Recent Randomized ARV Trials

Proportion with VL <50 copies/ml wk 48 (ITT)

Experienced Trials (overall)		2 or more active agents
Benchmrk	65%	75%
Victor E1 (Wk 24)	56%	67-72%
Motivate	52-56%	52-61%
Power	46%	73%
Duet	60-61%	66-80%
TITAN	61-70%	60-80%

Cooper, CROI 2008, Steigbigel, CROI 2008, Zingman, CROI 2008; Lalezari ICAAC 2007, Falkenheuer, EACS, 2007; Lazzarin, Lancet, 2007; Haubrich, CROI, 2008; Johnson CROI 2008; Madruga Lancet, 2007

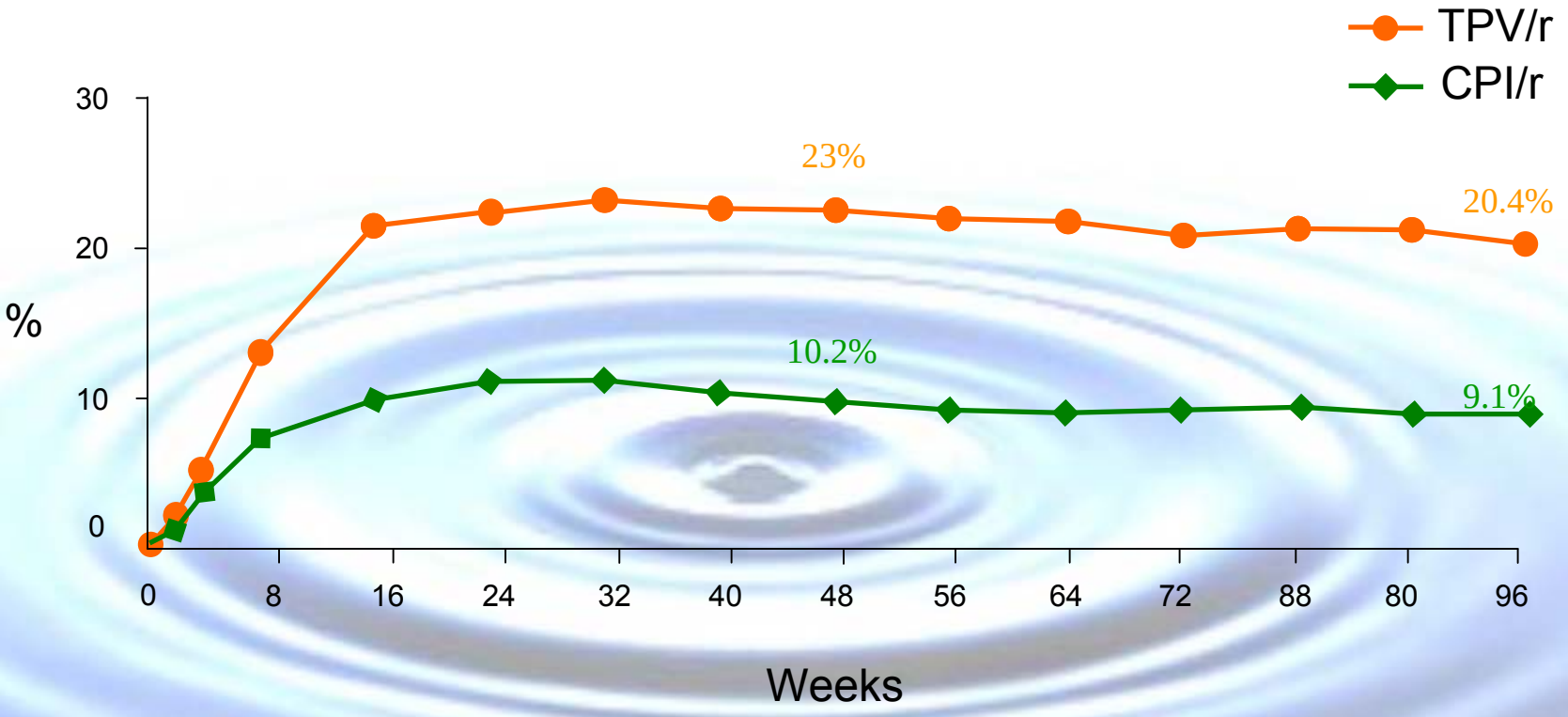
Randomized Controlled Clinical Trials in Treatment Experienced Patients

Based on the TORO model with enfuvirtide

- Multidrug experienced or resistant
- Viral load > 1000-5000 copies/mL
- No CD4 count restriction
- OBT (optimized background therapy) vs OBT plus new agent
- Two identical trials in different geographic areas
- Sub-analysis
  - Baseline VL, CD4, GSS or PSS, use of new agents

Lalezari, Lazzarin, NEJM, 2003

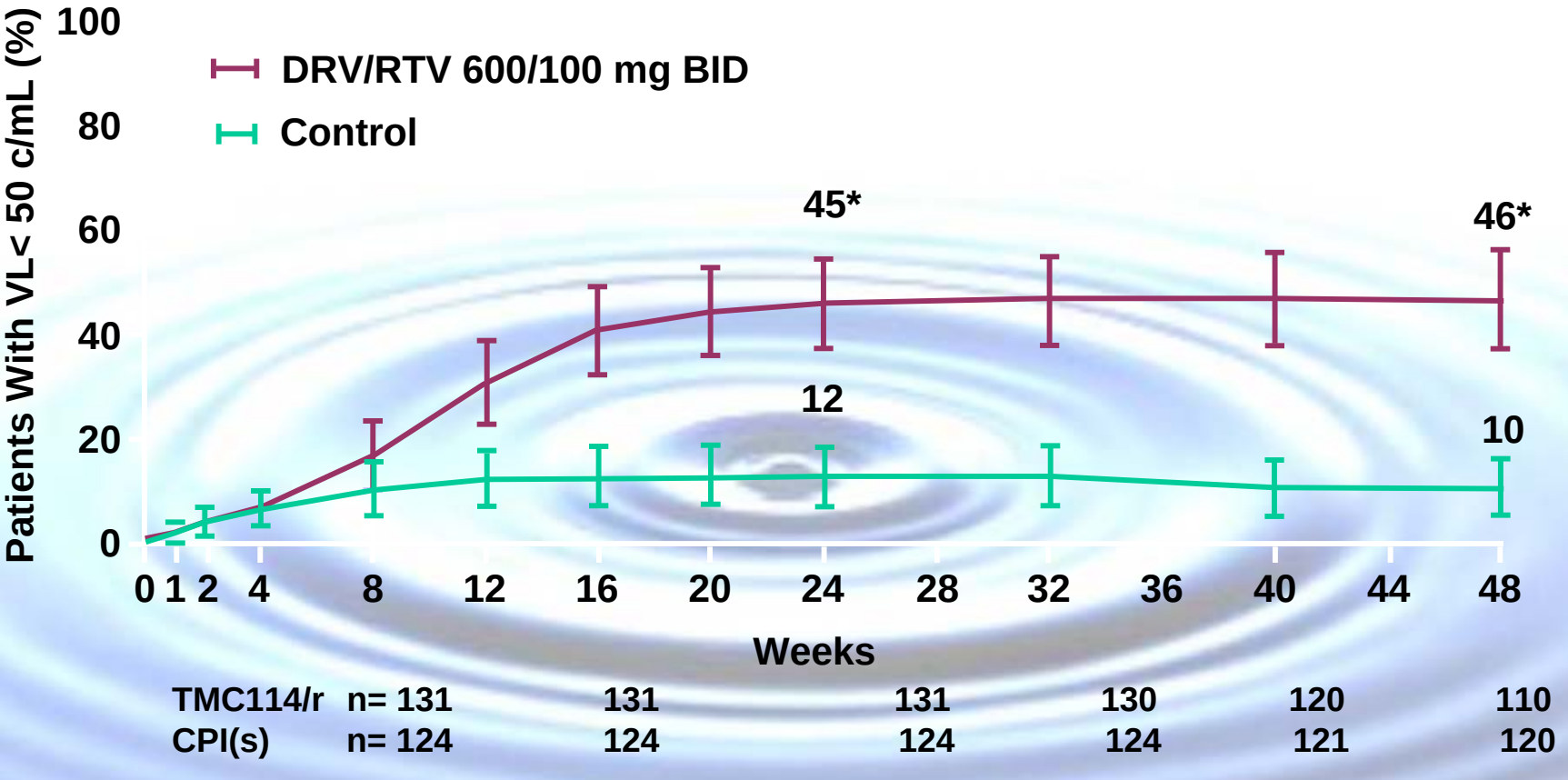
Tipranavir/r:
Proportion with VLs <50 copies/mL over 96 weeks



TPV/	98/746	169/746	170/746	152/746
CPI/r	54/737	82/737	75/737	67/737

Farthing ICAAC, 2006

Darunavir/r:
Percentage with VL < 50 copies/mL at Week 48

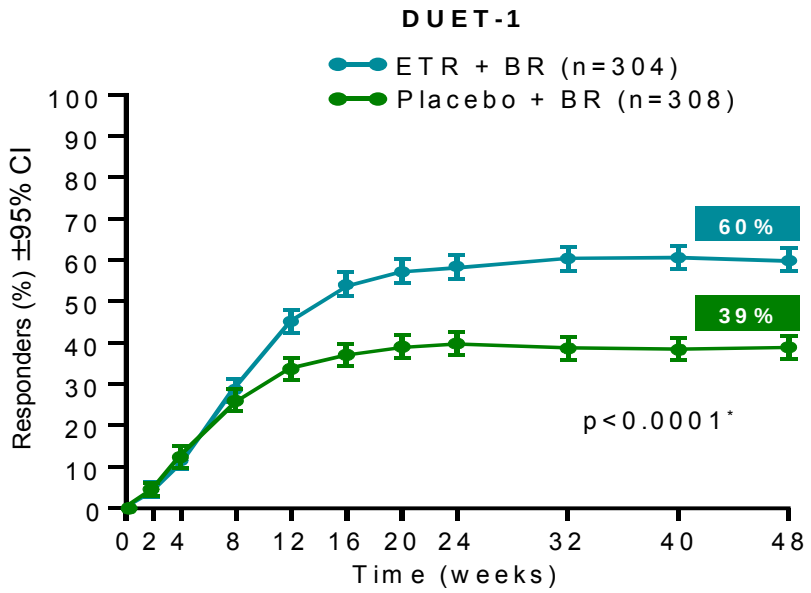


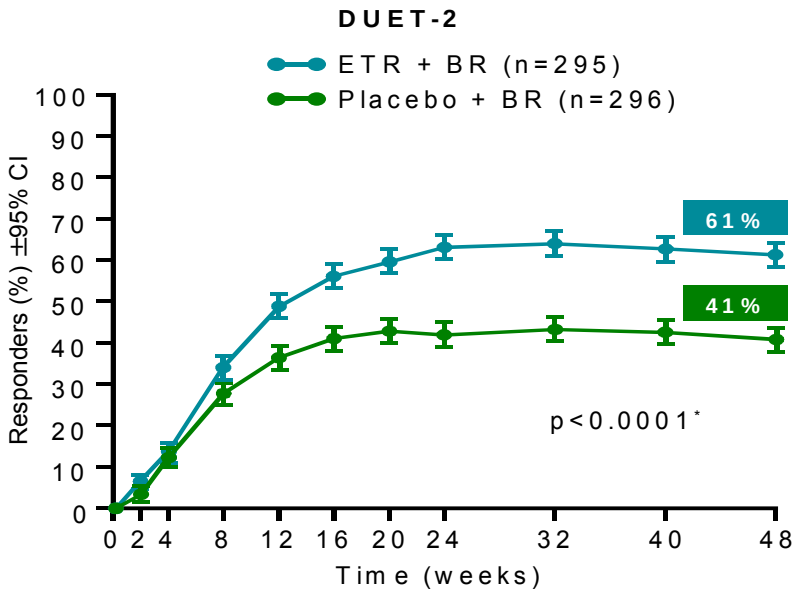
**P < .001 vs comparator PI/RTV.*

Clotet, Lancet, 2007

Etravirine (TMC 125)

Patients with viral load <50 copies/mL at Week 48 (ITT-TLOVR)



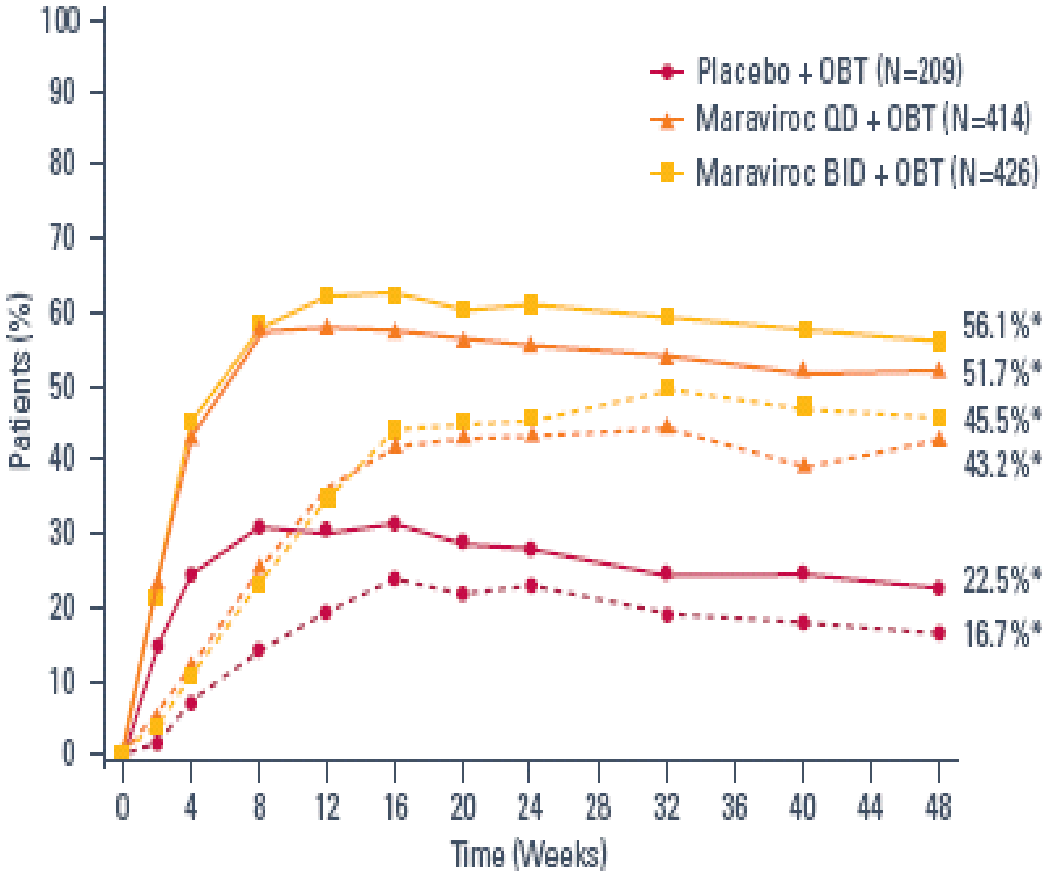


*Logistic regression model; ITT= intention to treat; TLOVR= time to loss of virologic response

Haubrich, Johnson, CROI, 2008

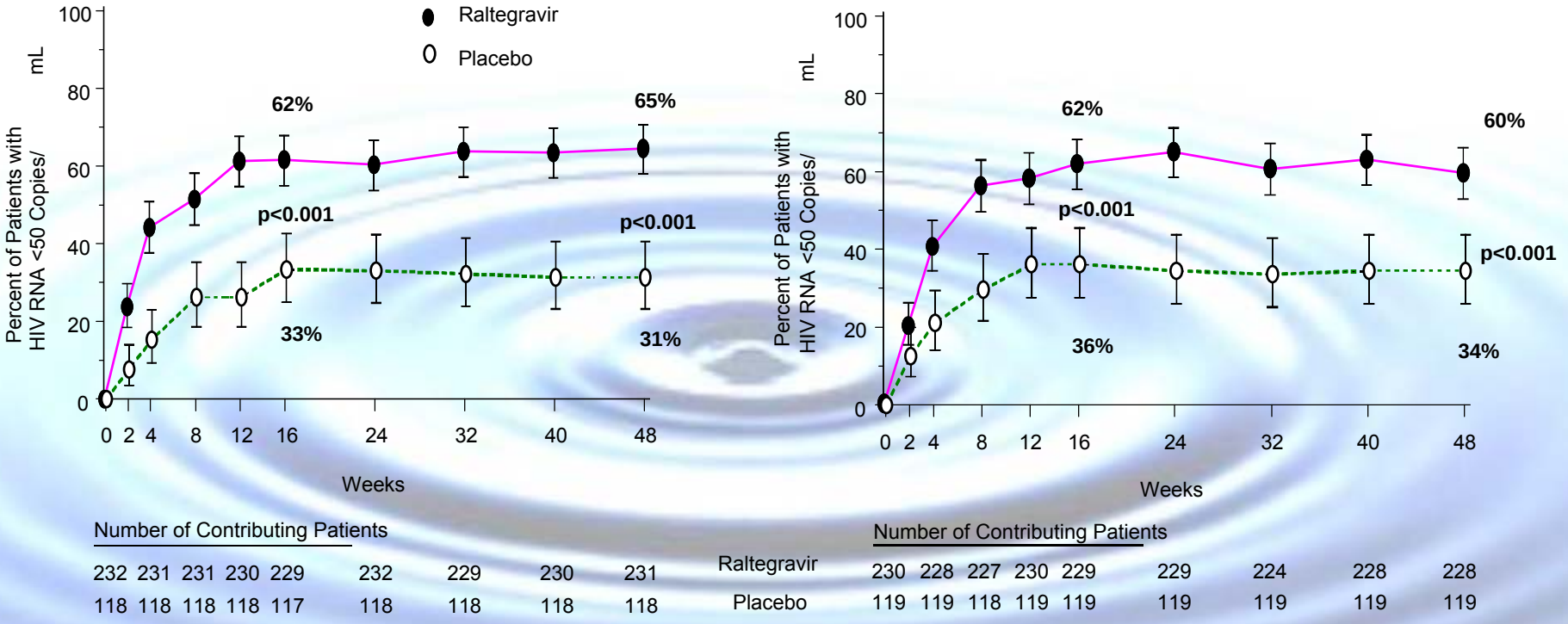
Maraviroc
MOTIVATE 1,2 combined analysis, 48 weeks

Figure 1: Percentage of patients with HIV-1 RNA suppression (solid lines, HIV-1 RNA <400 copies/mL; dashed lines, HIV-1 RNA <50 copies/mL)



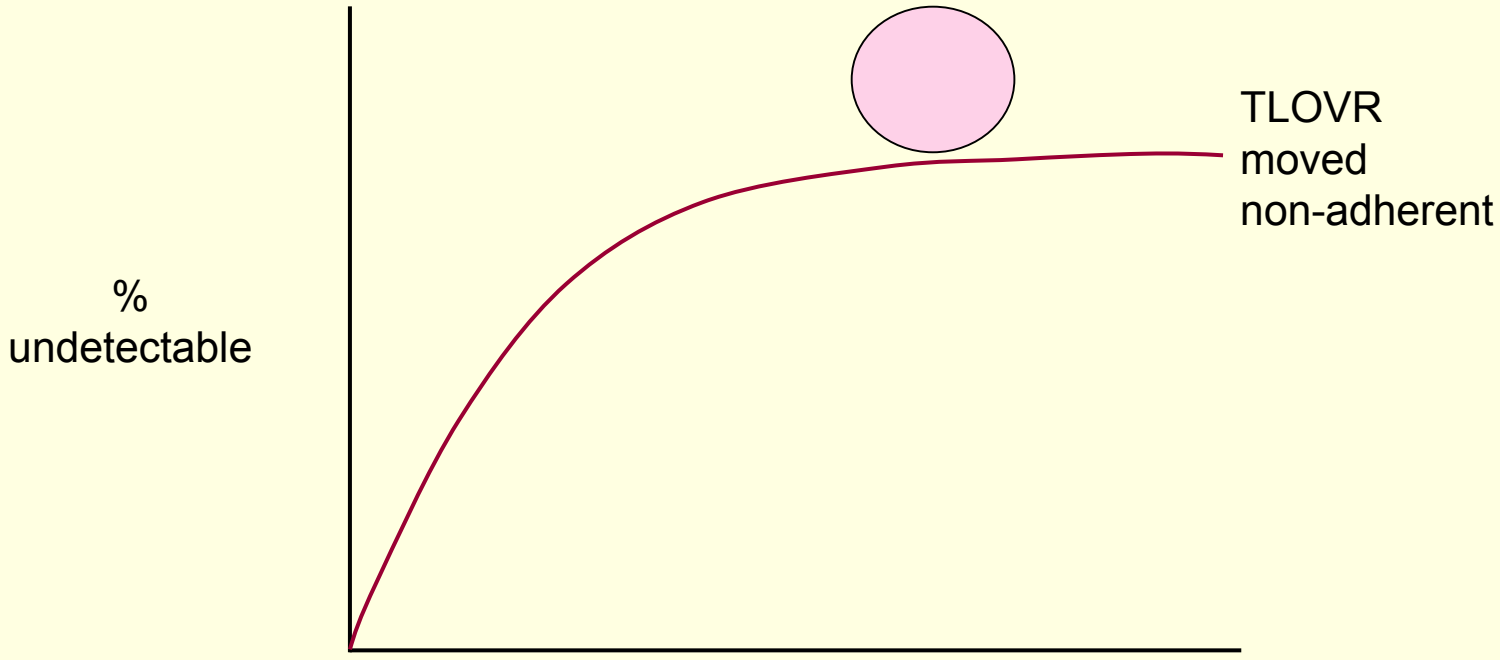
Hardy, CROI, 2008

Integrase Inhibitors: Raltegravir Benchmrk 1, 2 Efficacy - 48 weeks



Cooper, Steigbigel, CROI, 2008

What about missing patients?



Triple class experienced categories

1. Suboptimal therapy → will succeed
   good adherence
2. Always had toxicity → may succeed
3. Never taken pills → could succeed
4. Unlucky → will succeed

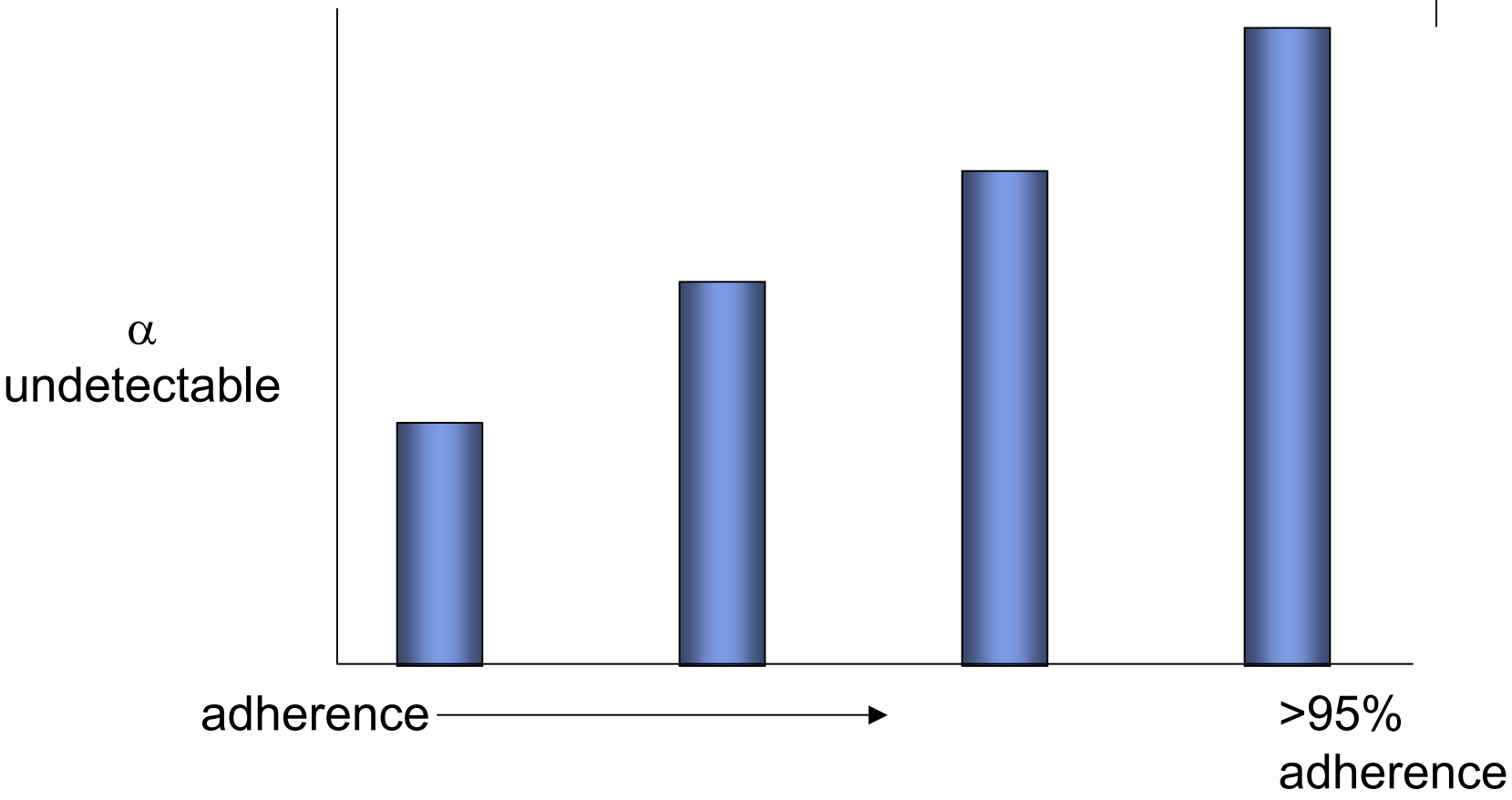
Adherence interaction

Adherence ↔ Toxicity

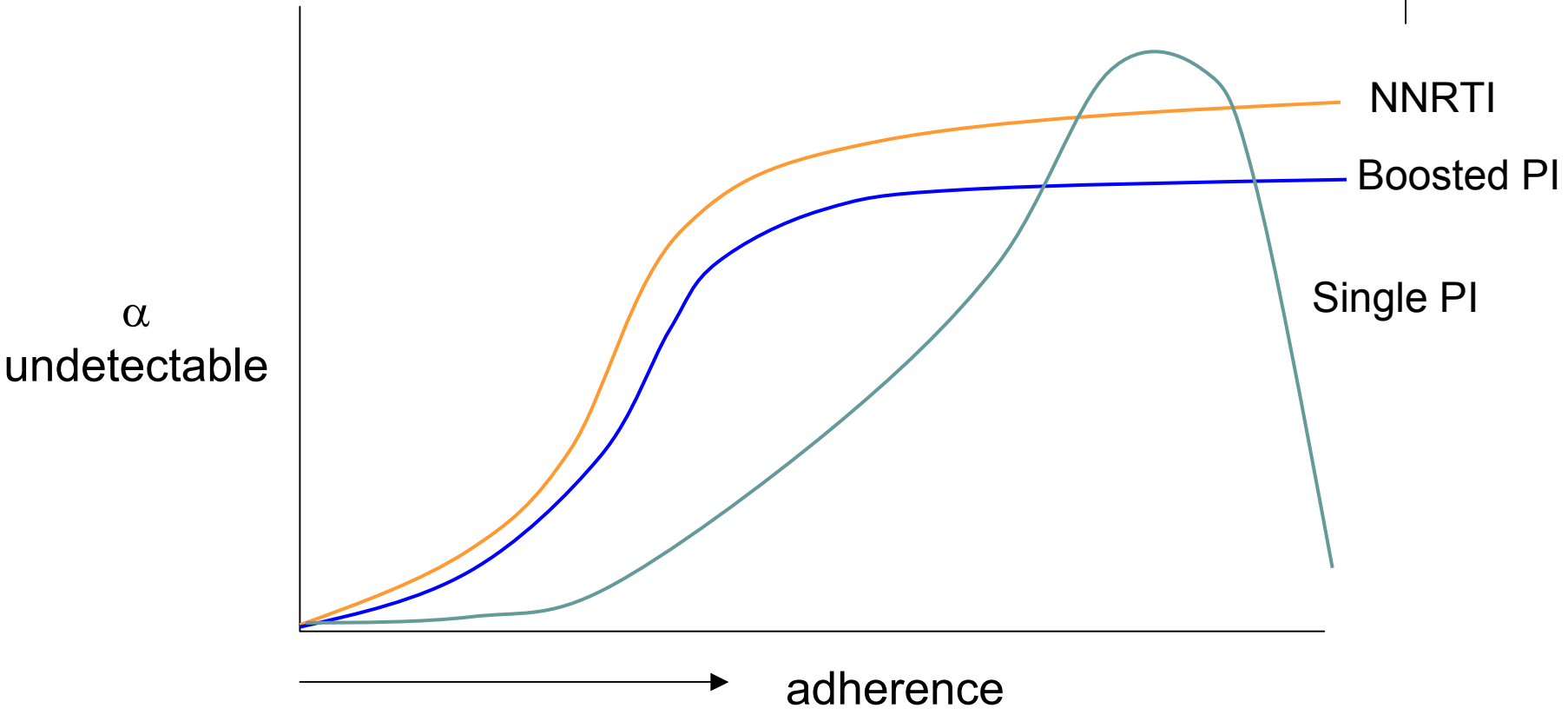
PC –

- Cannot predict 'good adherence'
- Reality – a group of people with very disturbed behaviour

'force' into Rx ⇌ wait 'til they are ready



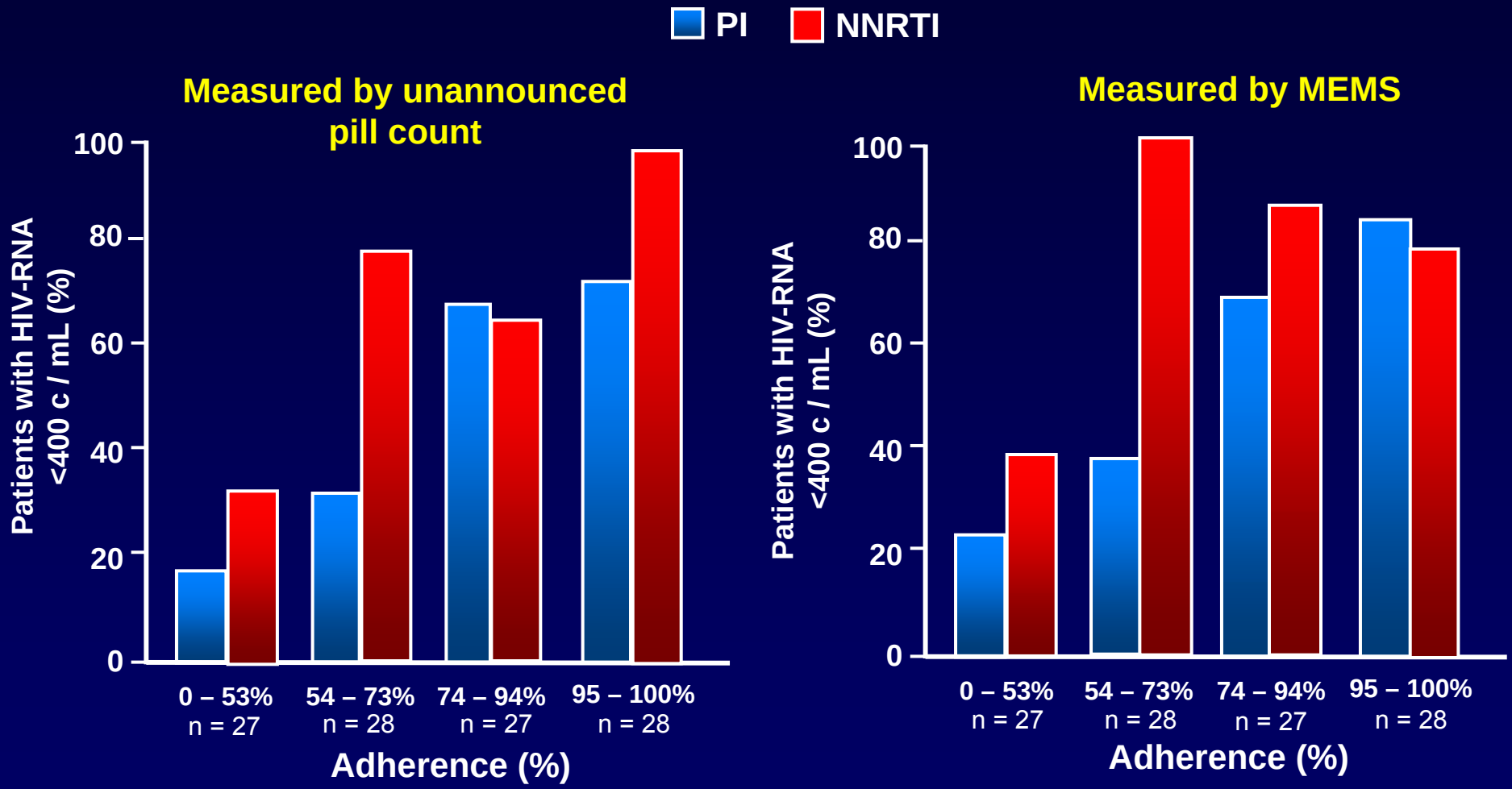
Paterson



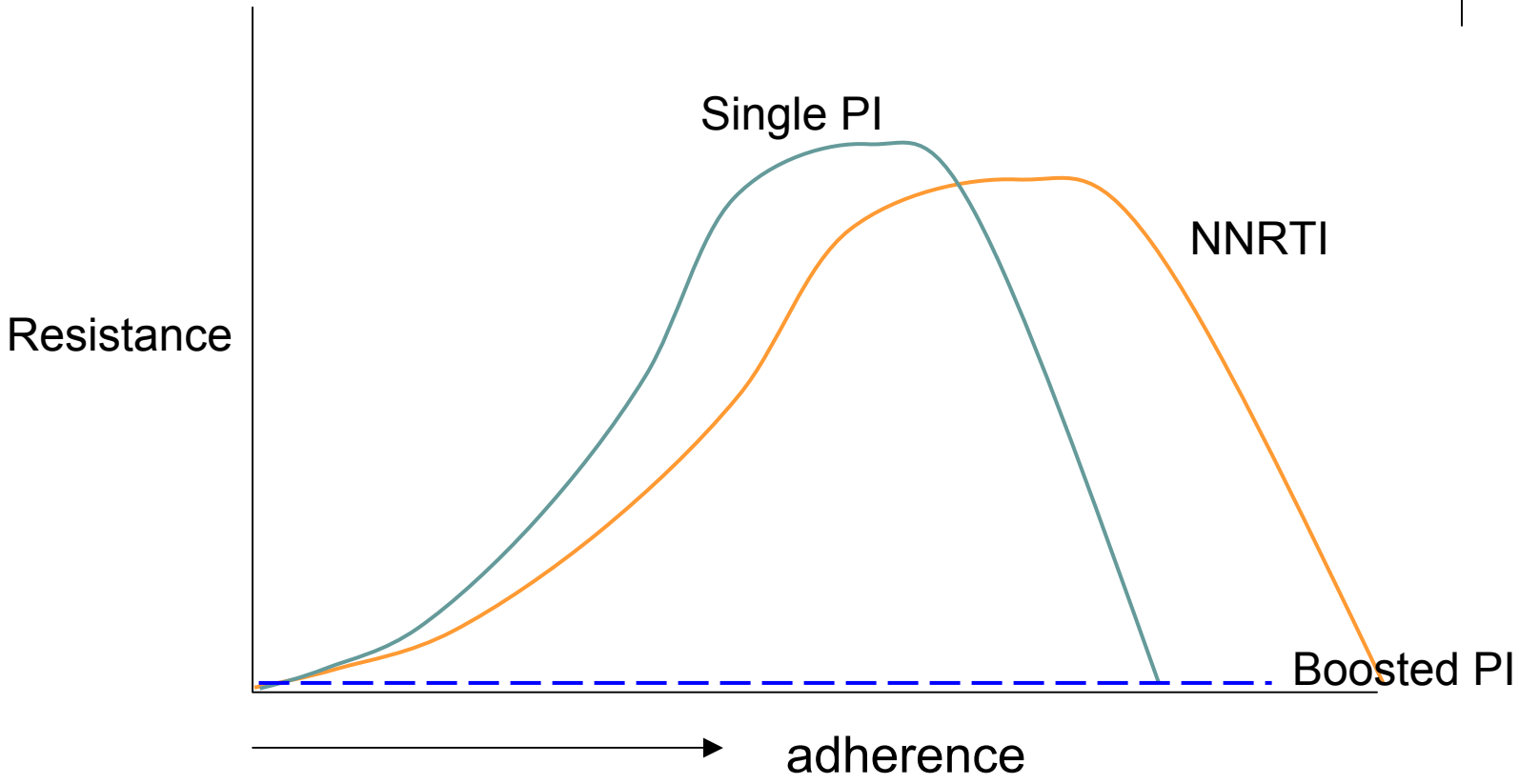
Deeks et al.

Less Than 95% Adherence to NNRTIs Can Still Lead to Viral Suppression

- Majority of NNRTI-treated individuals suppressed to <400 copies / mL at 54 – 100% adherence whereas majority of PI-treated individuals required 95 – 100% adherence



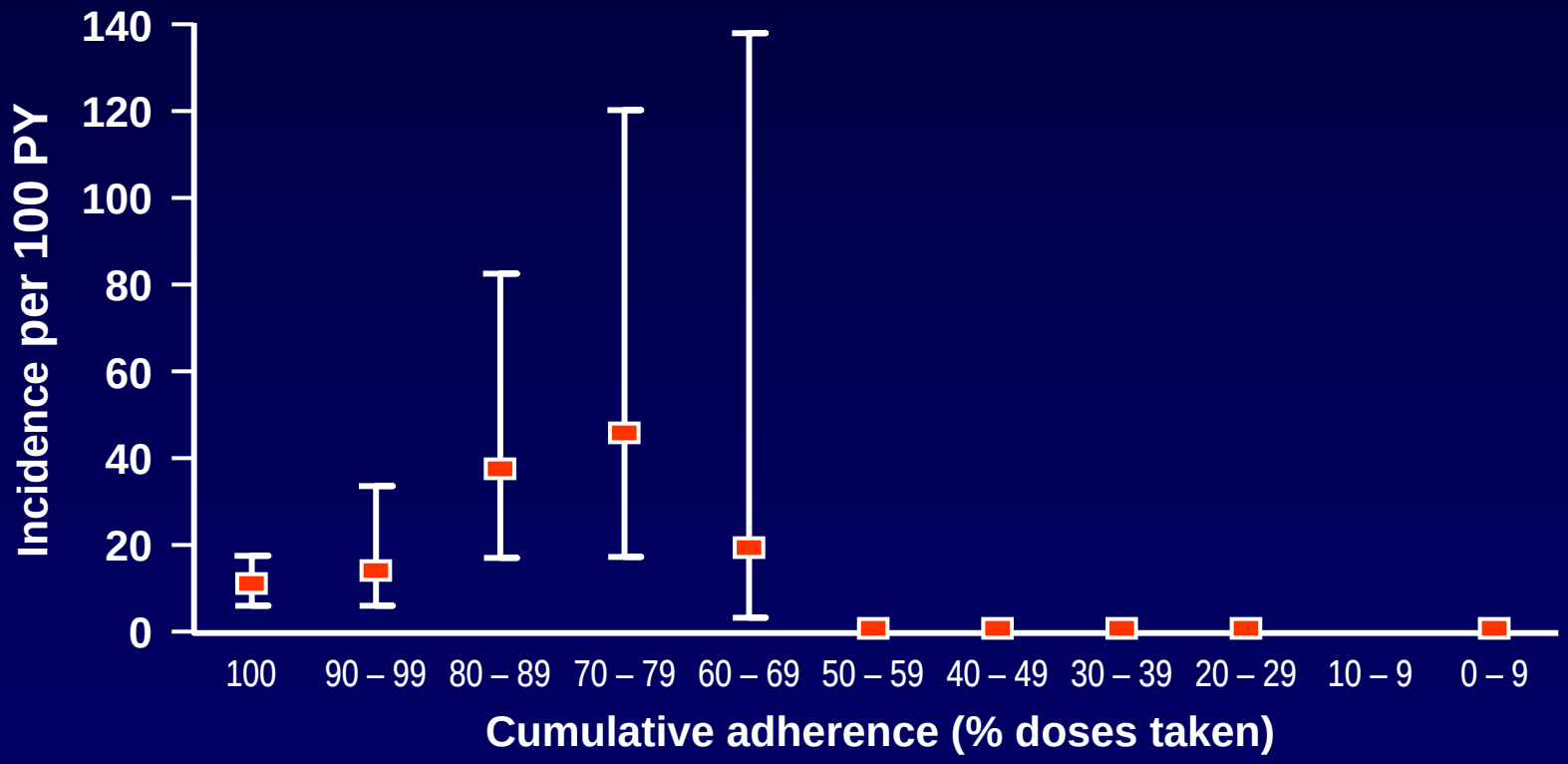
Adapted from Bangsberg DR. *CID* 2006; 43:939–941.



Deeks et al.

Adherence and Viral Resistance

- Study design: prospective cohort study (195 patients)
- Inclusion criteria: receiving HAART and having HIV-RNA <500 c / mL
- Endpoint: viral rebound with clinically significant resistance



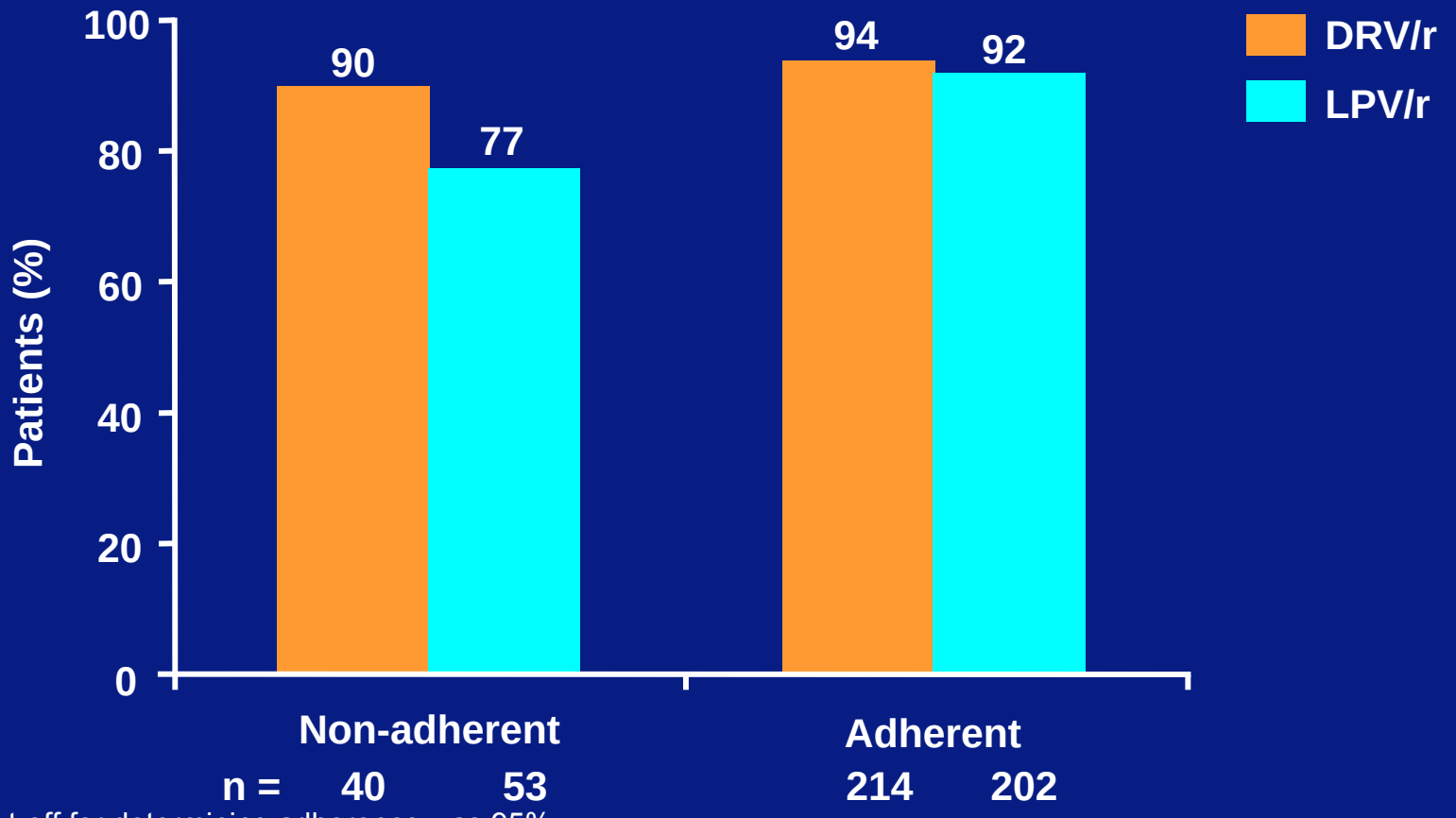
Adapted from Sethi AK et al. *CID* 2003; 37:1112–1118.

*Standard error bars / standard deviation values not mentioned

How Missed Doses Can Lead to Compromised Drug Levels

*This figure is a schematic representation.

Confirmed week 48 virological response (< 50 copies/mL) versus adherence* (M-MASRI)



*Cut-off for determining adherence was 95%.

M-MASRI = Modified Medication Adherence Self-Report Inventory.

Tibotec, data on file.

Boosted PI and adherence

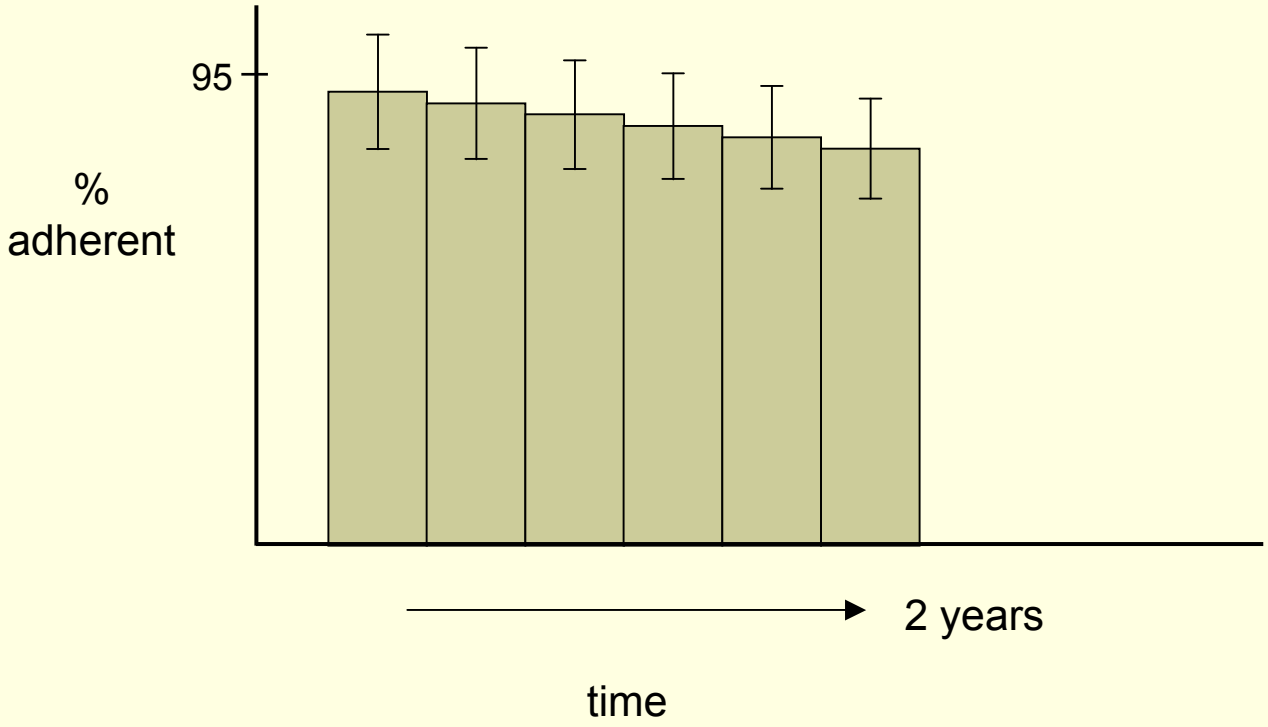
10% non adherent to Ritonavir

20% RT > 4hrs later

} Only 35 patients

Kemal 884 CROI 2008

CPCRA - adherence with time



C&W cohort

Undetectable at 1 yr → 90% undetectable at 5yrs

Intentional vs. Unintentional Non-Adherence

Unintentional non-adherence

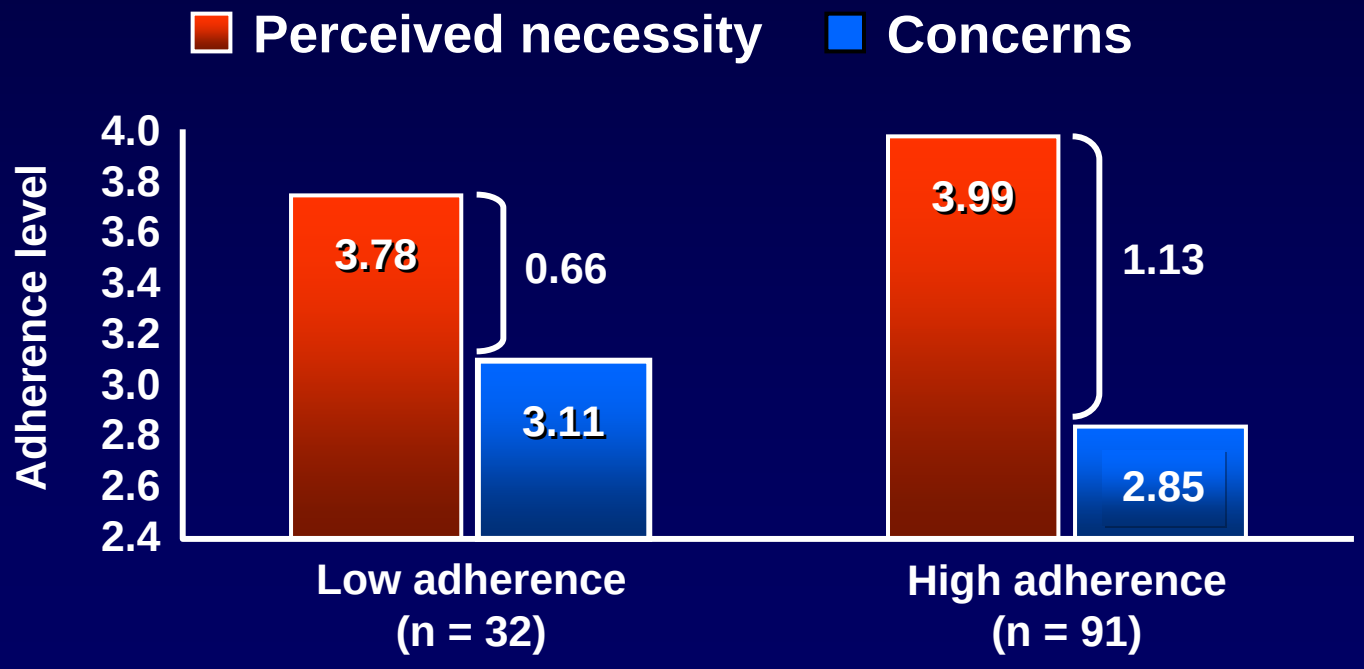
- Capacity and resource limitations
- Practical barriers
- Can help with practical solutions (e.g. text messaging)

Intentional non-adherence

- Motivational beliefs / preferences
- Perceptual barriers

Barriers to Adherence: Patients' Perceptions of Necessity and Concerns

- HAART patients received *Beliefs about Medicines Questionnaire* (BMQ)
- Statistical analysis determined associations between beliefs about HAART and reported adherence



Horne R et al., *Int J STD AIDS* 2004; 15:38–44.

Self belief systems

"Long term chemicals are bad"

→ lipodystrophy

Long term HIV is even worse

→ CV risk and Smart

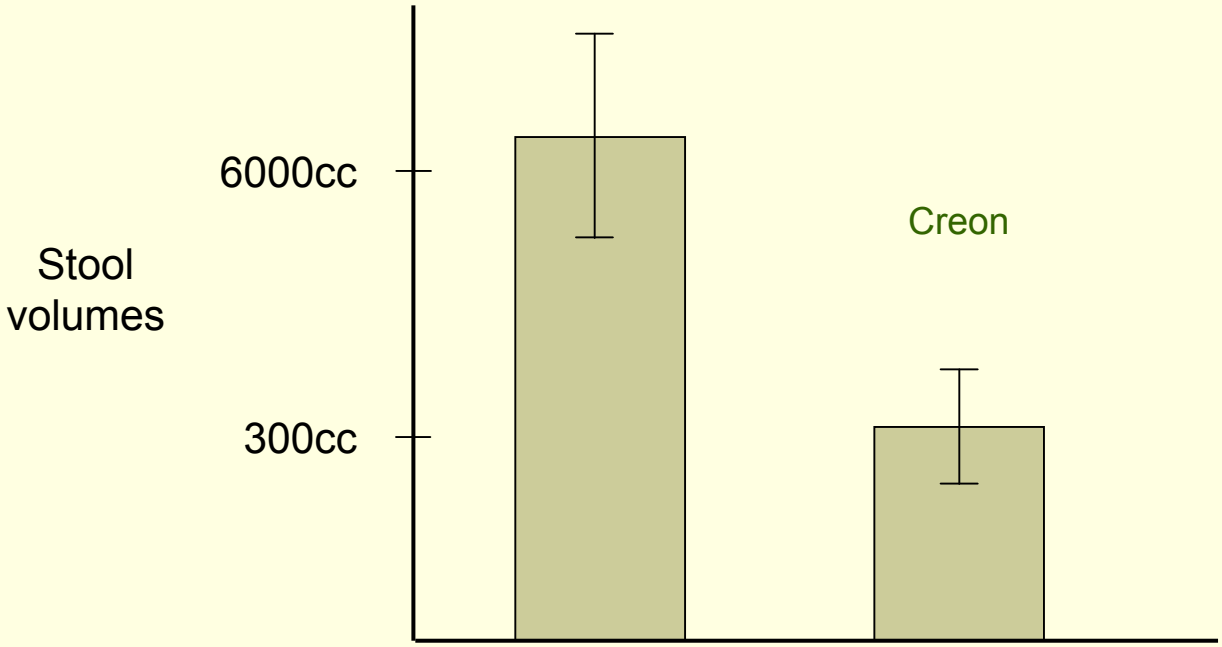
However - unknown toxicity

Lipoatrophy

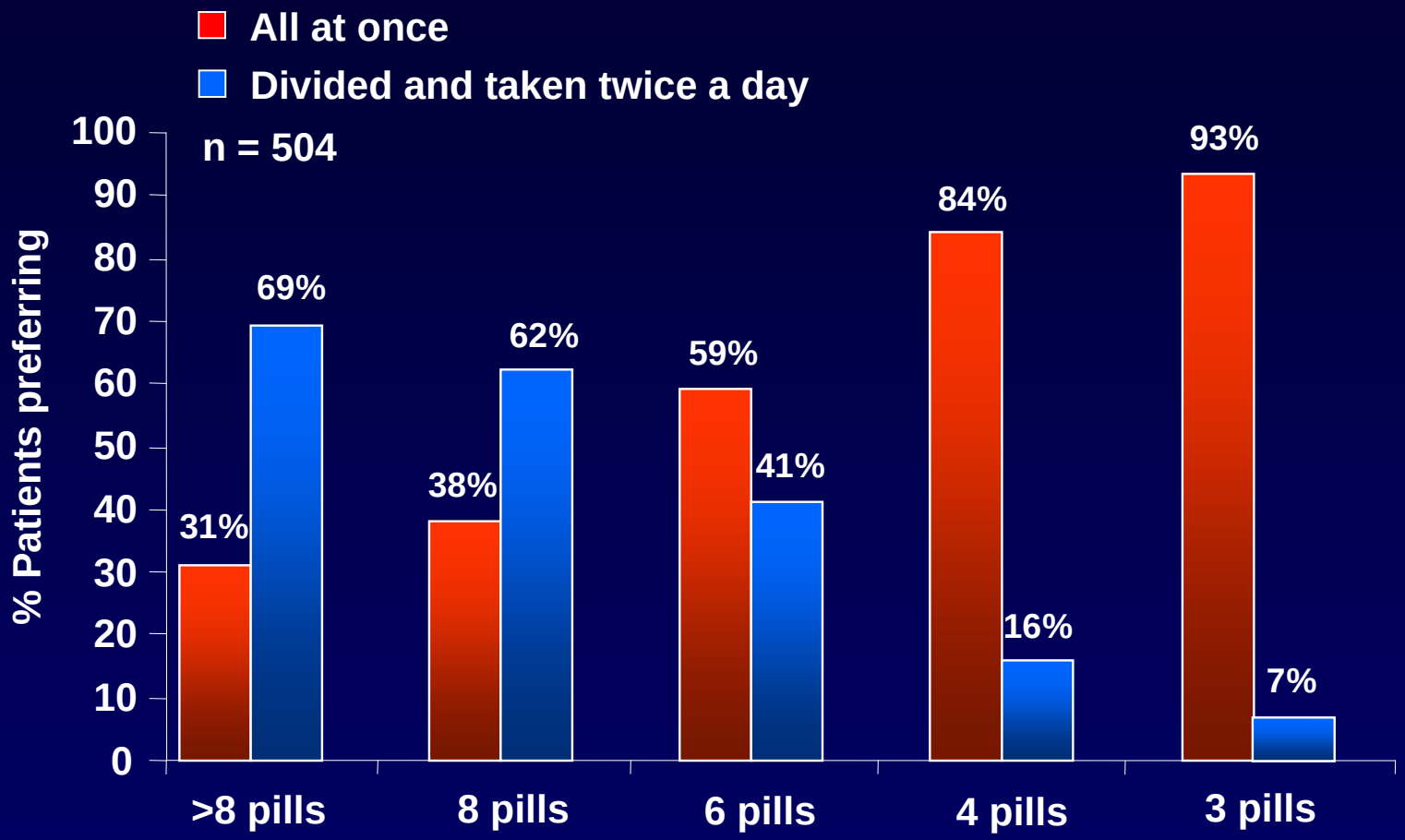
Pancreatic atrophy

Neoplasia

Pancreatic atrophy (20)



Influence of Pill Burden on Patient Dosing Preference

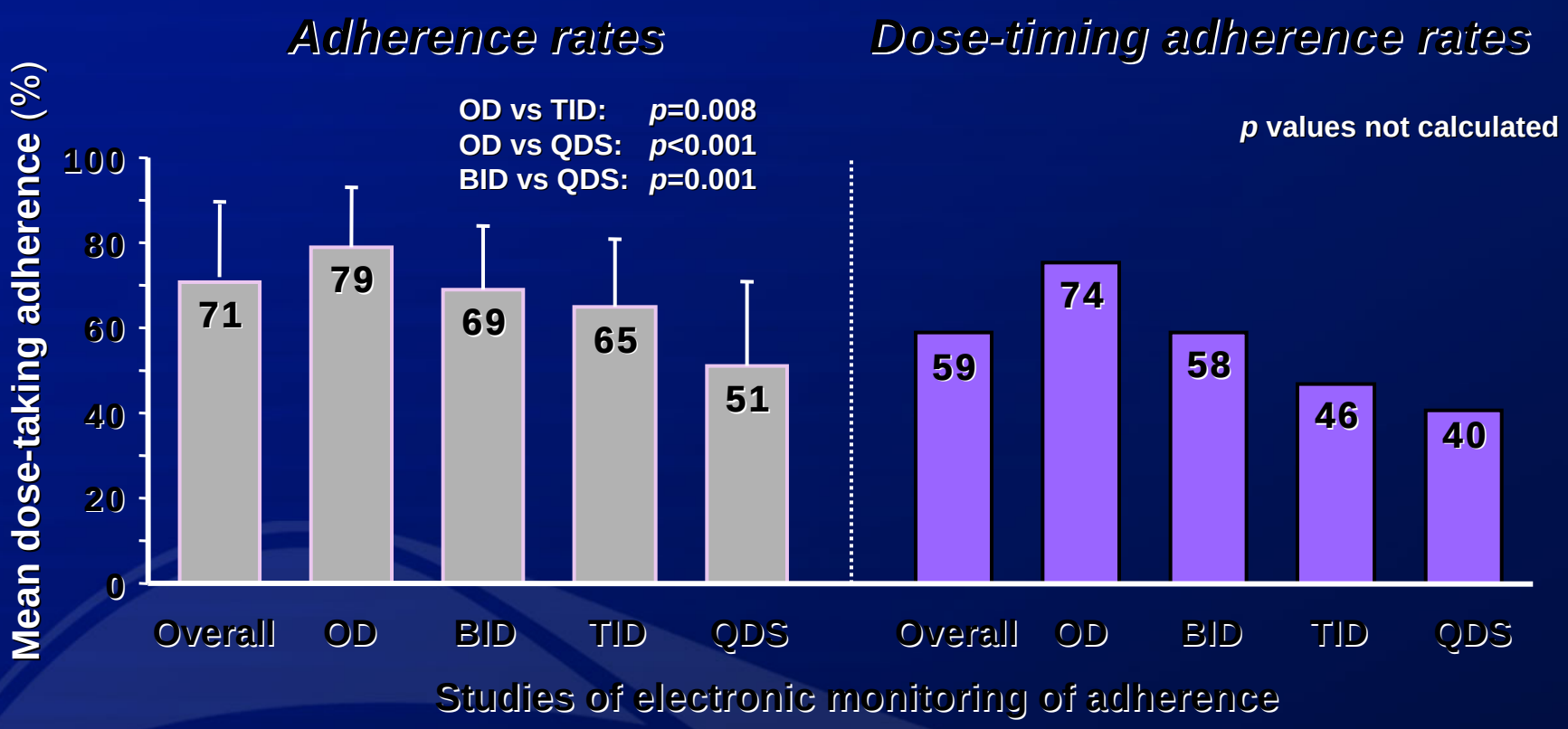


*Total number of pills also important factor.

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

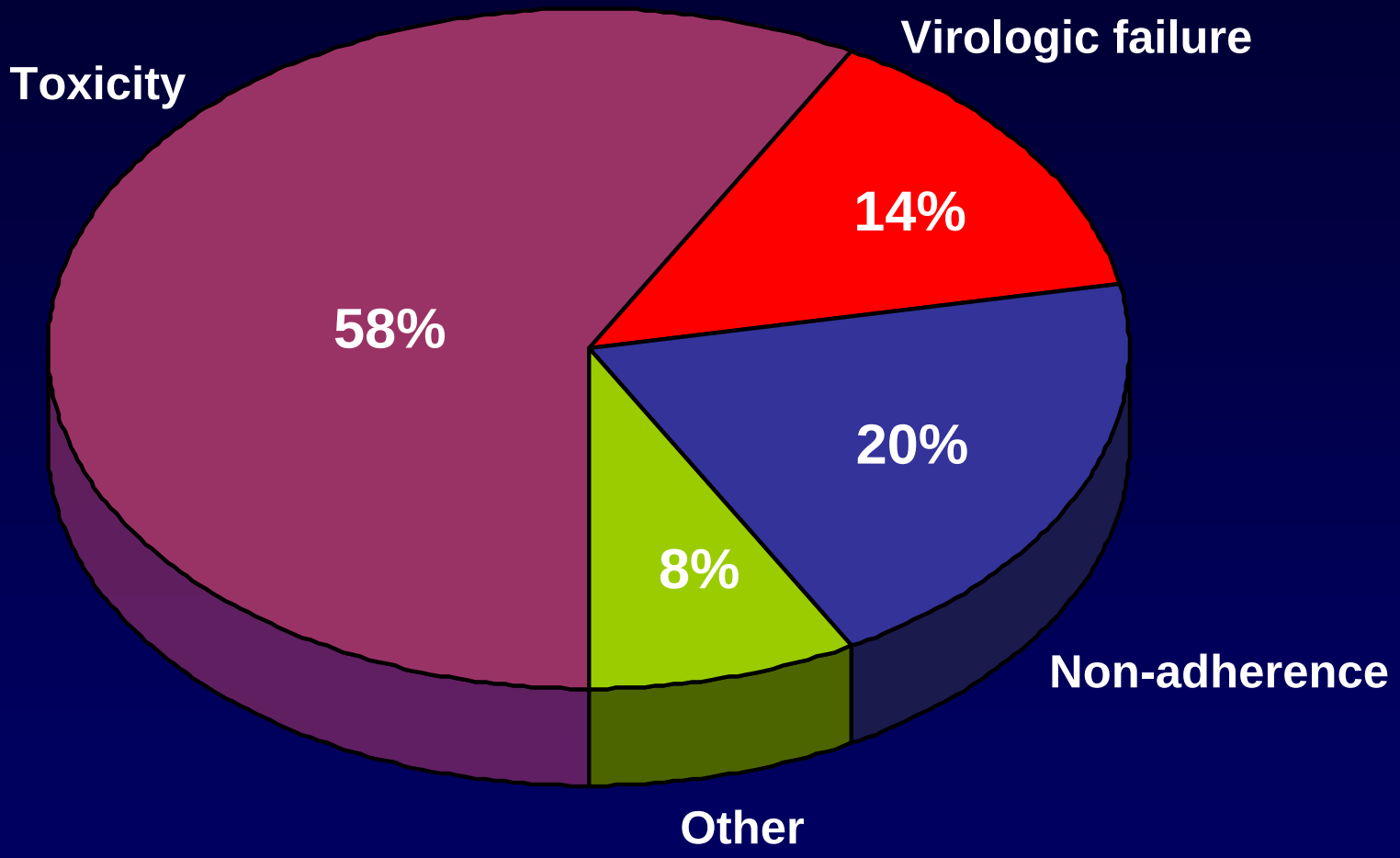
Impact of dose frequency upon adherence

Analysis of 76 studies of electronic monitoring of adherence



Adapted from: Claxton AJ *et al*. *Clin Ther* 2001; 23: 1296–1310

Main Reasons for Discontinuation of ART

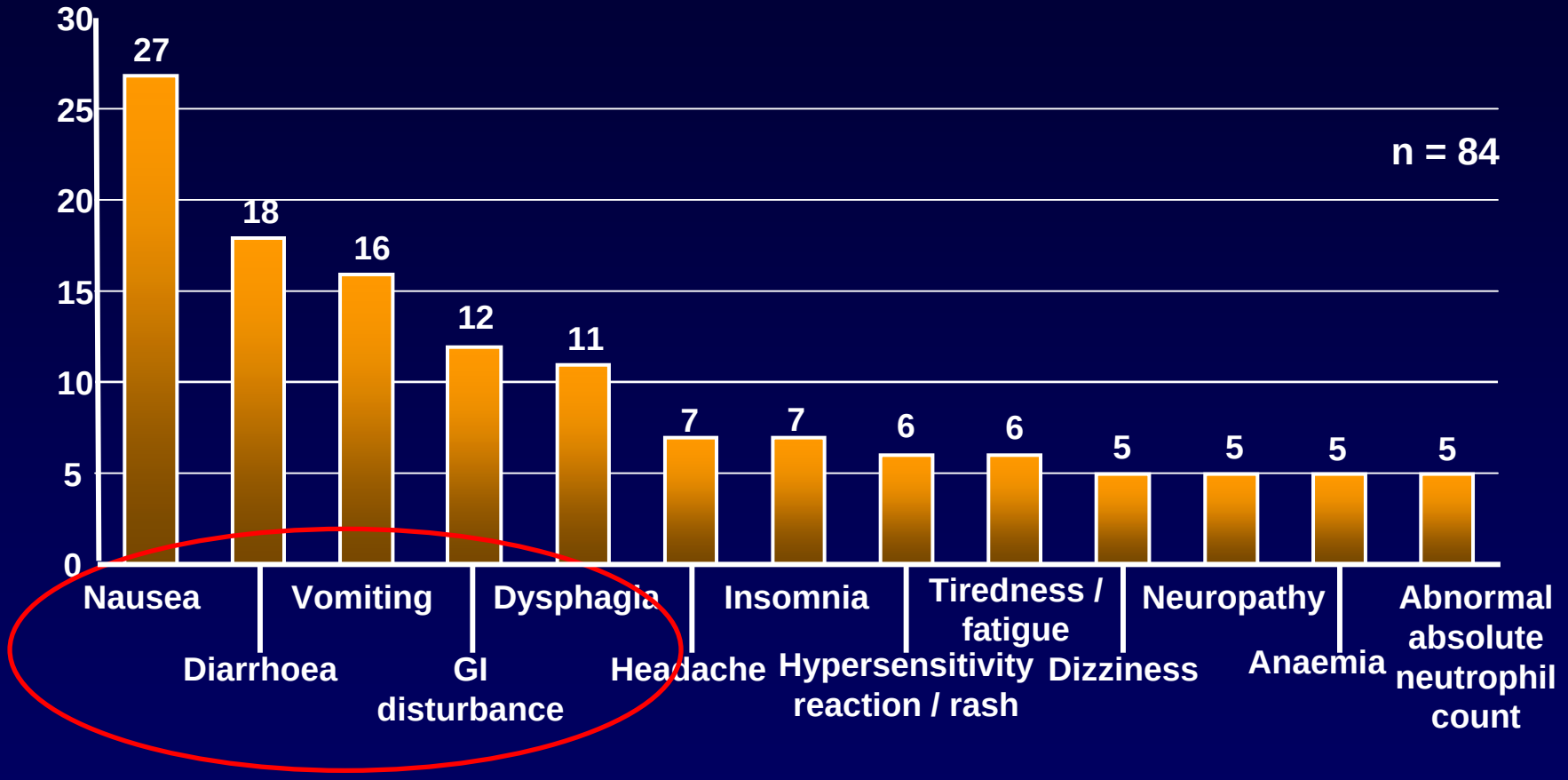


312 discontinuations among 862 pts who initiated HAART

Adapted from d'Arminio Monforte A et al. *AIDS* 2000; 14:499–507.

AE Reasons for Discontinuation of HAART

Patients (%) who discontinued HAART due to a particular AE*



Poor GI tolerability major reason for discontinuing

* >1 reason may have been noted from each individual.

Adapted from O'Brien ME et al. *JAIDS* 2003; 34:407–414.

Diarrhoea

Group	2	Up to 7 loose stools a day
	3	>7 + incontinence
	4	i/v fluids dehydrated

Diarrhoea

	Kaletra	Darunavir
Abbot od bd (3-4)	17-18%	
Artemis (2-4)	11%	4%
Titan (2-4)	14.5%	7.7%
Heat (2-4)	(18-19%)	
Castle (2-3)	11%	
5142 (2-4)	30-51%	GI effects

Abstract # 105 a&b LB

BENCHMRK-1 & 2: Summary of Clinical Adverse Experiences

Adverse Experiences (AE)	BENCHMRK-1		BENCHMRK-2	
	Raltegravir + OBT N = 232 %	Placebo + OBT N = 118 %	Raltegravir + OBT N = 230 %	Placebo + OBT N = 119 %
Mean Exposure (weeks)	26.0	23.0	25.3	22.5
Any AE	81.0	83.1	80.9	86.6
Drug-related* AE	43.5	50.8	53.0	52.1
Serious AE	10.8	13.6	9.6	14.3
Serious drug-related* AE	2.2	0.0	1.3	2.5
Death	1.3	0.8	1.3	0.0
AE leading to discontinuation	1.7	3.4	1.7	0.8

*Drug-related = considered possibly, probably, or definitely related to raltegravir/placebo ± OBT or to OBT alone

All comparisons have nominal p-values > 0.10

BENCHMRK-1 & 2: % with Drug Related* Clinical Adverse Experiences (≥ 3% - mild, moderate and severe)

	BENCHMRK-1		BENCHMRK-2	
	Raltegravir + OBT N = 232 (%)	Placebo+OBT N = 118 (%)	Raltegravir + OBT N = 230 (%)	Placebo+OBT N = 119 (%)
Mean Exposure (Wks)	26.0	23.0	25.3	22.5
Abdominal Distension	0.4	3.4	3.9	0.8
Abdominal Pain	1.3	3.4	4.3	0
Diarrhea	6.5	11.0	12.2	9.2
Flatulence	0.4	1.7	4.3	1.7
Nausea	3.9	6.8	9.1	8.4
Vomiting	2.2	7.6	2.6	2.5
Injection Site Reaction	6.9	11.9	10.9	8.4
Pyrexia	0.9	1.7	1.3	3.4
Headache	2.6	6.8	7.8	4.2
Insomnia	1.7	3.4	0.9	0
Fatigue	1.7	0	4.3	2.5

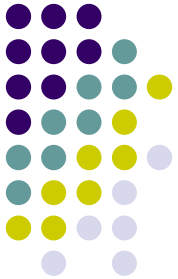
*Drug-related = judged possibly, or probably, or definitely related to raltegravir/placebo ± OBT or to OBT alone

Adverse event rate by time on study

All casualties and severities All patients receiving one dose	VCV 30 mg + OBT Rate	VCV 20 mg + OBT Rate	Placebo + OBT Rate
Total exposure in person-years (P-Y)*	33.2	34.67	22.39
SAE's N (P-Y)	4 (12)	5 (14.4)	5 (22.3)
Any adverse events	111.4	112.5	147.4
Diarrhoea	45.2	31.7	40.2
Respiratory symptoms	24.1	51.9	22.3
Nausea	15.1	8.7	22.3
Pyrexia	15.1	11.5	17.9
Dizziness	15.1	2.9	17.9
Headache	15.1	8.7	31.2
Tinea Pedis	12.1	0	4.5
Lymphadenopathy	9.0	20.2	8.9
Depresssion	9.0	11.5	26.8
Musculoskeletal Pain	9.0	8.7	40.2
Asthenia	6.0	2.9	13.4
Fatigue	6.0	14.4	13.4
Upper abdominal pain	3.0	14.4	0
Flatulence	3.0	5.8	17.9
Anorexia	0	0	13.4

Zingman B. *et al*., Oral 39LB. VICTOR-E1 48 Wks. CROI Boston 05-02-2008.

Adherence



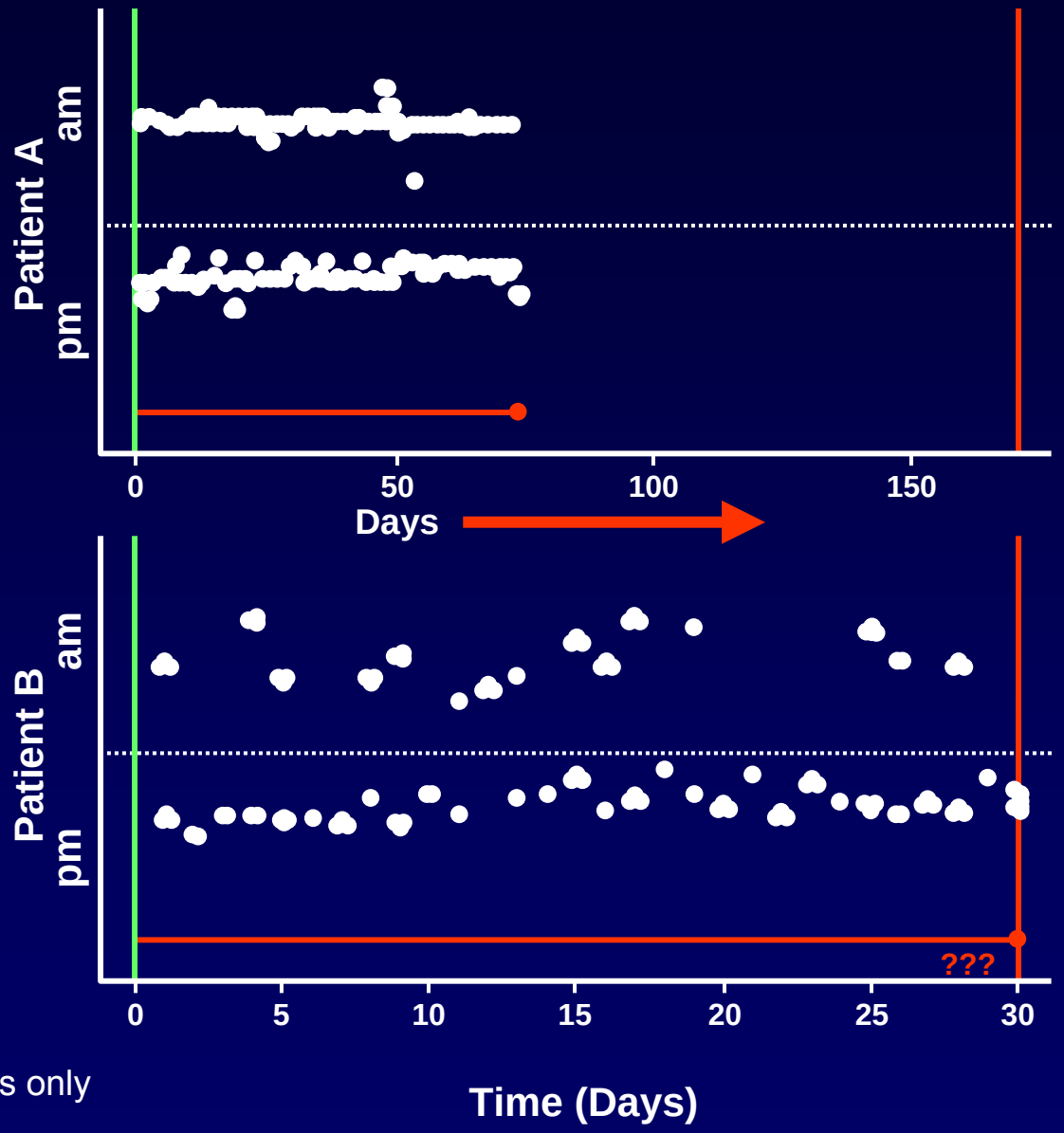
What to do:

- Complex
- Continuous reinforcement
- All members of the team

Components of Adherence

- **Persistence:** Time between treatment *initiation* and treatment *discontinuation*

- **Compliance:** correspondence between *actual* and *prescribed* dosing



*This graph is for illustrative purposes only

Visible and Invisible Adverse Effects

‘Visible’ to patient

- CNS side effects
- GI tolerability
- Lipodystrophy

Not ‘visible’ to patient

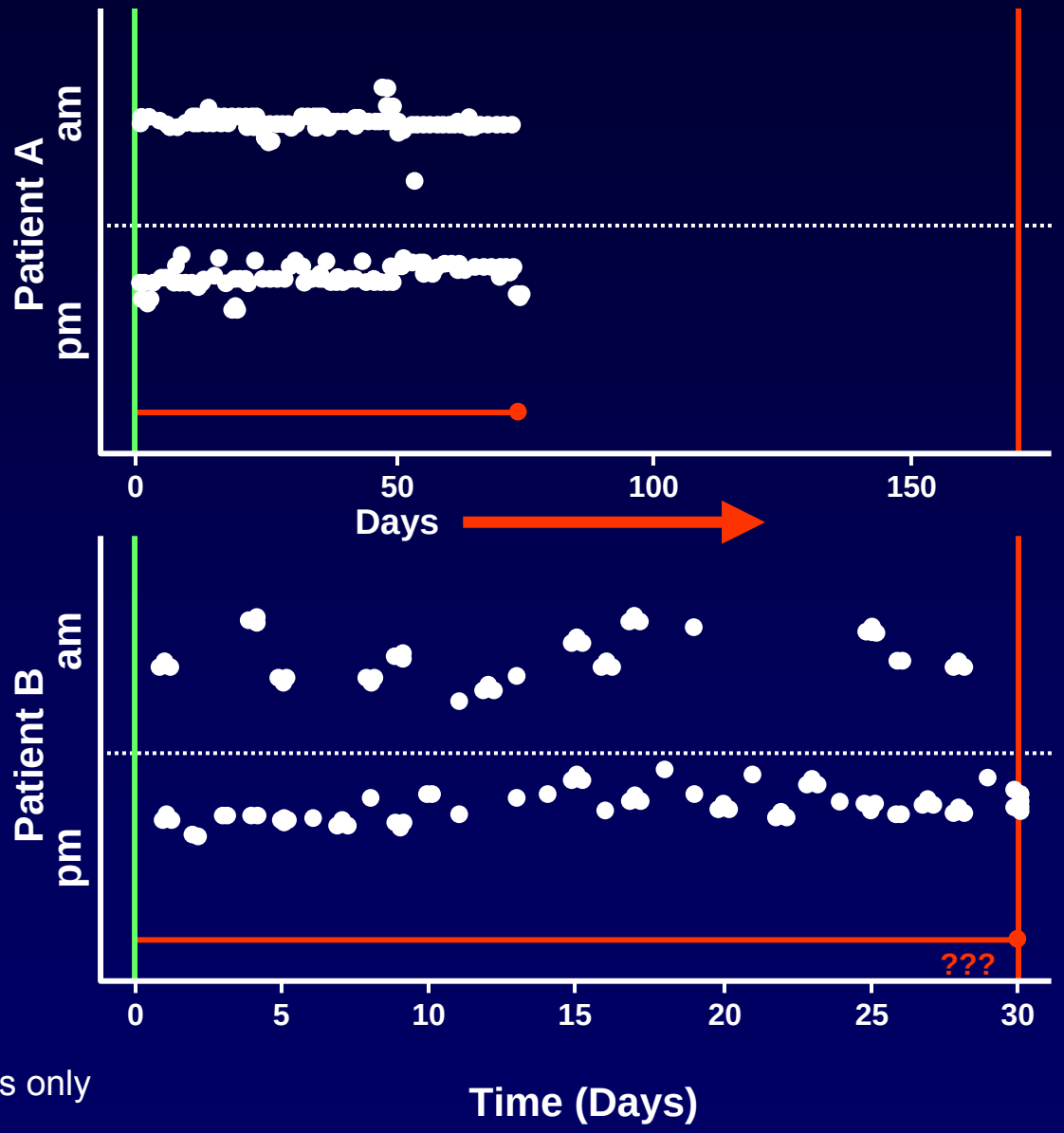
- Metabolic impact

Both short and long-term tolerability are important in maintaining high adherence

Components of Adherence

- **Persistence:** Time between treatment *initiation* and treatment *discontinuation*

- **Compliance:** correspondence between *actual* and *prescribed* dosing



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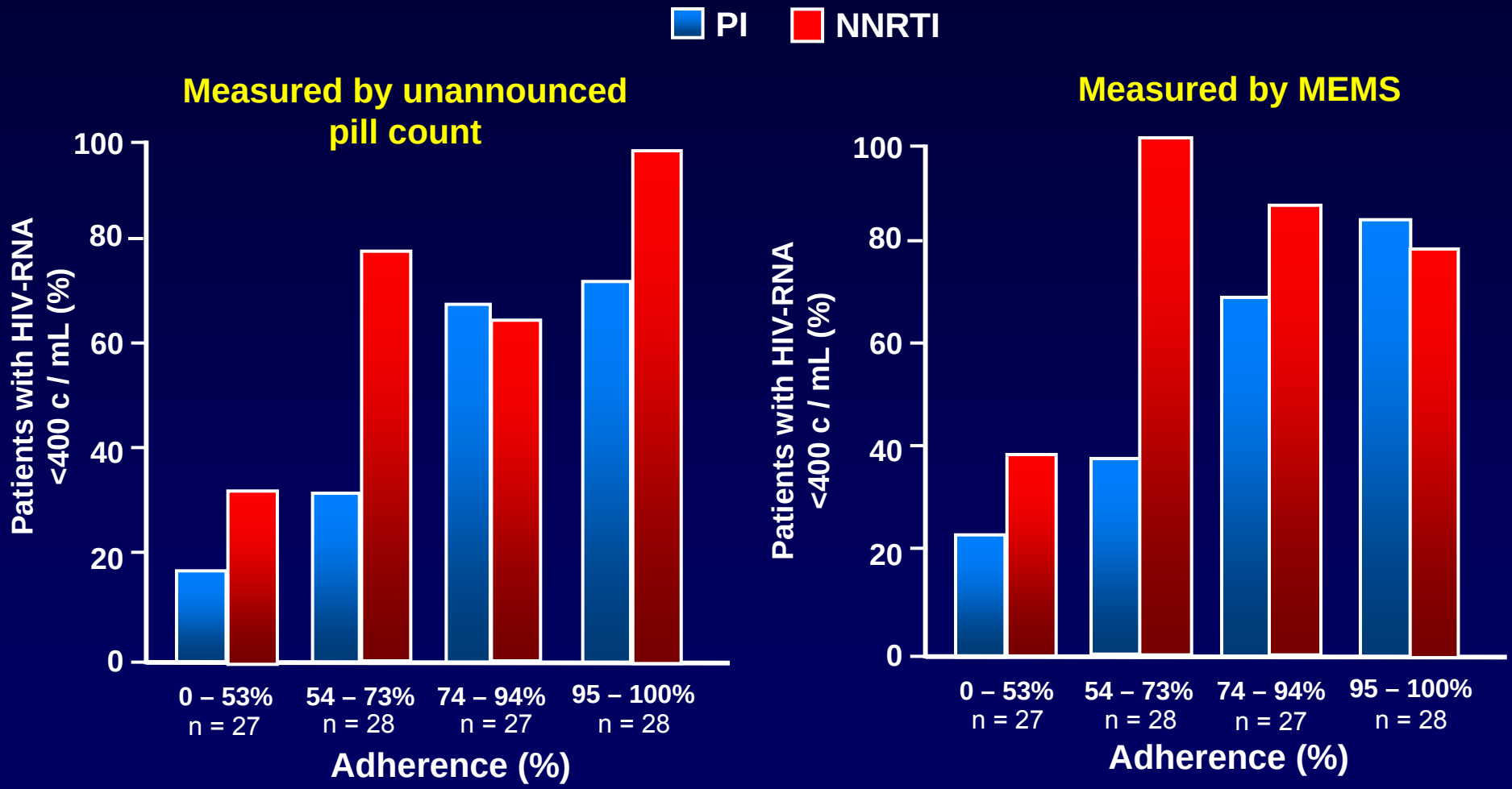
Less Than 95% Adherence to NNRTIs Can Still Lead to Viral Suppression

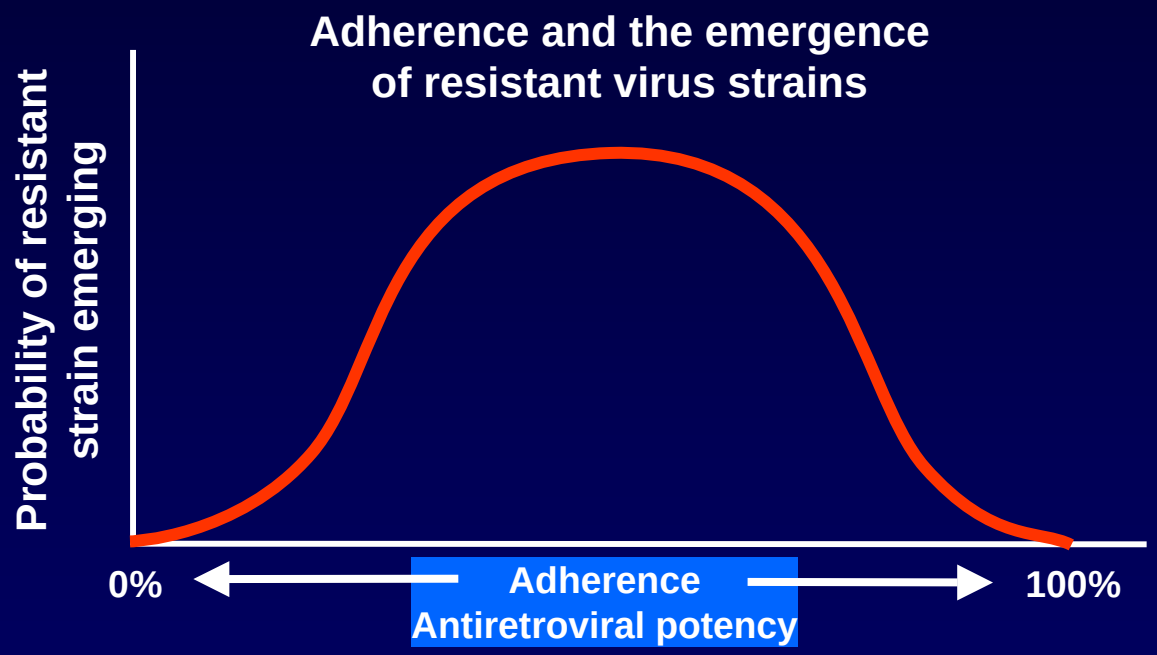
- Majority of NNRTI-treated individuals suppressed to <400 copies / mL at 54 – 100% adherence whereas majority of PI-treated individuals required 95 – 100% adherence



Adapted from Bangsberg DR. *CID* 2006; 43:939–941.

Resistance as the Ultimate Consequence of Non-Adherence

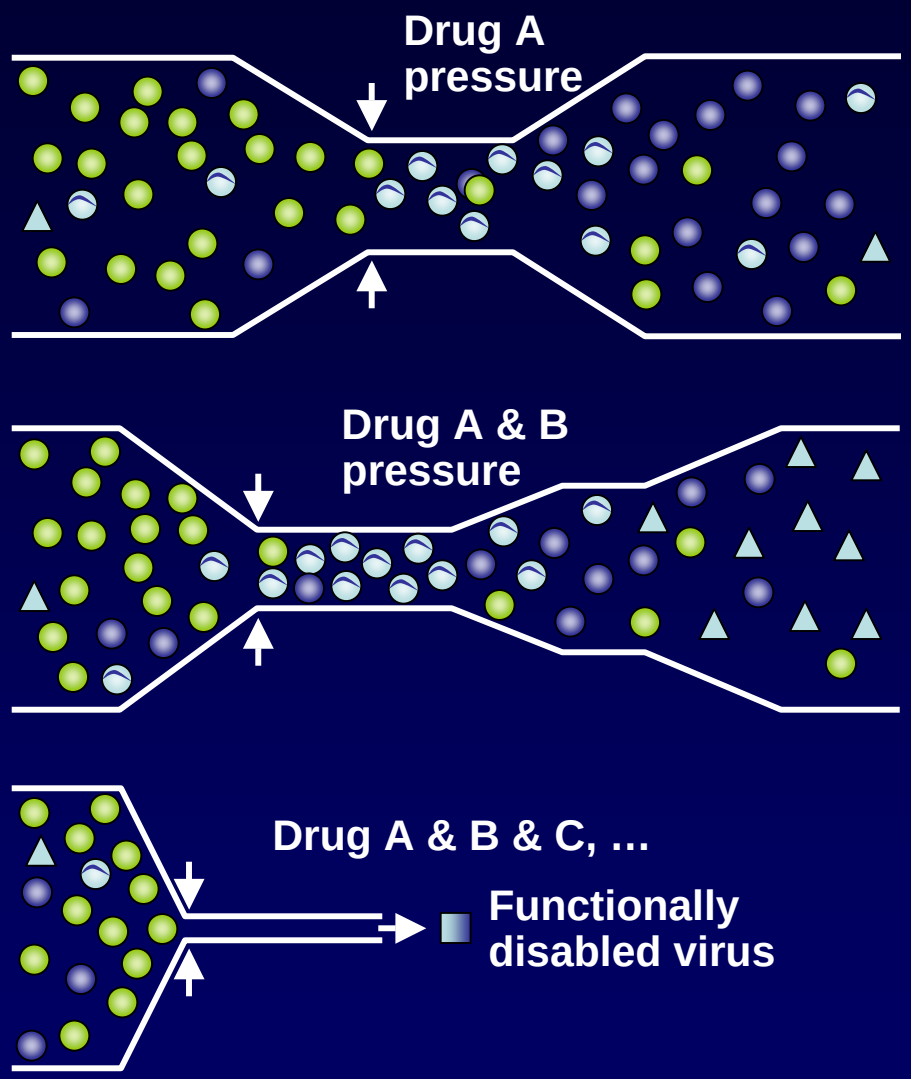
Resistance



Intermediate Adherence Leads to Drug-Resistant HIV

Adapted from Friedland GH et al. *AIDS* 1999; 13(Suppl 1):S61–S72.

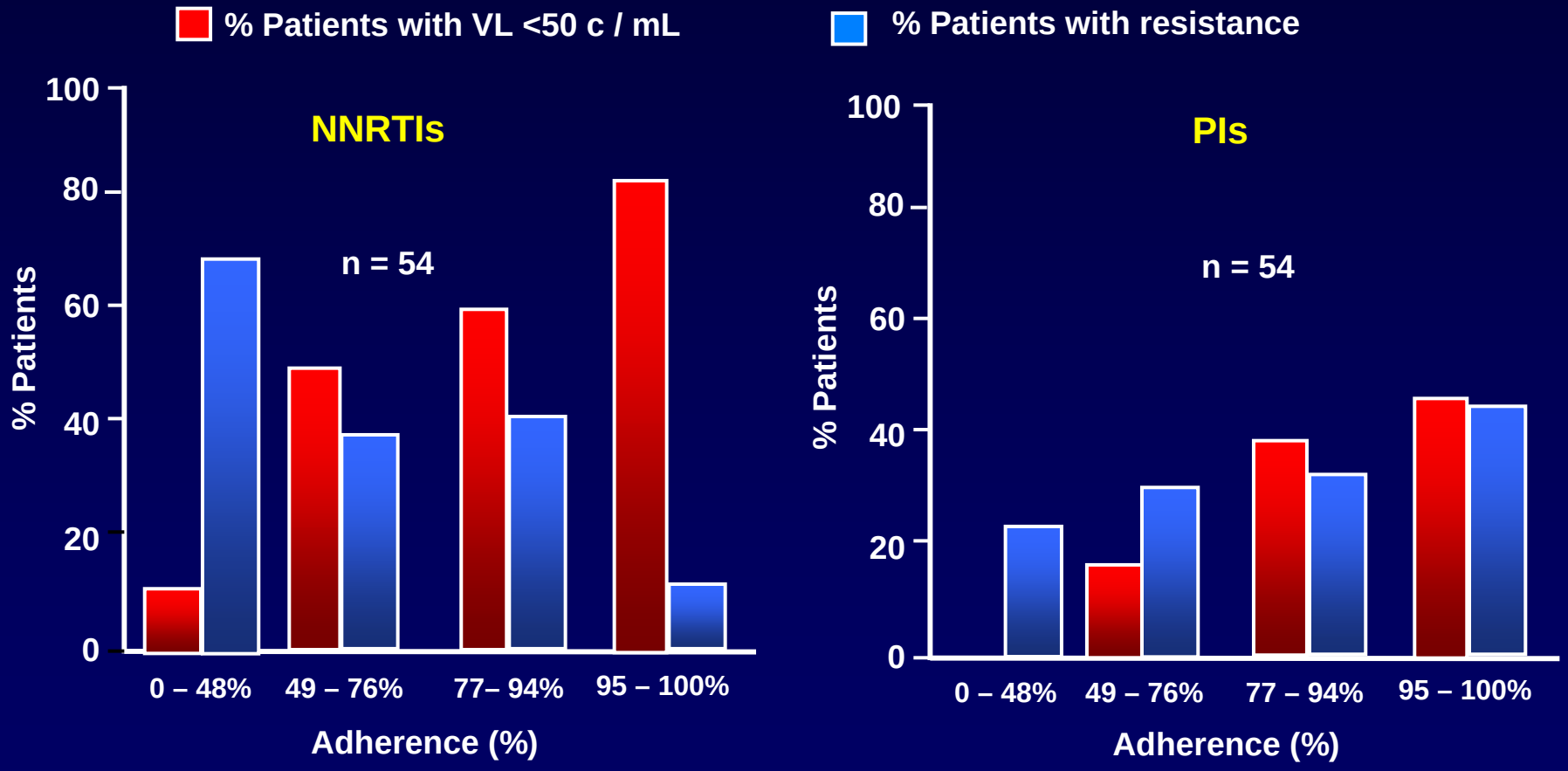
Selection of Resistant Variants Under Drug Pressure



These figures are a schematic representation.

Difference in Relationship Between Adherence, Viral Suppression and Resistance for NNRTIs vs. PIs

- NNRTI-treated patients significantly more likely to achieve viral suppression to < 50 copies / mL than PI-treated patients (50% vs. 22%; p < 0.005)
- PI resistance less common than NNRTI resistance at very low levels of adherence (0 – 48%)



Adapted from Bangsberg et al. *AIDS* 2006; 20:223–231.