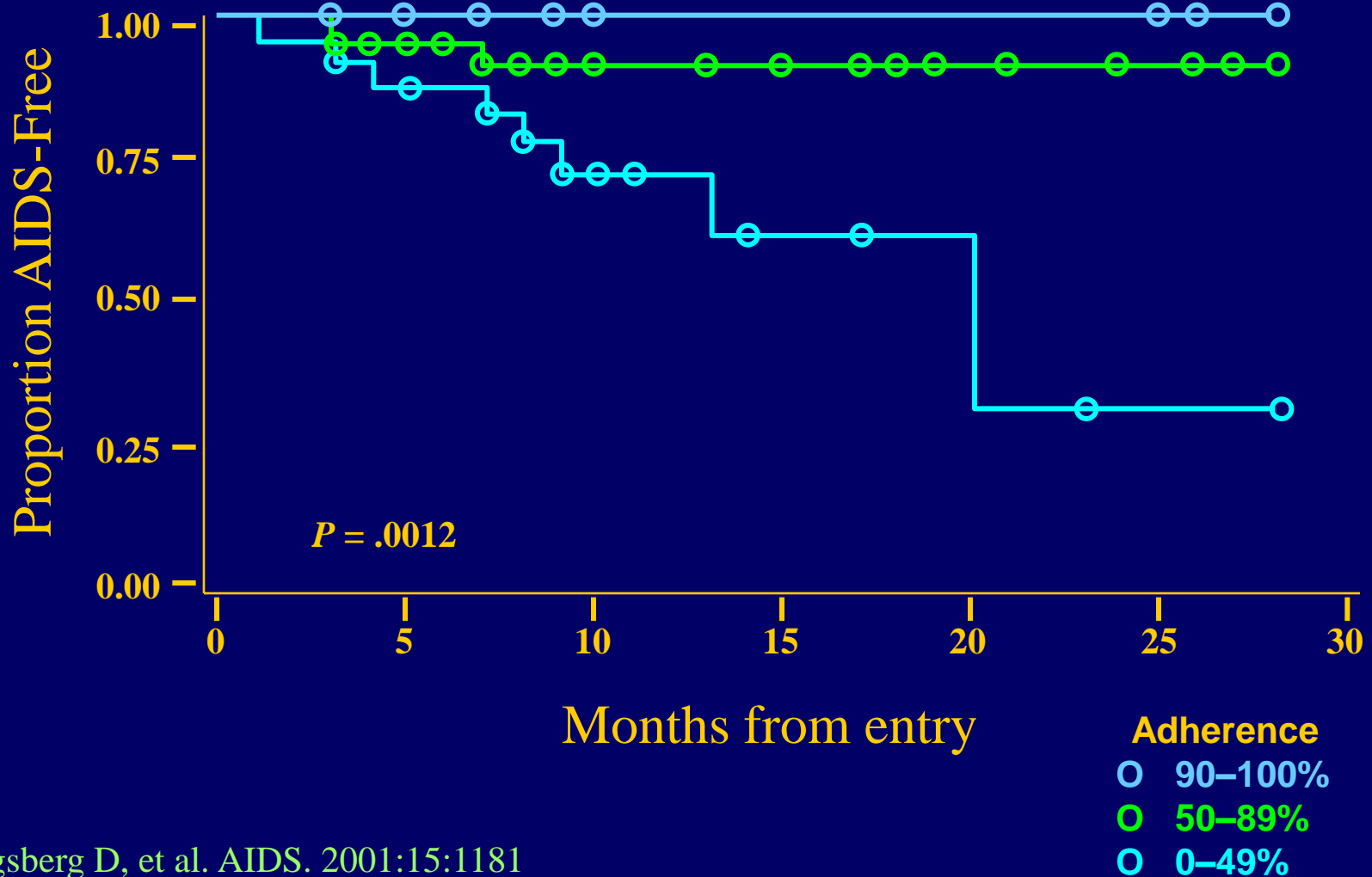
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# Adherence and AIDS-Free Survival

10% Adherence difference = 21% reduction in risk of AIDS



# Benefits of consistent adherence

- 98 patients interviewed
- 58% classified as consistent adherers (CA)
- Consistent adherence is associated with better outcomes including
  - improved quality of life
  - higher CD4 counts
  - lower health care costs.

CA vs non-CA	p value
Better physical function	0.001
Better general health	0.009
Increased vitality	0.016
Better social functioning	0.001
Mental health	0.023
Higher CD4 cell	0.028

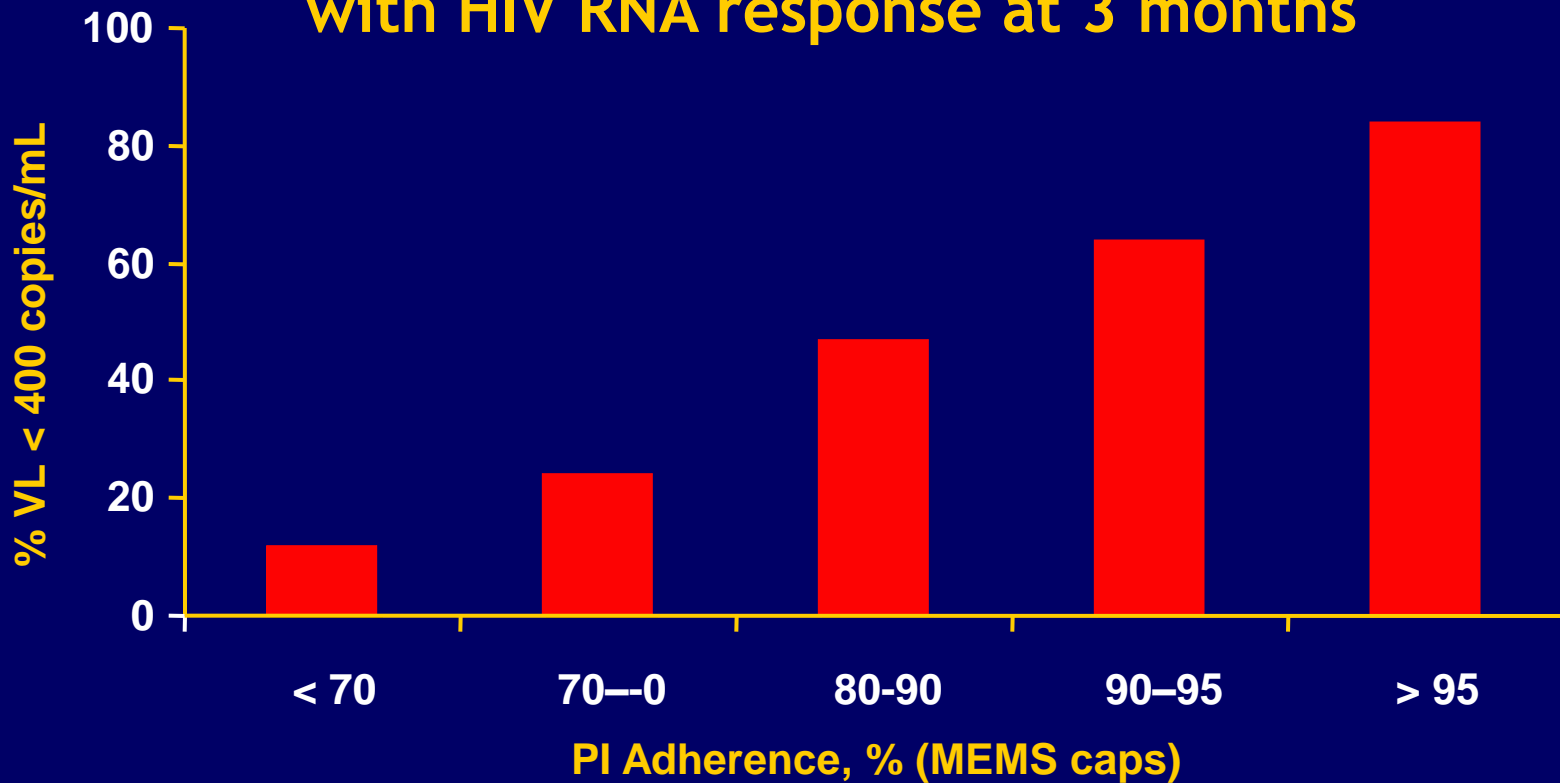
# Effects of ART adherence

Adherence strongly correlated with

- Viral suppression
- Reduced rates of resistance
- Increased survival
- Improved quality of life

# What Degree of Adherence is Needed? Data From Unboosted PIs

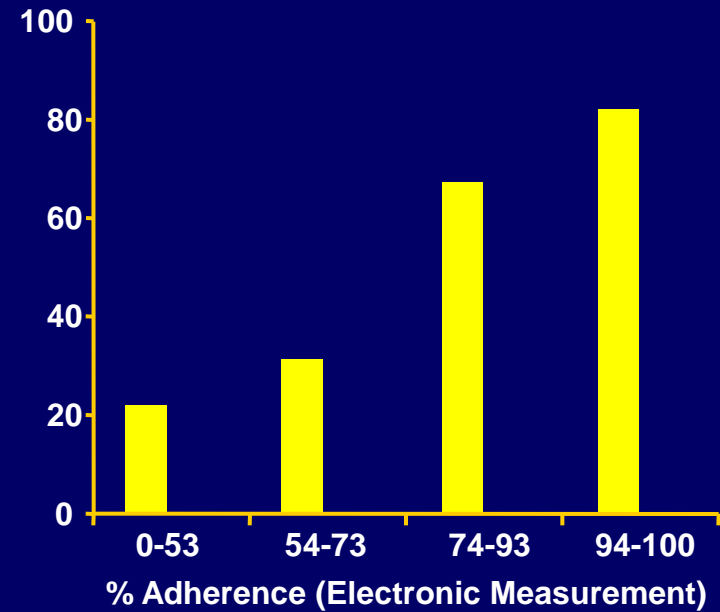
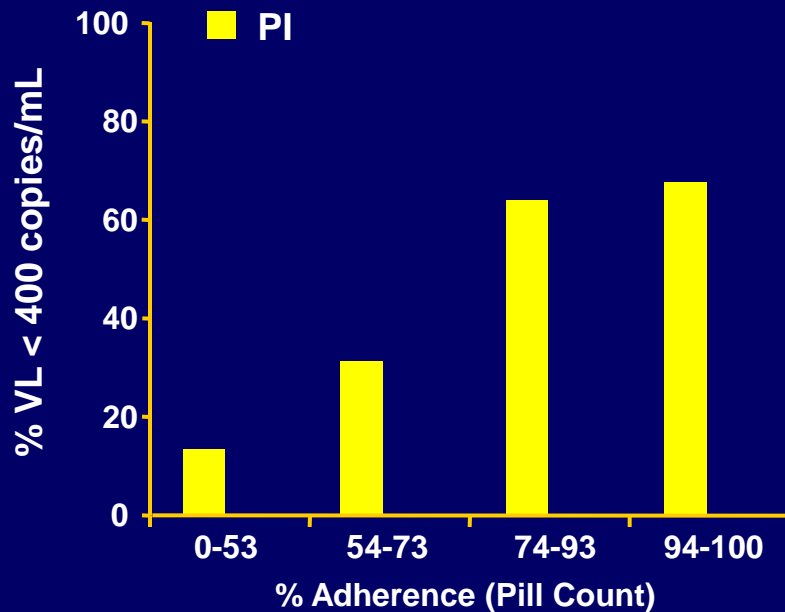
Adherence to a PI-containing regimen correlates with HIV RNA response at 3 months





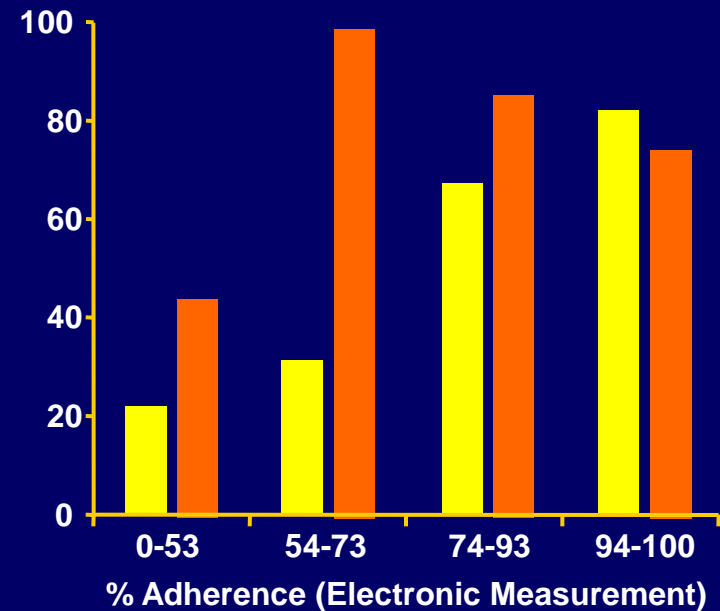
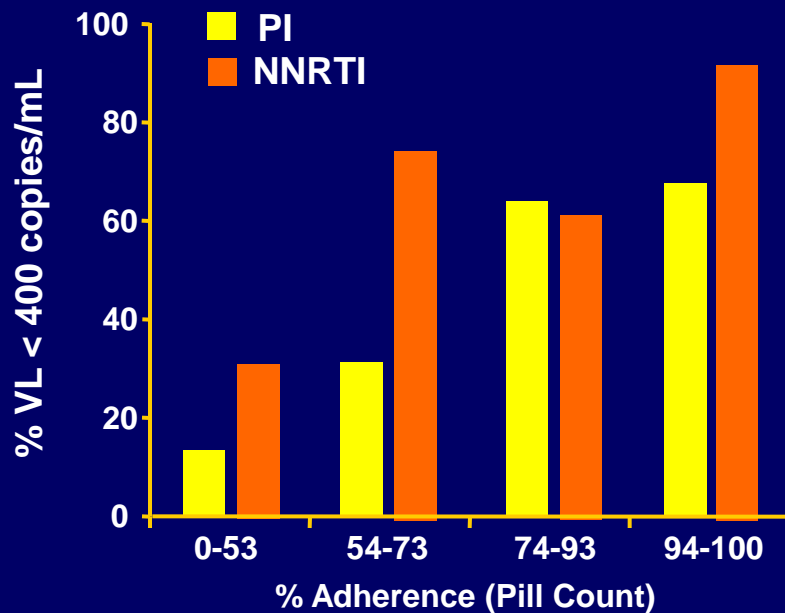
# NNRTI Regimens May Be More Forgiving of Suboptimal Adherence

- 109 indigent patients in San Francisco
  - 56 unboosted PI

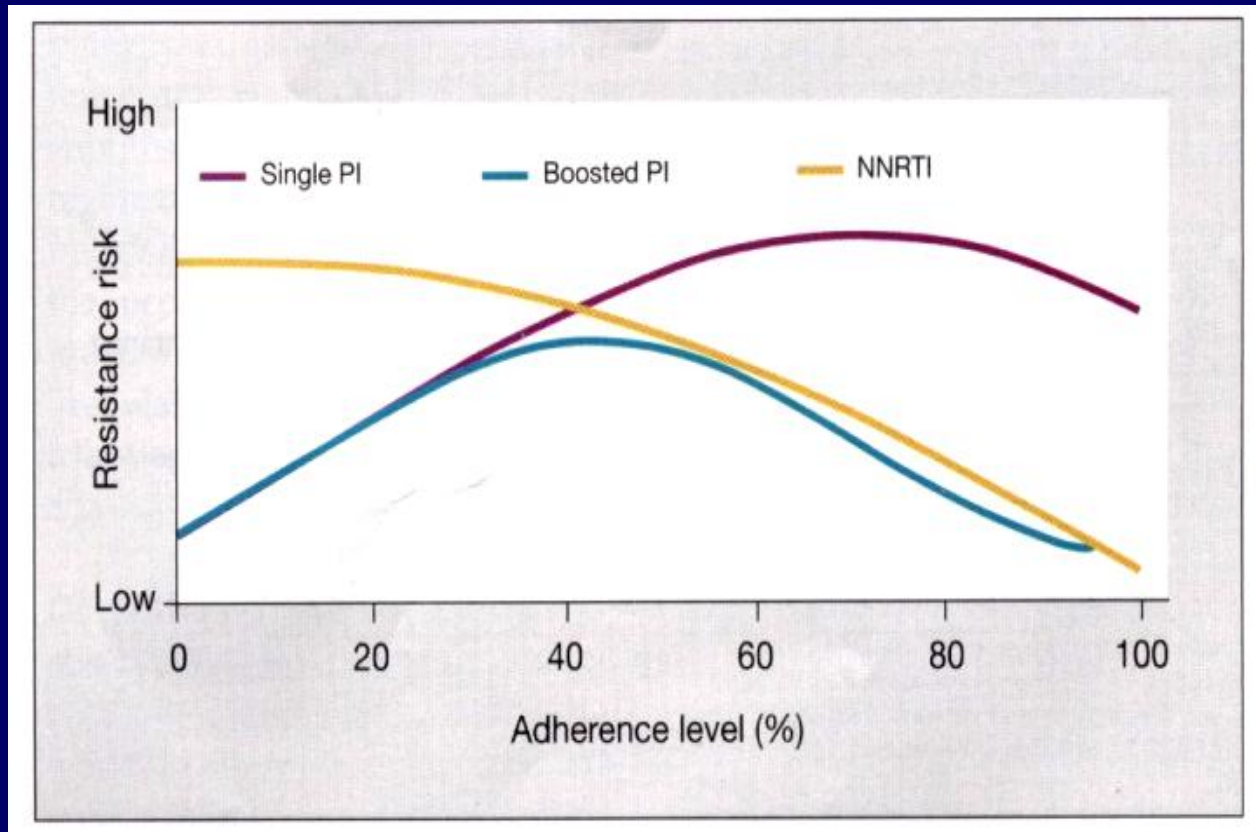


# NNRTI Regimens May Be More Forgiving of Suboptimal Adherence

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



# Estimated risk of resistance by level of adherence and drug class



Bansberg DA et al, J Antimicrob Chemother 2004(53)

# Development of Post-NVP Resistance Mutations

- K103N found in 16 (40%) of 40 women with previously undetectable levels
- Y18C found in 5 (11%) of 46 women with previously undetectable levels
- K103N appears to emerge readily and decay slowly, outlasting Y181C

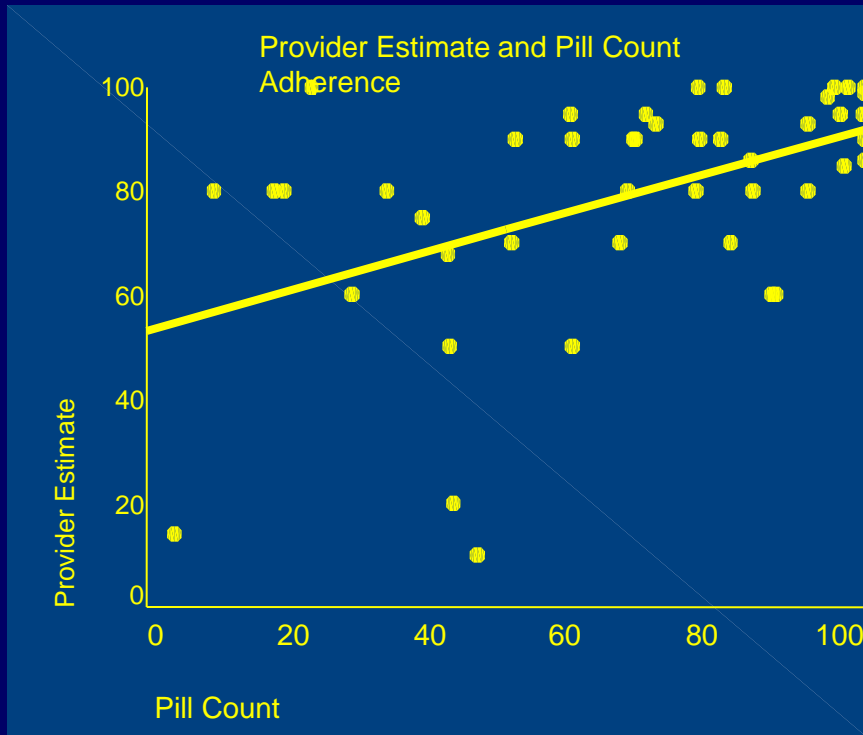
PCR Analysis of NVP Resistance Mutations				
NVP Resistance Mutation	Mean Post-NVP $\Delta$ CT, Cycles	Mean Post-NVP $\Delta\Delta$ CT, Cycles	Mean Weeks Since NVP	Mean Post-NVP VL, copies/mL
K103N	8.9*	-6.0	15.81	52,625
Y181C	6.7*	-5.8	8.00	121,800

$\Delta$ CT, different in amplification cycles at threshold;  $\Delta\Delta$ CT, change between pre-, post-NVP  $\Delta$ CT values; VL, viral load\*P < .0001 compared with pre-NVP  $\Delta$ CT

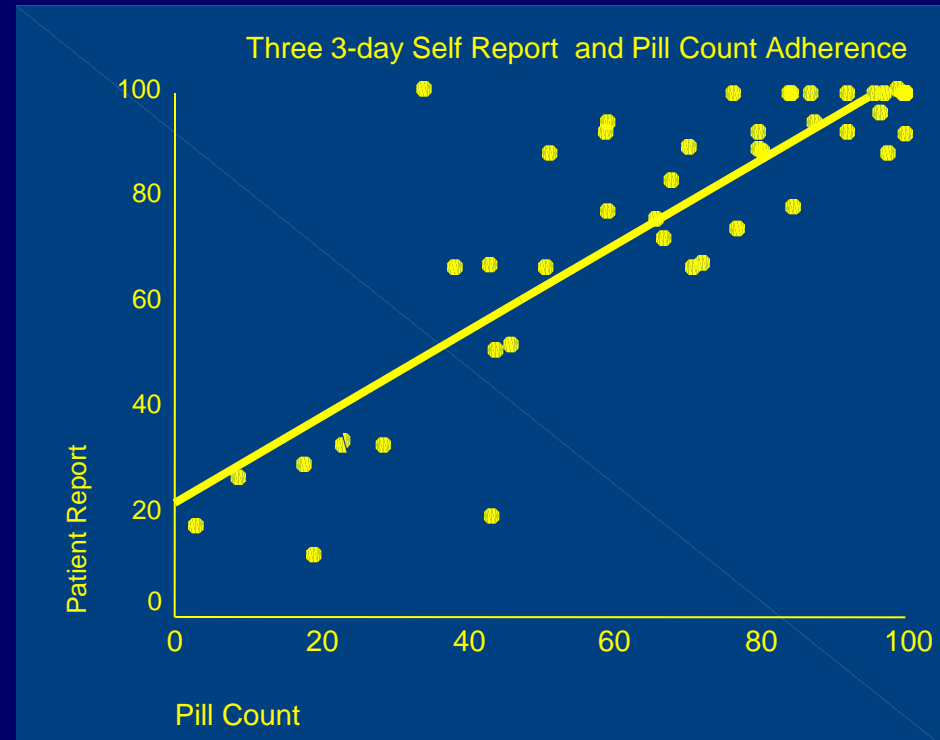
# ARS Question

# Provider Estimate vs. Three 3-Day Patient Report Compared to Pill Count

n=45



Provider Estimate  
 $R^2 = 0.26$



Patient Report  
 $R^2 = 0.72$

# Measuring adherence

- **Biologic markers**
  - Drug levels: Limited usefulness due to variability, confounders
  - Surrogate markers: Limited usefulness due to lack of specificity
- **Pill counts**
  - Advantage: easy, low cost
  - Disadvantage: time consuming, possible “pill dumping”
- **Electronic monitoring**
  - Advantage: Objective data
  - Disadvantage: Expensive, “pocket dosing”, “curiosity opening”
- **Patient self report**
- **Pharmacy refill records**



# Measurement of Adherence: Self Report

- Advantages
  - Low cost, minimal participant burden, ease of administration, flexibility, ability to yield specific data (timing, food requirements)
- Disadvantages
  - Recall bias, inaccurate memory, potential social desirability bias
  - Overestimates adherence by as much as 20%
  - Report of suboptimal adherence strong indicator of non adherence
- Format
  - simple
  - nonjudgmental
  - structured format
  - normalizes less than perfect adherence
  - minimizes socially desired responses



# Self Report Techniques

- Interview
- Diaries
- Short time frame recall
  - 3 to 7 or more days
- Visual analog scales



- Validated questionnaires
  - Patient Medication Adherence Questionnaire
  - CASE report

# Helpful Adherence Interview Questions

- How do you feel things are going with your adherence to your medications?
- Tell me a little about how you are fitting your medications into your day.
- Is anything making it hard for you to take your pills?
- What keeps you from taking your medicine?
- When did you last get your medications refilled?
- Who in your life helps you to remember your pills?
- A lot of my patients find sticking to a schedule really hard and sometimes miss doses; does that ever happen to you?

# Not Helpful Adherence Interview Questions

- You're taking your pills, aren't you?
- You haven't missed any, have you?
- Everything is going great, right? Missed no doses?
- I will be really disappointed if you aren't taking these medications right -- any problems?
- I thought we discussed this last time. Why are you unable to do this right?
- You are taking these correctly, right?
- This looks really easy to me -- what's the problem here?
- Come on, it can't be that bad, can it?

# Center for Adherence Support Evaluation (CASE) Index

- Mannheimer et al, AIDS Care 2006 Oct 18(7)
  - Strongly related to 3 day adherence data ( $p < 0.001$ )
  - Superior to 3 day adherence data on outcomes
    - VL decline ( $p < 0.05$ )
    - VL  $< 400$  ( $p < 0.05$ )
  - CD4 response
    - CASE index  $> 10$  + 98 cells
    - CASE index  $\leq 10$  + 41 cells

# Center for Adherence Support Evaluation (CASE) Index

1. How often do you feel that you have difficulty taking your HIV medications on time? By 'on time' we mean no more than two hours before or two hours after the time your doctor told you to take it.  
  
(4) Never (3) Rarely (2) Most of the time (1) All of the time
2. On average, how many days per week would you say that you missed at least one dose of your HIV medications?  
  
(1) Everyday (2) 4-6 days/week (3) 2-3 days/week (4) Once a week  
(5) Less than once a week (6) Never
3. When was the last time you missed at least one dose of you HIV medications?  
  
(1) Within the past week (2) 1-2 weeks ago (3) 3-4 weeks ago  
(4) Between 1 and 3 months ago (5) More than 3 months ago (6) Never

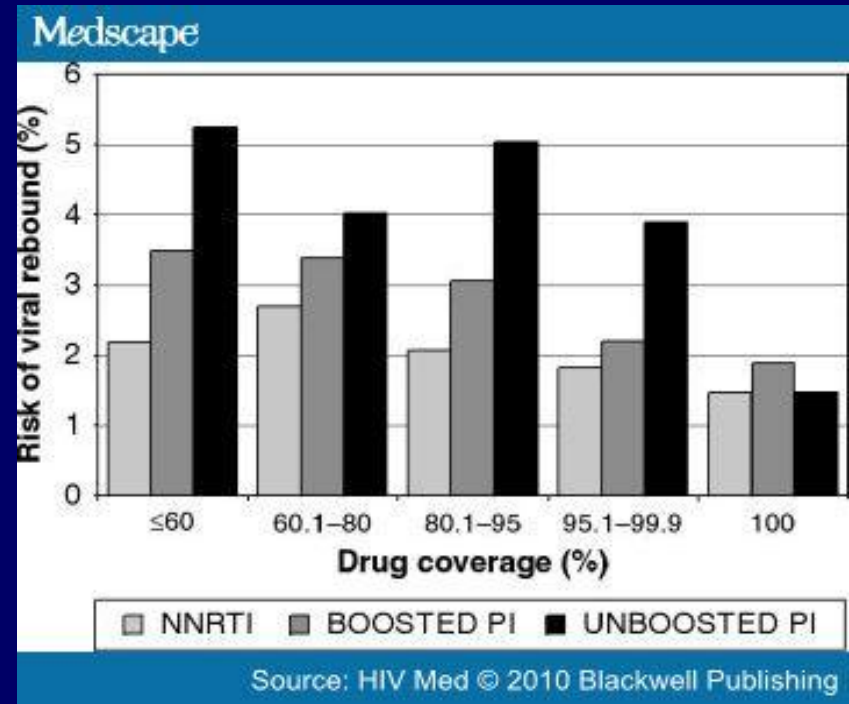
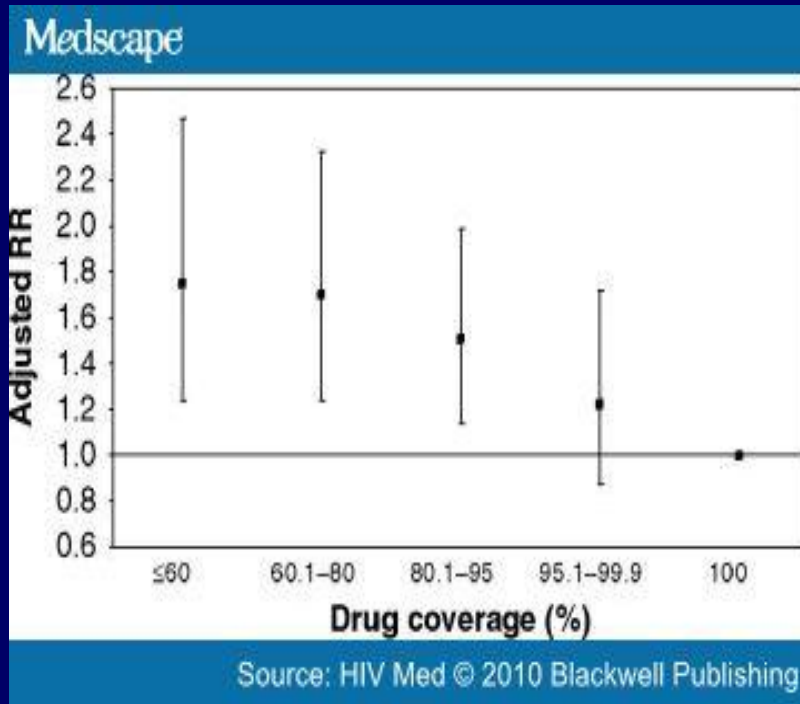
INDEX SCORE: \_\_\_\_\_

>10 = good adherence ≤10 = poor adherence

# Measuring Adherence

## Pharmacy Refill Records

- 1632 patients in United Kingdom
- 376 episodes of viral load rebounds (<200 copies/ml)



# Medication Possession Ratio:

days supply of meds  $\div$  total days X 100

- KW
- Rx: AZV/r, TDF, FTC
- Refill dates:
  - 5-14-09
  - 6-10-09
  - 7-9-09
  - 8-8-09
  - 9-9-09
- MPR =  $120 \div 116 = 103\%$
- VL 9-19-09: <50 copies
- LT
- Rx: AZV/r, TDF, FTC
- Refill dates:
  - 9-3-09
  - 10-13-09
  - 11-10-09
  - 1-10-10
- MPR =  $90 \div 129 = 69\%$
- HIV VL 1-11-10: 257,000

# Factors associated with poor adherence

Characteristics of patient

Characteristics of the regimen



# Effect of literacy on adherence

- 204 patients in Chicago and Shreveport
- Literacy assessed with Rapid Estimate of Adult Literacy in Medicine (REALM)
  - Results:
    - Low (6 grade or below)
    - Marginal (7-8<sup>th</sup> grade)
    - Adequate (9<sup>th</sup> grade or higher)
- Adherence measured
  - Patient Medication Adherence Questionnaire (PMAQ)
  - Self report

## Adjusted Odds for Non-Adherence

Literacy Level	AOR	95%CI
Adequate	1.0	
Marginal	2.1	0.8-5.5
Low	3.3	1.3-8.7

# Effect of aging and neurocognition on adherence

- 431 patients on antiretroviral therapy
- Neurocognitive testing results correlated with adherence
  - Adherence measured by (MEMS caps) and self report
- No correlation for subjects <50 years
- Significant correlation for subject >50
  - Executive functioning
  - Motor functioning
  - Processing speed

# Effect of depression on adherence

- Evaluation of 3359 patient on HAART from 2 large HMOs
  - 42% depressed
  - 15% on SSRI
- Adherence measure by pharmacy refill records

## Results:

↓ odds of achieving 90% adherence

– OR 0.81 (0.70 – 0.98)  $p=0.03$

↓ odds of achieving viral load <500

– OR 0.77 (0.62 – 0.95)  $p=0.02$

CD4 over 12 months -19 for depressed patient vs +19 for non depressed

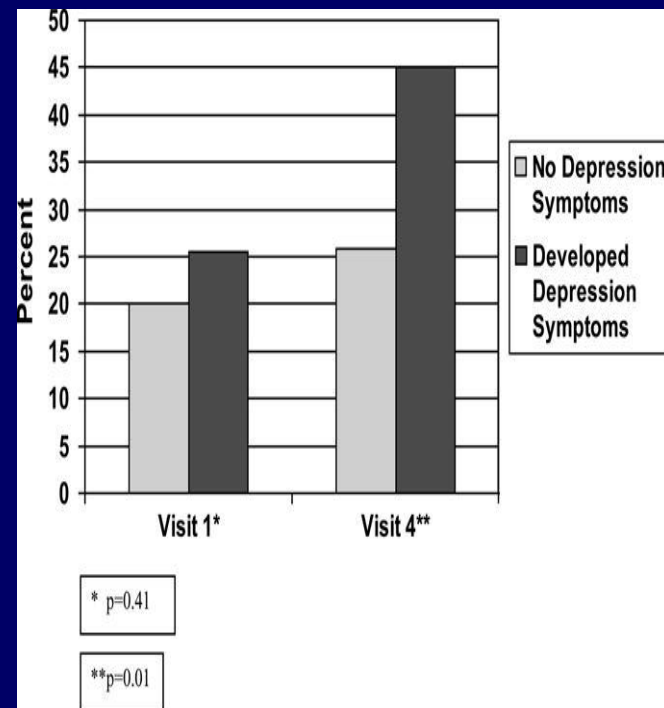
# Effect of treatment for depression on adherence

- Evaluation of cognitive behavioral therapy (CBT) to reduce depression and enhance medication adherence
- Two arms/45 patients/crossover design
  - single session adherence intervention
  - single session adherence intervention plus 10-12 sessions of CBT
- Adherence measured by MEMS
- Significant better adherence in CBT group
  - Average increase in adherence 25.35% (from 62.26% to 87.61%)

# Effects of incident depression on adherence

- Cohort of 225 patient
- Depression screened at 4 study visits
- Incident depression defined as 2 visits with negative screening followed by 2 visits with positive screening (n = 22)
- Adherence measured
  - Suboptimal > 5 % missed over last 7 days

% patient with suboptimal adherence



# Effect of housing and social supports on adherence

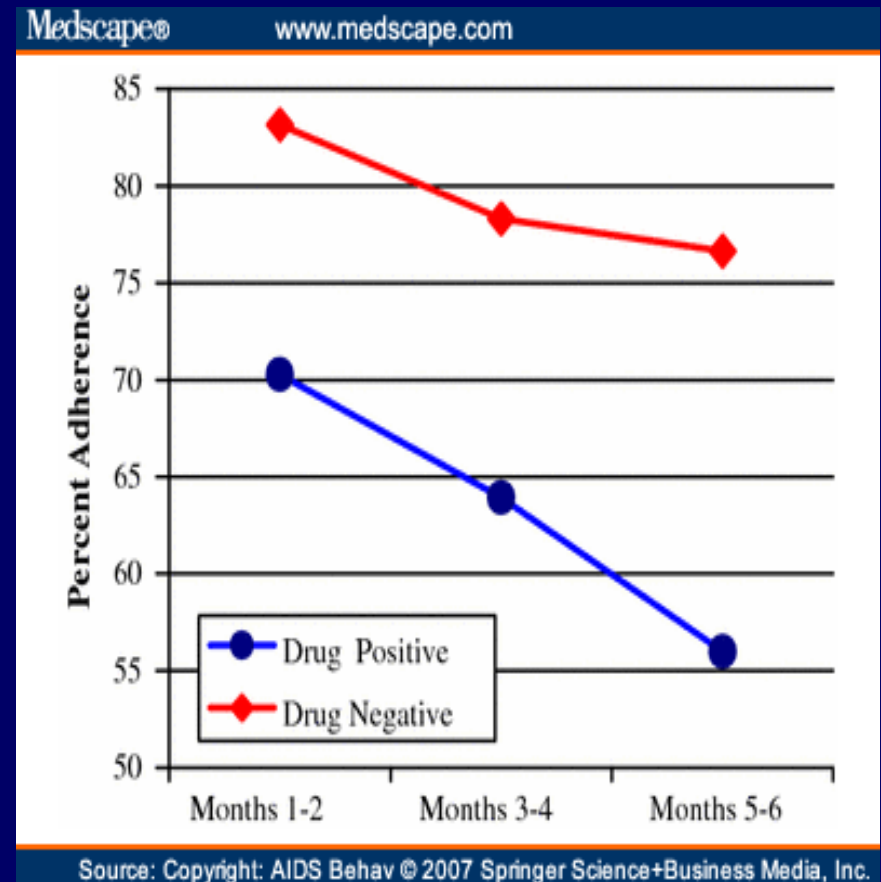
- Prospective cohort study in methadone program
- 103 patients
- ART adherence measured by MEMS caps
- Social and behavioral characteristics evaluated

## Factors affecting adherence

	Adherence rate with vs without	P value
Long term housing	75% vs 42%	0.003
Living with partner	73% vs 46%	0.04
HIV support group	84% vs 54%	0.006
2 or more side effects	81% vs 45%	0.009
Active crack cocaine use	29% vs 72%	0.005
Active heroin use	40% vs 70%	0.04

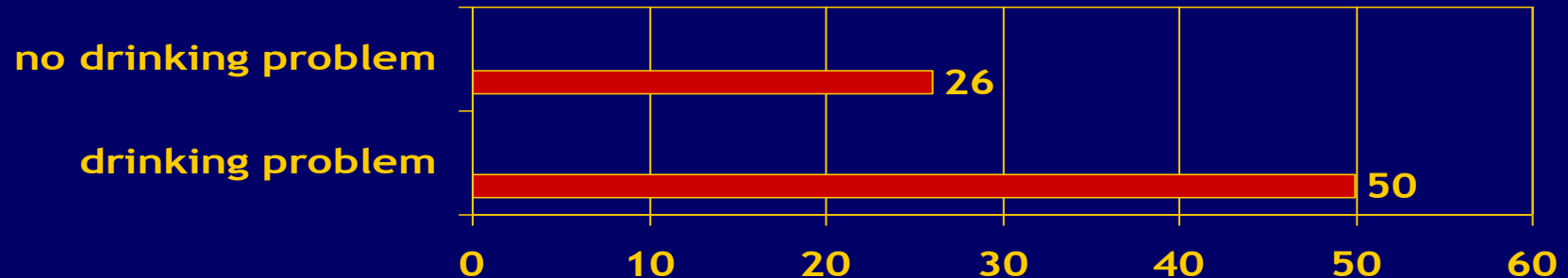
# Effect of substance use on adherence

- 150 HIV infected persons
  - 102 positive urinalysis for recent illicit drug use
- Medication adherence measured over 6 months
  - MEME caps



# Effect of Alcohol Consumption on Medication Adherence

- Samet et al 2004
  - 267 HIV infected persons with history of alcohol problems
  - Alcohol consumption most significant predictor of non adherence
- Cooke et al 2001
  - % of patients taking medications off schedule



- Parsons et al 2008
  - 272 HI positive persons with alcohol problem
  - 9 times higher odds of medication non adherence on days drank; each drink increasing odds by 20%



# Effect of stigma on adherence

- 204 pts in Chicago and Shreveport
- Adherence measured
  - Patient Medication Adherence Questionnaire (PMAQ)
- 3 questions addressing stigma
  - “I am embarrassed to get my medications from a drug store.”
  - “I don’t want people to see me take my HIV medications.”
  - “Taking my medications reminds me that I have HIV.”
- Respond in three point scale
  - A=Agree, not sure, disagree

## Adjusted Odds for Non-Adherence

Stigma Concern	AOR	95%CI
Low	1.0	
Moderate	1.9	0.8-4.5
High	3.7	1.5-9.1

# Effect of Health Beliefs on Adherence

- Interviewed 214 men and reported agreement with 9 conspiracy beliefs
- Adherence measured by MEMS for next month
- Reduced adherence when treatment conspiracy belief present

HIV Conspiracy Belief	% Agree (Strongly or Slightly)
HIV is a manmade virus*	44
AIDS was produced in a government laboratory*	35
There is a cure for AIDS, but it is being withheld from the poor*	33
AIDS is a form of genocide, or planned destruction, against Blacks*	31
AIDS was created by the government to control the Black population*	31
HIV was created and spread by the CIA*	21
People who take the new medications for HIV are human guinea pigs for the government†	22
The medicine that doctors prescribe to treat HIV is poison†	17
The medication used to treat HIV causes people to get AIDS‡	7

\*Genocidal-related conspiracy belief.  
 †Treatment-related conspiracy belief.  
 ‡Dropped from scale, as suggested by exploratory factor analysis.

	≥95% of Doses Taken (Unadjusted) OR (95% CI)	≥95% of Doses Taken (Adjusted*) OR (95% CI)
HIV conspiracy beliefs—genocidal†	0.90 (0.66 to 1.23)	1.20 (0.81 to 1.77)
HIV conspiracy beliefs—treatment related‡	0.66 (0.45 to 0.96)‡	0.60 (0.37 to 0.96)‡

\*Adjusted for age and health care barriers.  
 †Average agreement on scale (1 = strongly disagree; 2 = slightly disagree; 3 = neutral; 4 = slightly agree; 5 = strongly agree).  
 ‡P < 0.05.  
 CI, confidence interval; OR, odds ratio.

# Effect of Weekends on Adherence

- In hypertension higher number of doses missed on weekends
- Observations cohort 116 HIV patients
  - Adherence measured with electronic monitoring
  - Weekday adherence 95.3%; weekend adherence 93.2% (p 0.012)

# Factors associated with poor adherence

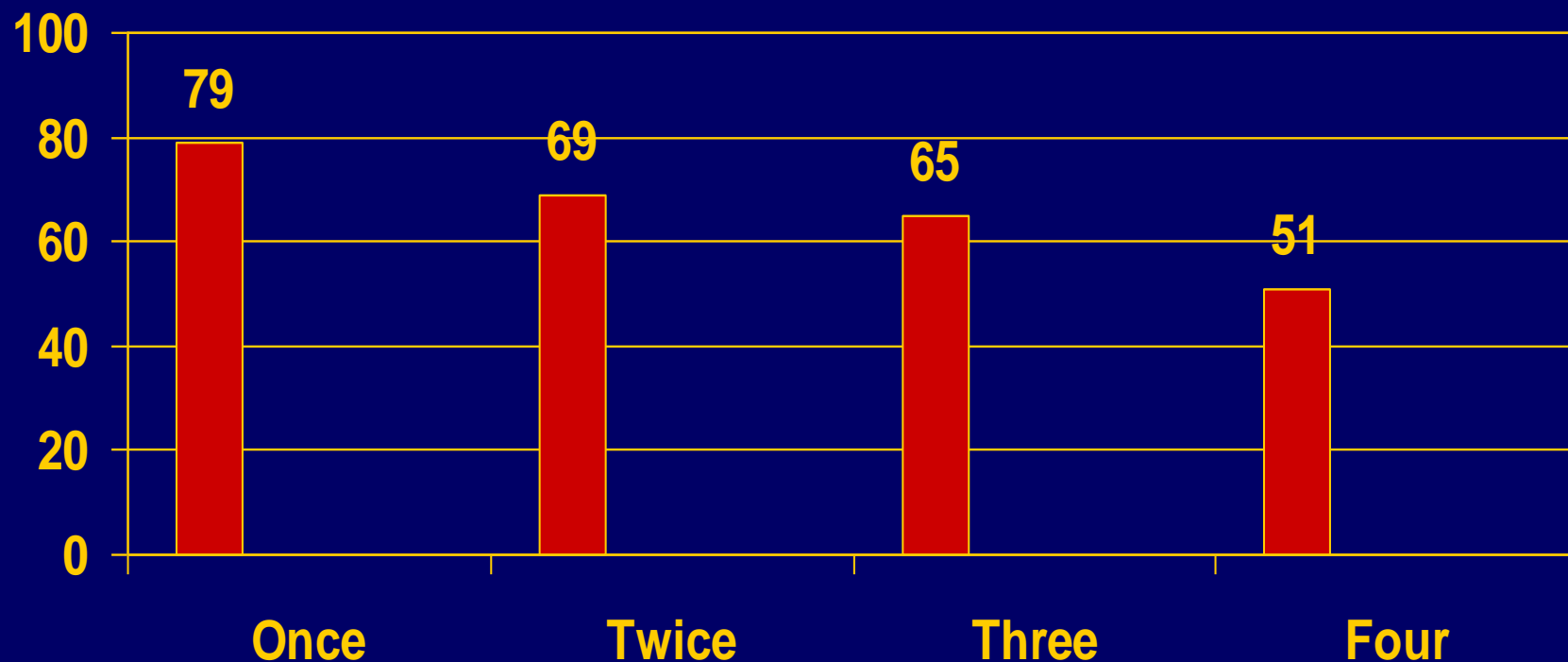
## Characteristics of patient

- Low level of literacy
- Age related challenges
- Psychosocial issues
  - untreated mental illness
  - homelessness
  - low social support
  - stressful life events
- Active substance use
- Stigma
- Health Beliefs
- Difficulty with medication taking
  - trouble swallowing pills
  - daily schedule issues

## Characteristics of the regimen

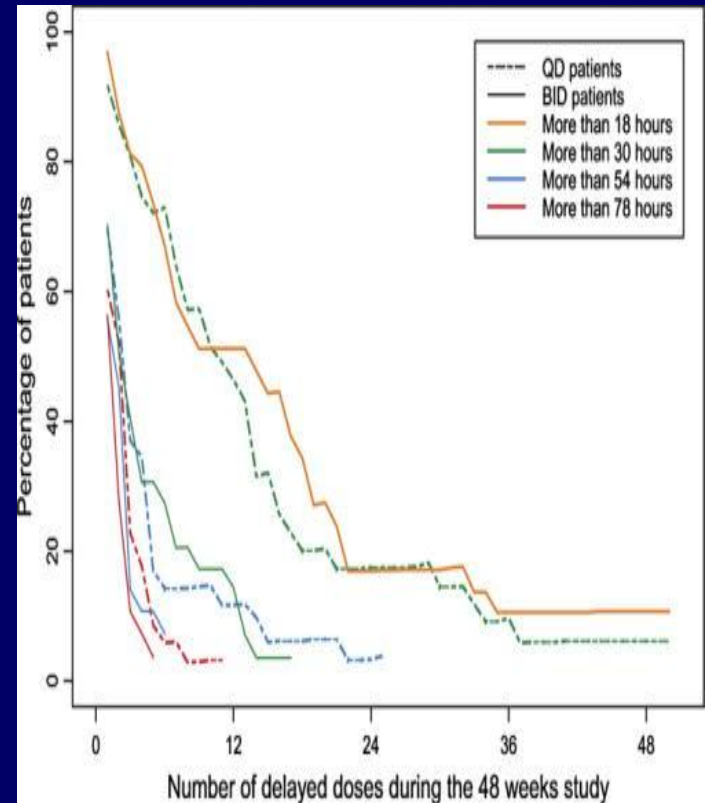
# Review of dose regimens and adherence rates in HIV therapy based on 85 trials

Adherence rate based on # dosing times/day



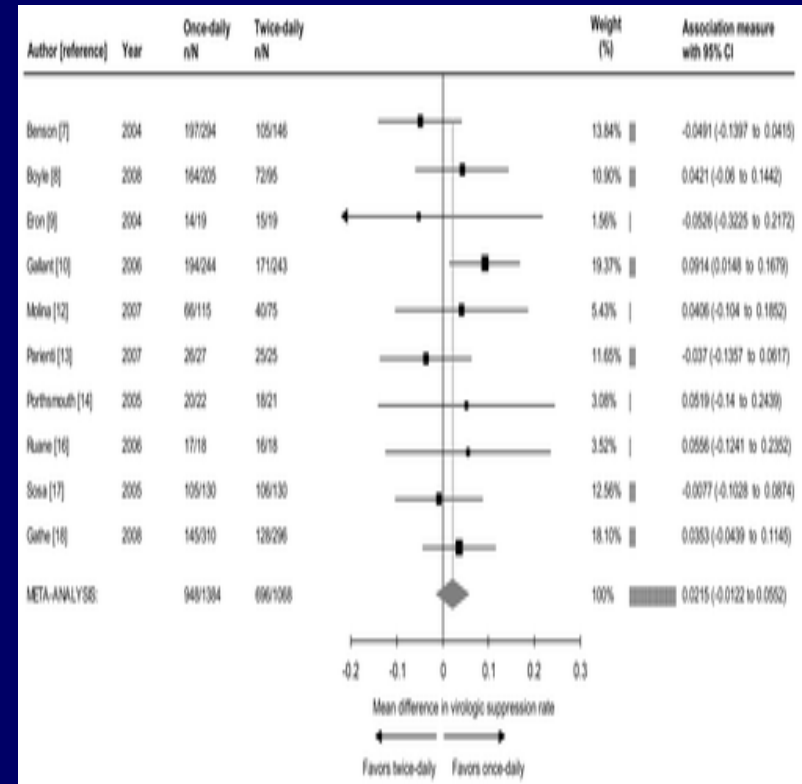
# Effect of once vs twice daily regimen on adherence

- 44 patients taking once daily regimen
  - efavirenz, didanosine, lamivudine
- 43 patient taking twice daily
  - efavirenz, zidovudine, lamivudine
- Adherence measured by MEMS
- Better overall adherence in once daily arm
  - $p = 0.0327$

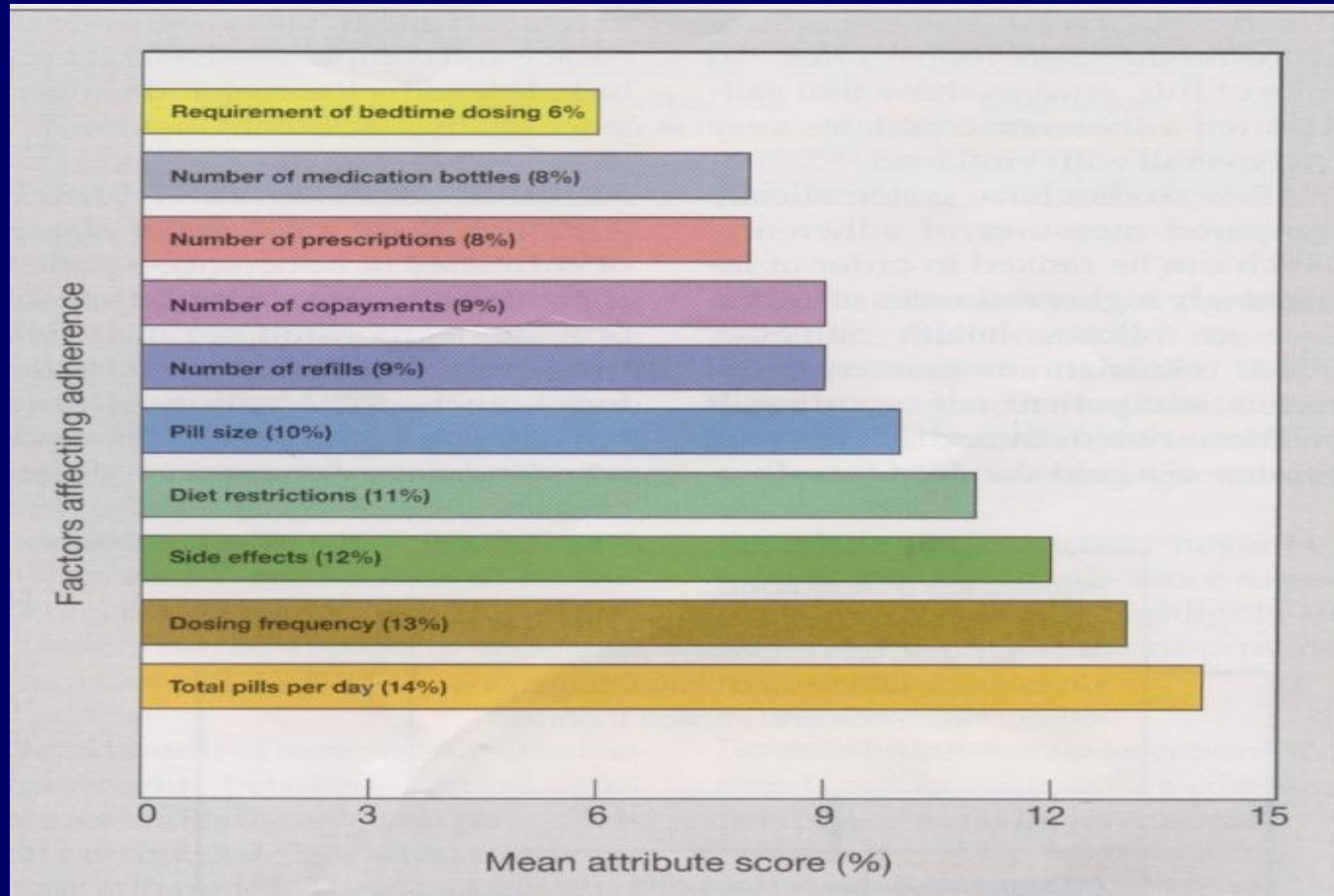


# Effect of regimen complexity on adherence

- Meta-analysis of 11 randomized controlled trials
  - 3029 Total subjects
- Better adherence with once daily regimen
  - + 2.9%, CI 1.0-4.8%
  - $p = 0.003$



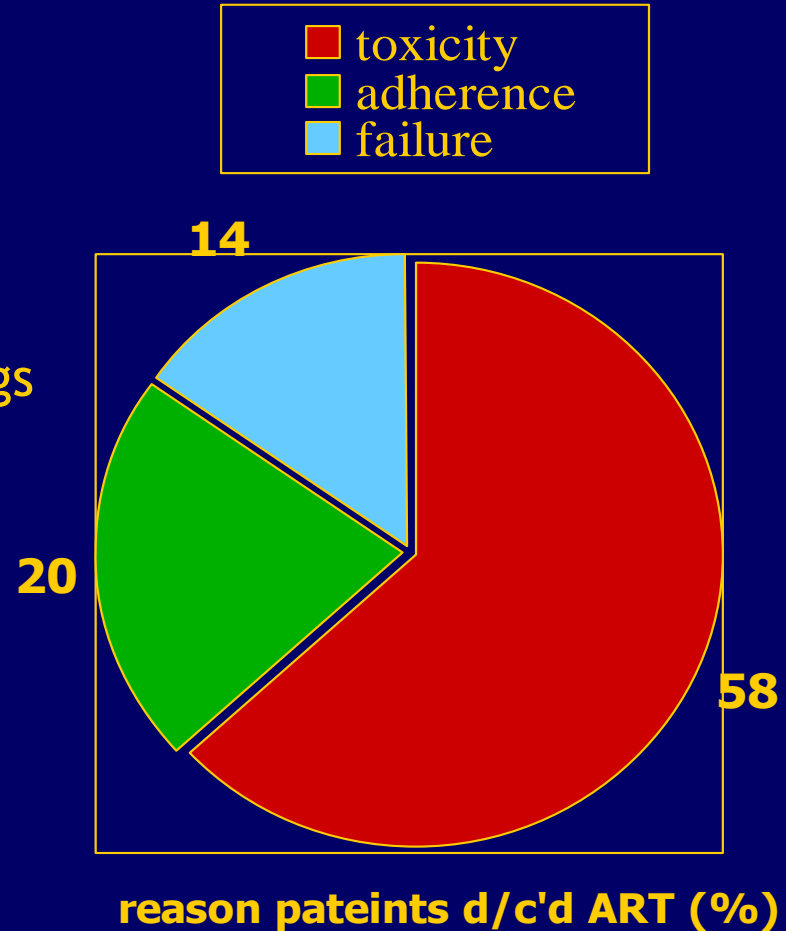
# Factors perceived by patients to impact their ability to adhere





# Adverse Drug Reactions of ART

- Italian Cohort of Antiretroviral Naïve Pts (ICONA, 2000)
- 862 ART naïve patients
- 83.4% received 2 NRTIs and 1 PI
- 9.6% received four or more drugs
- 3.8% received 2 NRTIs + NNRTI
- 312 patient discontinued in by week 12
  - 58% toxicity
  - 20% poor adherence
  - 14 % virologic failure



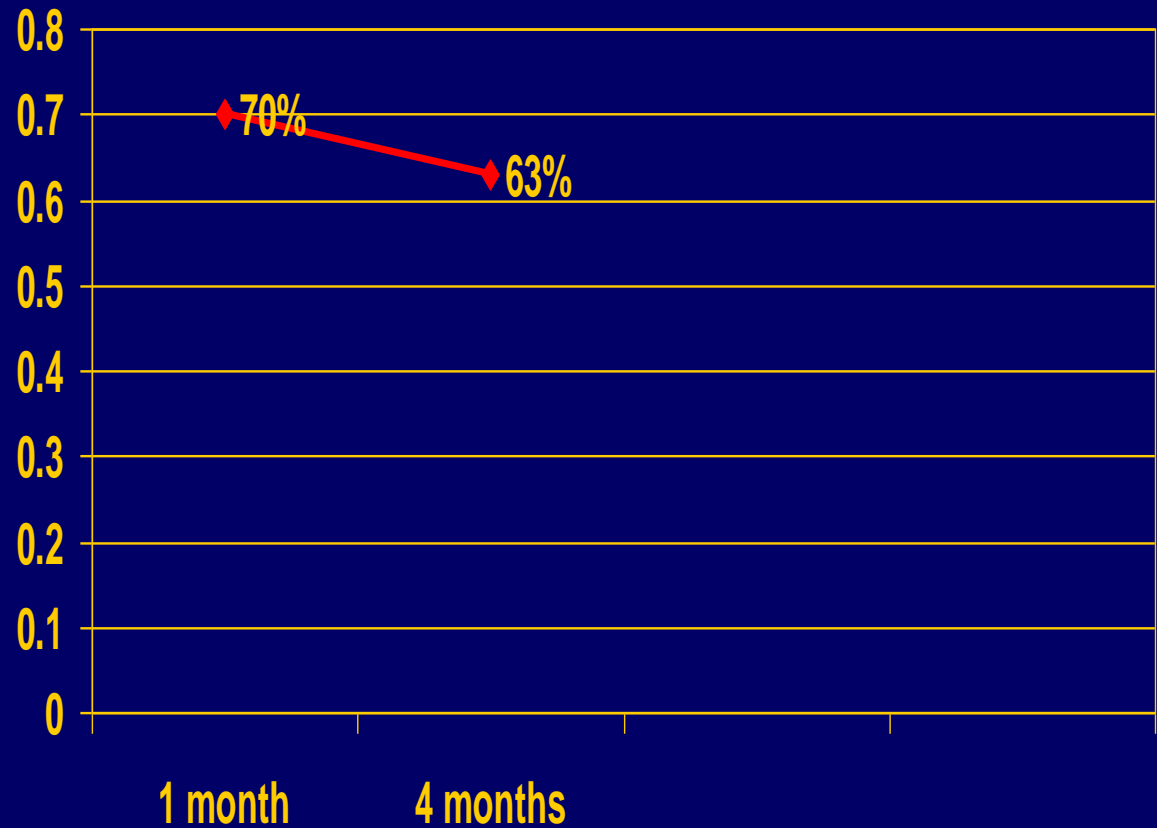
# Patients reporting 100% adherence over time

- Mannerherimer et al. (2000)
- 96 patients in 2 ongoing randomized trials
- completed 8 months of follow-up



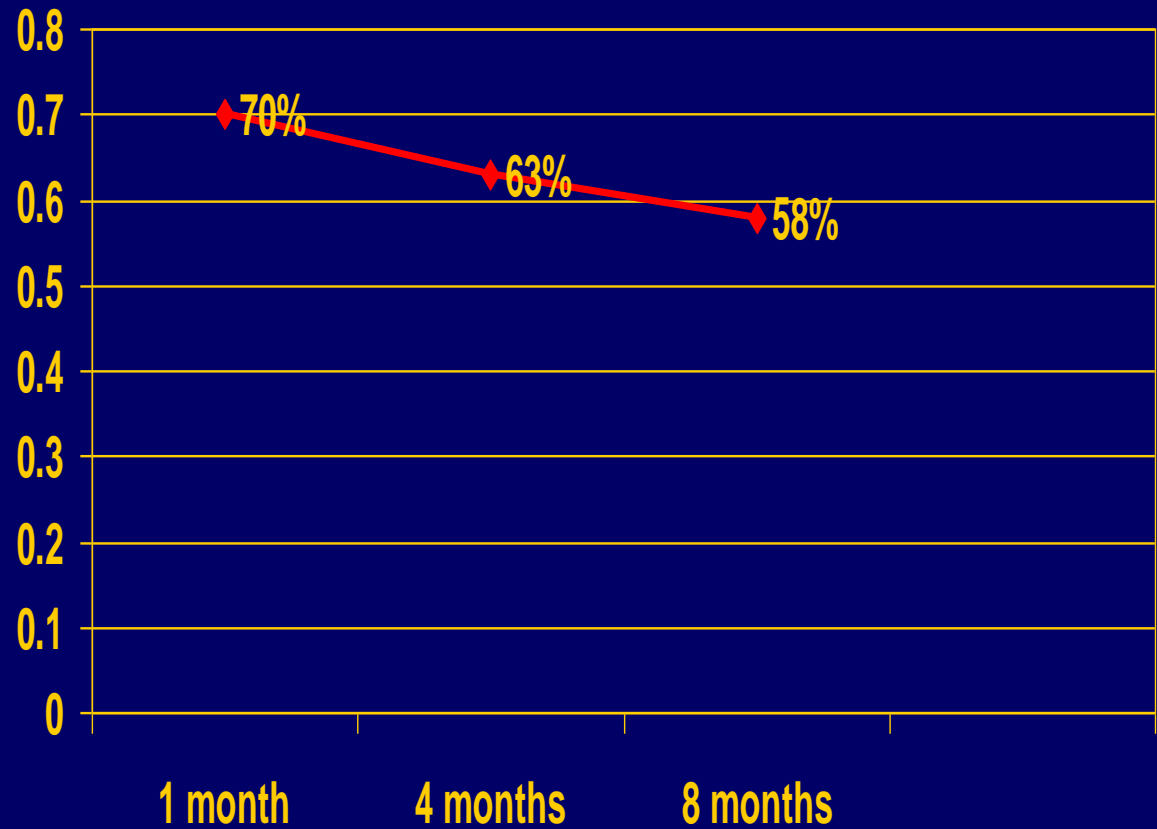
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# Effect of Physician-Patient Relationship on Medication Adherence

## Multivariable Relationship of Physician-Patient Quality with Adherence

Physician-Patient Relationship Quality Measure	Odds Ratio	95% Confidence Interval	P value
General communication	1.15	1.07 to 1.23	0.001
HIV specific information	1.09	1.01 to 1.16	0.02
Participatory decision making	1.07	0.99 to 1.15	0.12
Overall physician satisfaction	1.14	1.04 to 1.25	0.004
Willingness to recommend physician	1.09	1.02 to 1.15	0.009
Physician trust	1.10	1.01 to 1.21	0.03
Adherence dialogue	1.20	1.10 to 1.30	<0.001

# Factors associated with poor adherence

## Characteristics of patient

- Low level of literacy
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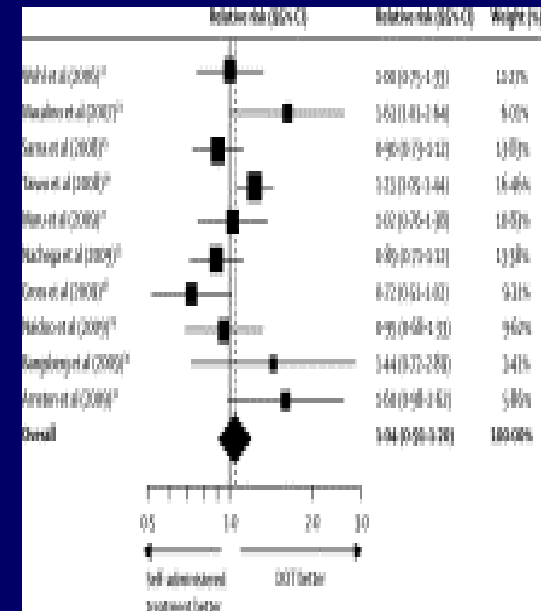
## Characteristics of the regimen

- Complex regimen
  - pill burden
  - dosing frequency
  - food requirements
- Adverse drug effects
- Treatment fatigue
- Lower strength of provider/patient relationship

# ARS Question

# Effect of Directly Observed Therapy (DOT)

- Meta analysis of 12 studies
- End point virologic suppression
- No benefit overall
- May be benefit in selected groups
  - Homeless
  - Substance users



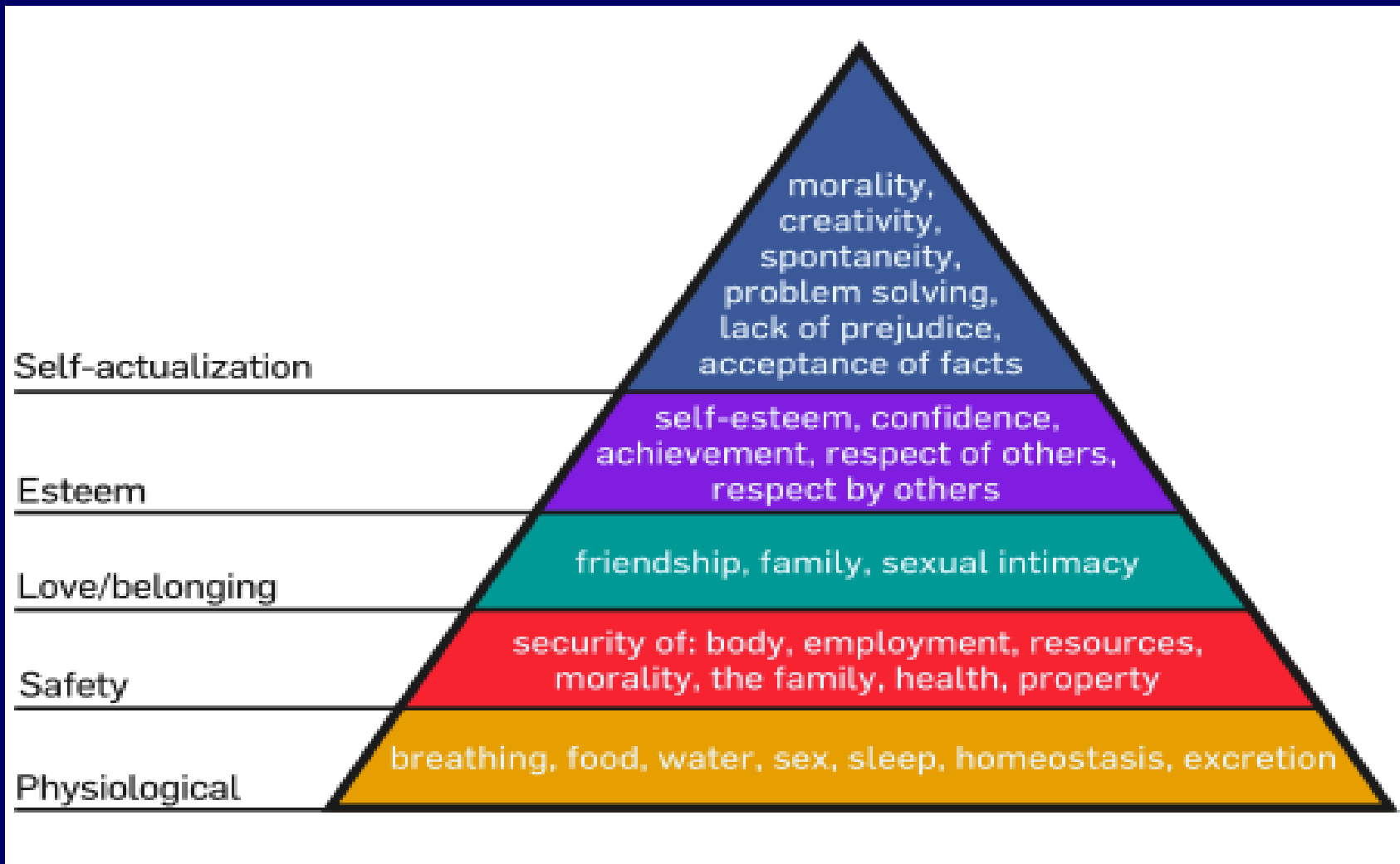


# Interventions to improve adherence

## Establish readiness to start ART

- Identify potential barriers
  - Psychosocial issues
  - Active substance use/risk of relapse
  - Low literacy level
  - Lack of disclosure
  - Health beliefs/skepticism about ART
  - Lack of prescription drug coverage/co pays
  - Busy daily schedule/travel away from home
  - Poor social supports
- Provide resources
  - Referral for case management
  - Referrals for mental health/substance abuse treatment
  - Resources to obtain prescription drug coverage
  - Referral to support groups
  - Pill boxes, reminder devices

# Social Barriers: Maslow's Hierarchy of Needs



# Transtheoretical Model of Change

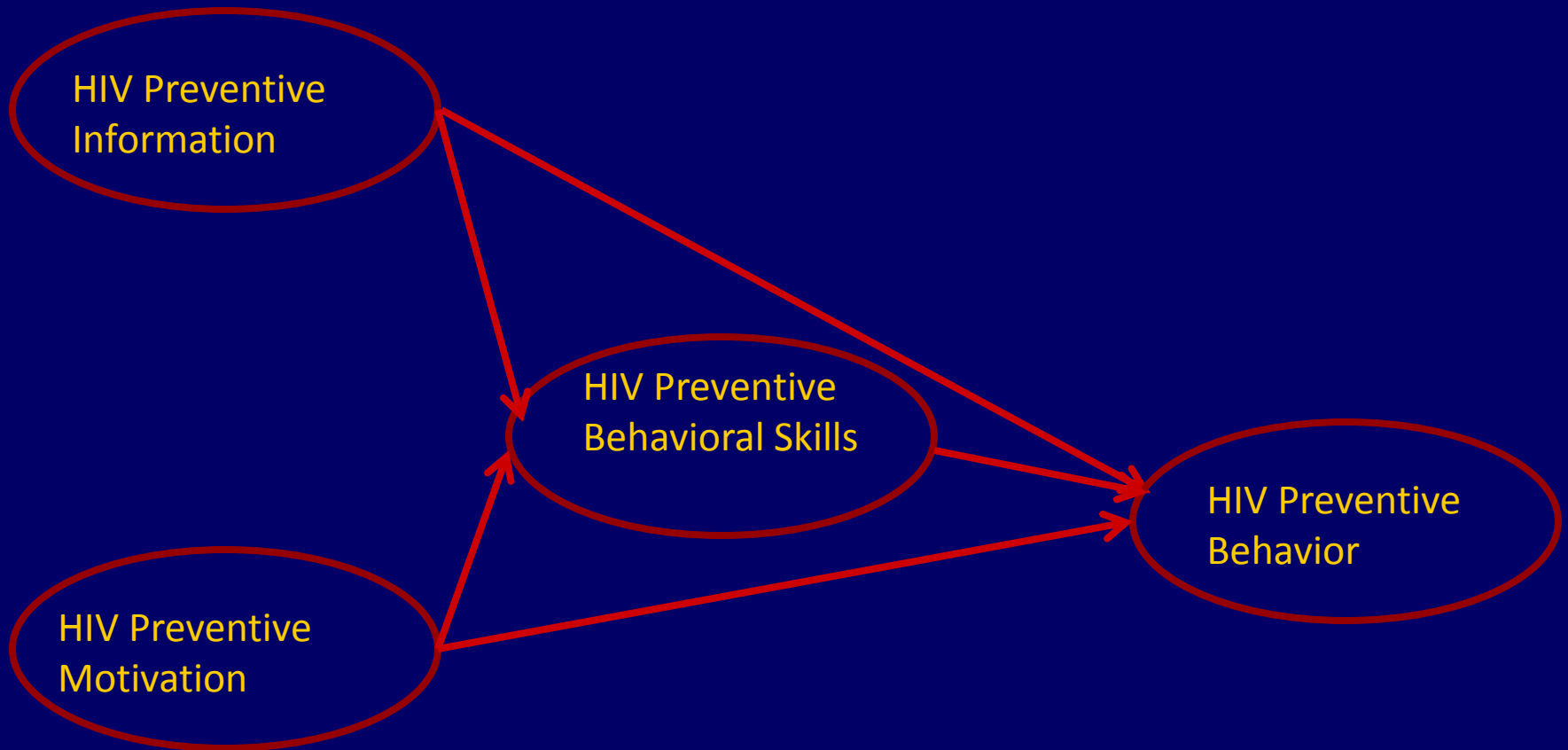
Stage	Description	Adherence Activities
Pre-contemplation	Not considering change; feeling no control; in denial	<ul style="list-style-type: none"> <li>-initial HIV education</li> <li>-assist patient in identifying goals</li> <li>-develop discrepancy between desired health and lack of ART</li> <li>-explore medical doubts</li> </ul>
Contemplation	Acknowledges concern but is ambivalent about change	<ul style="list-style-type: none"> <li>-begin to consider meds</li> <li>-consider mock medicine trial</li> <li>-explore patient's support network</li> <li>-referral to support groups</li> </ul>
Preparation	Committed to/planning change in near future	<ul style="list-style-type: none"> <li>-assess for potential barriers</li> <li>-identify temptations to skip</li> </ul>
Action	Taking steps to change	<ul style="list-style-type: none"> <li>-select regimen</li> <li>-provide reminder devices, written instructions</li> </ul>
Maintenance	Maintaining new behavior over time	<ul style="list-style-type: none"> <li>-monitor for side effects</li> <li>-ongoing monitoring</li> </ul>

# Interventions to improve adherence

## Select appropriate ART regimen

- Establish relationship of trust
- Involve patient in selection
  - Include patient's support system
- Educate
  - Factual information
    - Drug names/administration schedule
      - Proximal cue for action
    - Storage/food requirements
    - Potential side effects/side effect management
    - Use written instructions
    - Contingency plans for potential missed doses
  - Conceptual information
    - HIV basics
    - Expected benefits of therapy
      - Identify patient's goals of therapy
    - Consequence of non adherence

# IMB Model



*Motivation includes subjective norms, behavioral intentions, and attitudes*

# Motivational Interviewing

- Express Empathy
- Develop Discrepancy
  - how patients want their life to be vs. how it is
  - values vs. behavior
- Role with Resistance
  - reluctance to change is normal, not pathologic
- Support Self Efficacy
  - embrace client autonomy
  - help clients move toward change successfully and with confidence.

Miller, W.R. and Rollnick, S. *Motivational Interviewing: Preparing People to Change*. NY: Guilford Press, 2002.

# Interventions to improve adherence

## Ongoing monitoring

- Utilize a multidisciplinary team approach
- Provide accessible team
  - Consider home visits
- Encourage goal making
  - Establish link between adherence and goal achievement
  - Identify “salient pro”
- Measure adherence regularly
- Identify reason for non adherence
- Develop management plan that address reason and reassess