HIV-1 Drug Penetration into the Male Genital Tract: Implications for Sexual Transmission

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Overview

Important factors which may influence sexual transmission of HIV

1. Effect of ART on genital tract shedding
2. Effect of STIs on genital tract shedding

- Review data on drug penetration into MGT
- Data on STI/HAART interactions and seminal HIV shedding

Hypothetical Outcomes

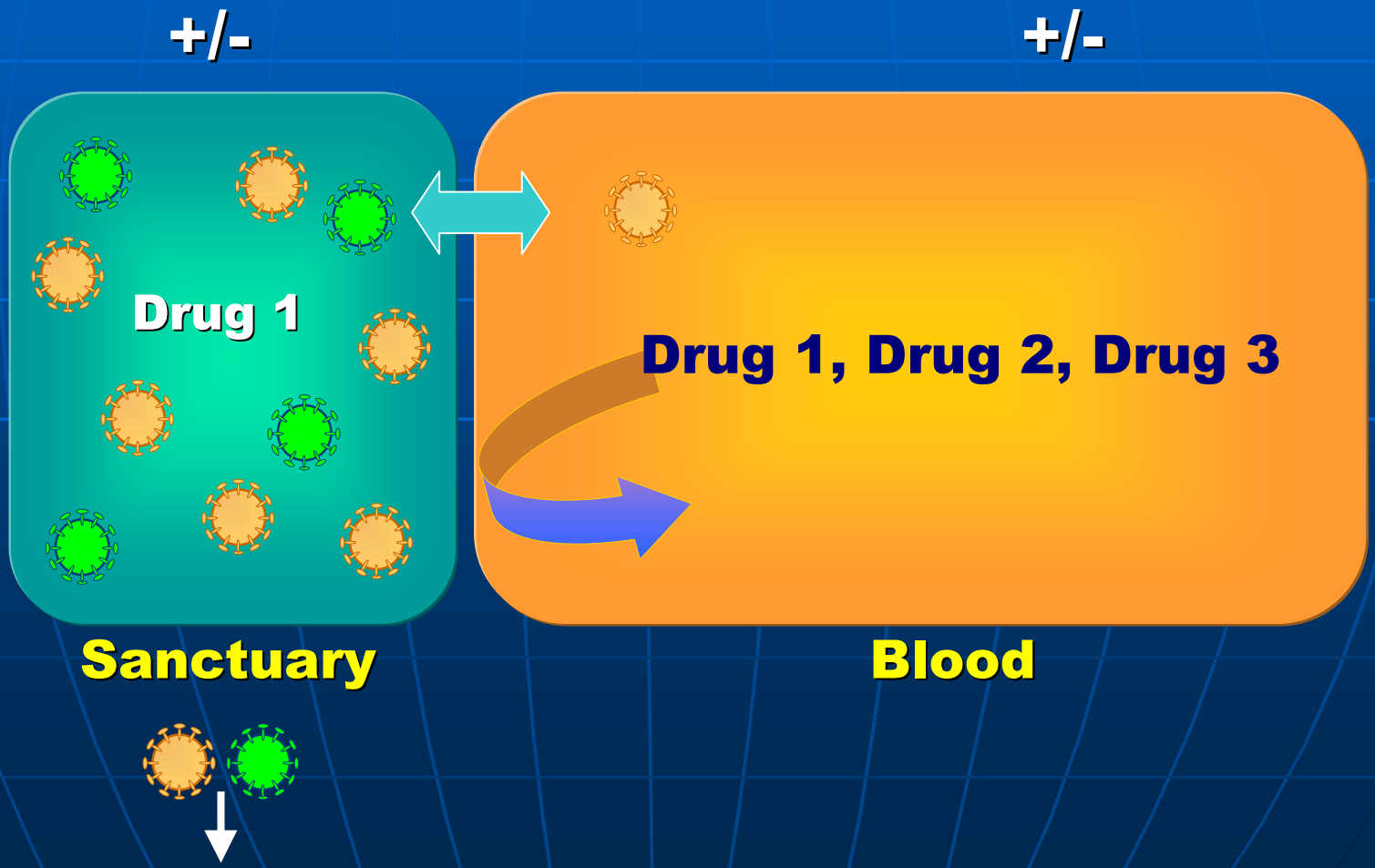
- Best case scenario
  - All antivirals penetrate into the genital tract
  - Genital tract replication stops
  - STIs no effect
  - The sexual transmission of HIV reduced
- Worst case scenario
  - Partial penetration of ARV into the genital tract
  - STIs enhance genital tract replication
  - Evolution and spread of resistant HIV

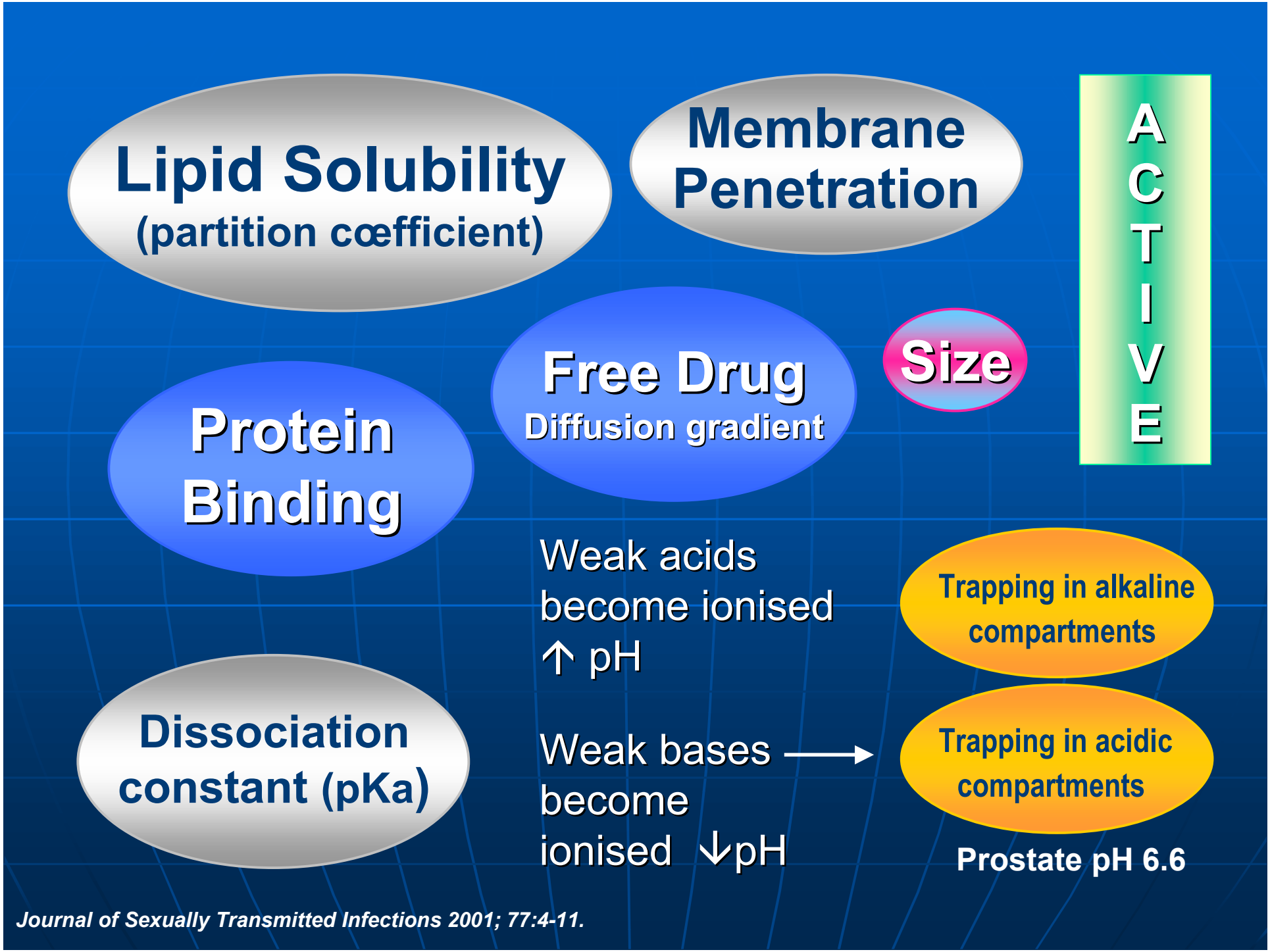
Drug concentration heterogeneity facilitates the evolution of drug resistance

Kepler and Perlson PNAS 1998

Sanctuary Site Hypothesis

Target cells, biological barriers, immune surveillance/activation





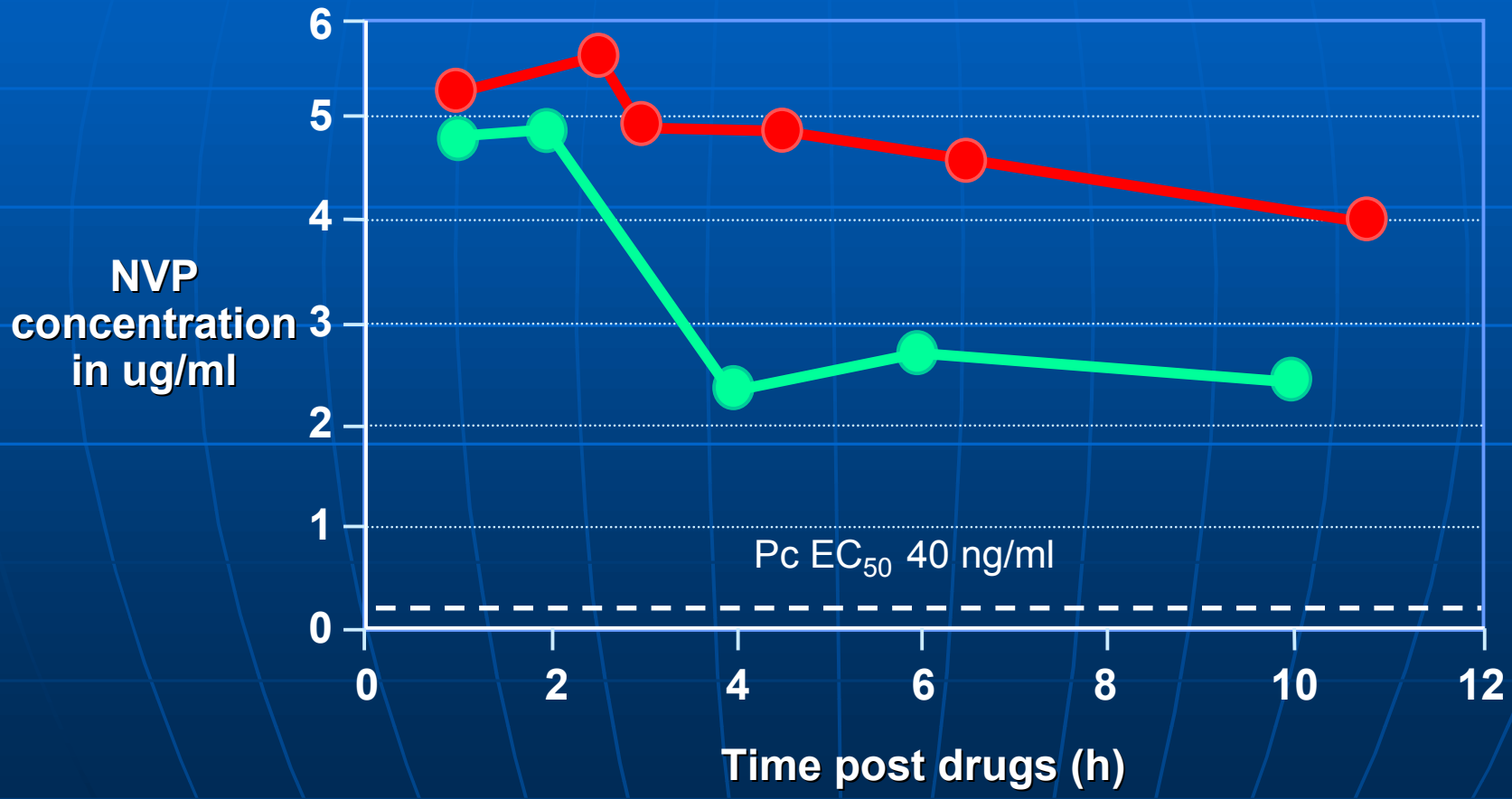
Journal of Sexually Transmitted Infections 2001; 77:4-11.

The problem with semen…..

- Patient co-operation and patience!
- Small sample volume and "*difficult*" consistency.
- Multiple same day sampling.
- When is the T_{max}, C_{max}, etc. for drugs in semen?
- Delay in uptake and elimination?
- Effect of seminal protein binding?

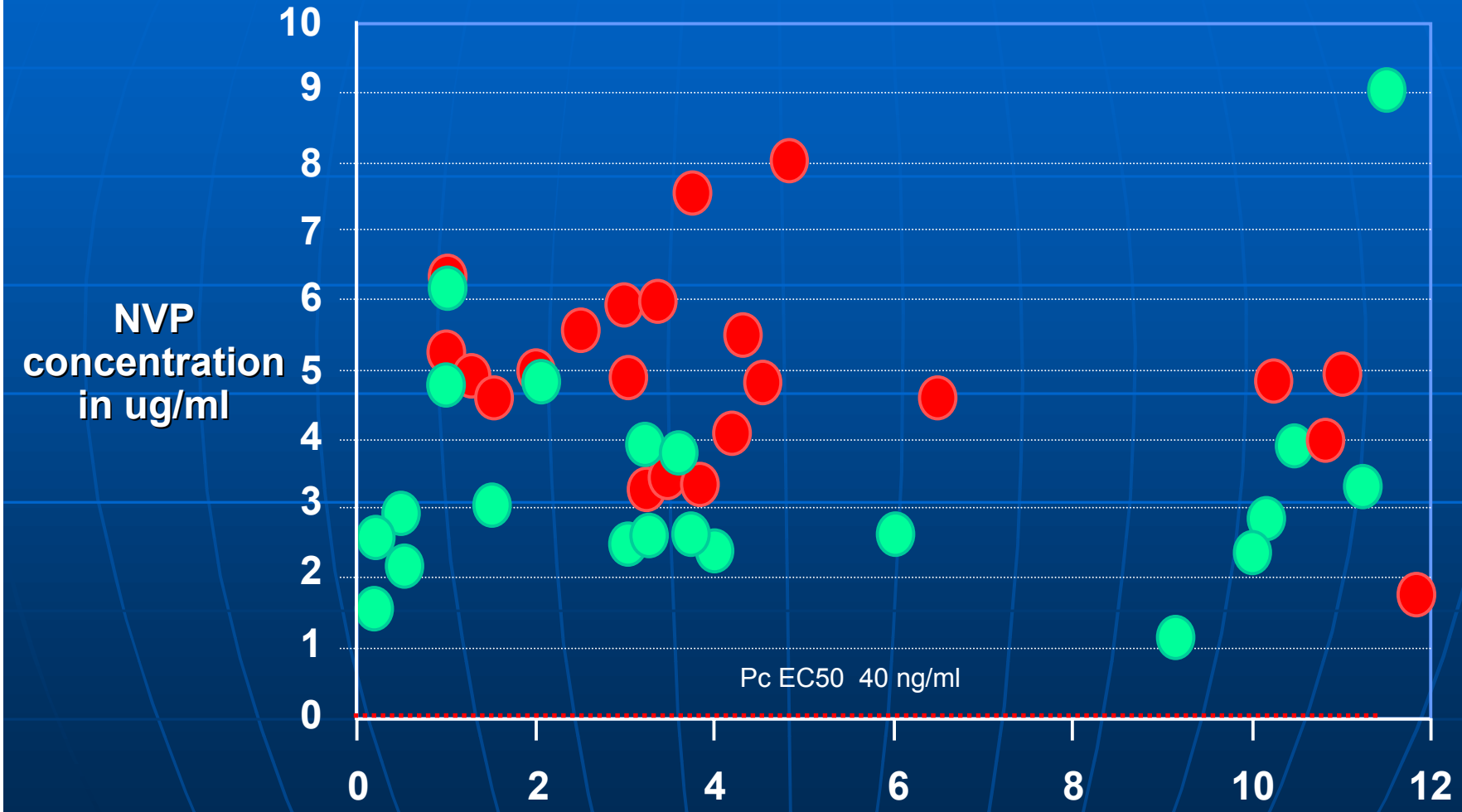
Non- nucleoside reverse transcriptase inhibitors

Nevirapine (NVP) drug concentration time curve for BP and SP in a single patient



AIDS 2000, 14:1979-1984

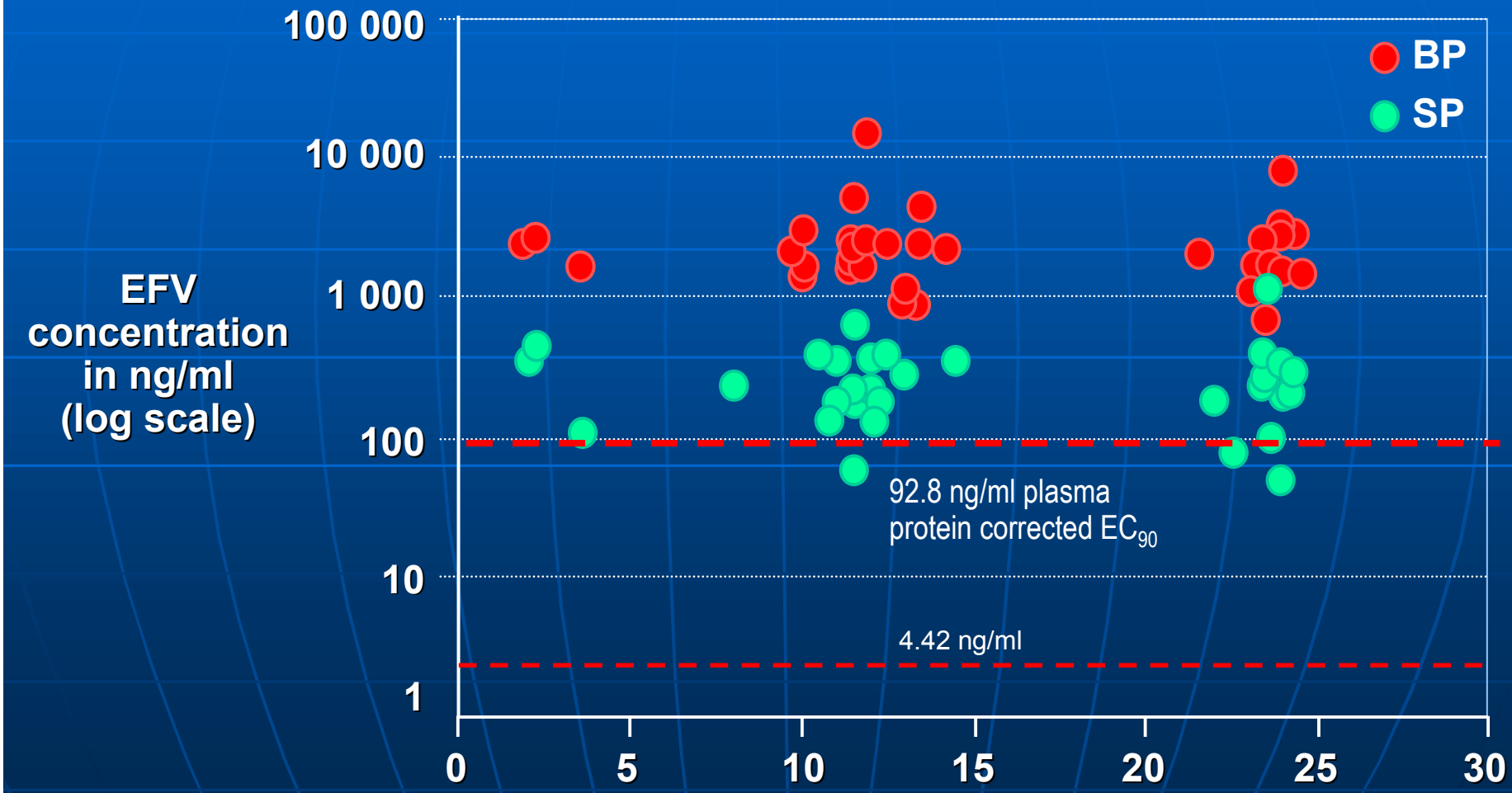
Nevirapine (NVP) concentration in blood plasma and semen plasma in 12 patients



AIDS 2000, 14:1979-1984

n=12

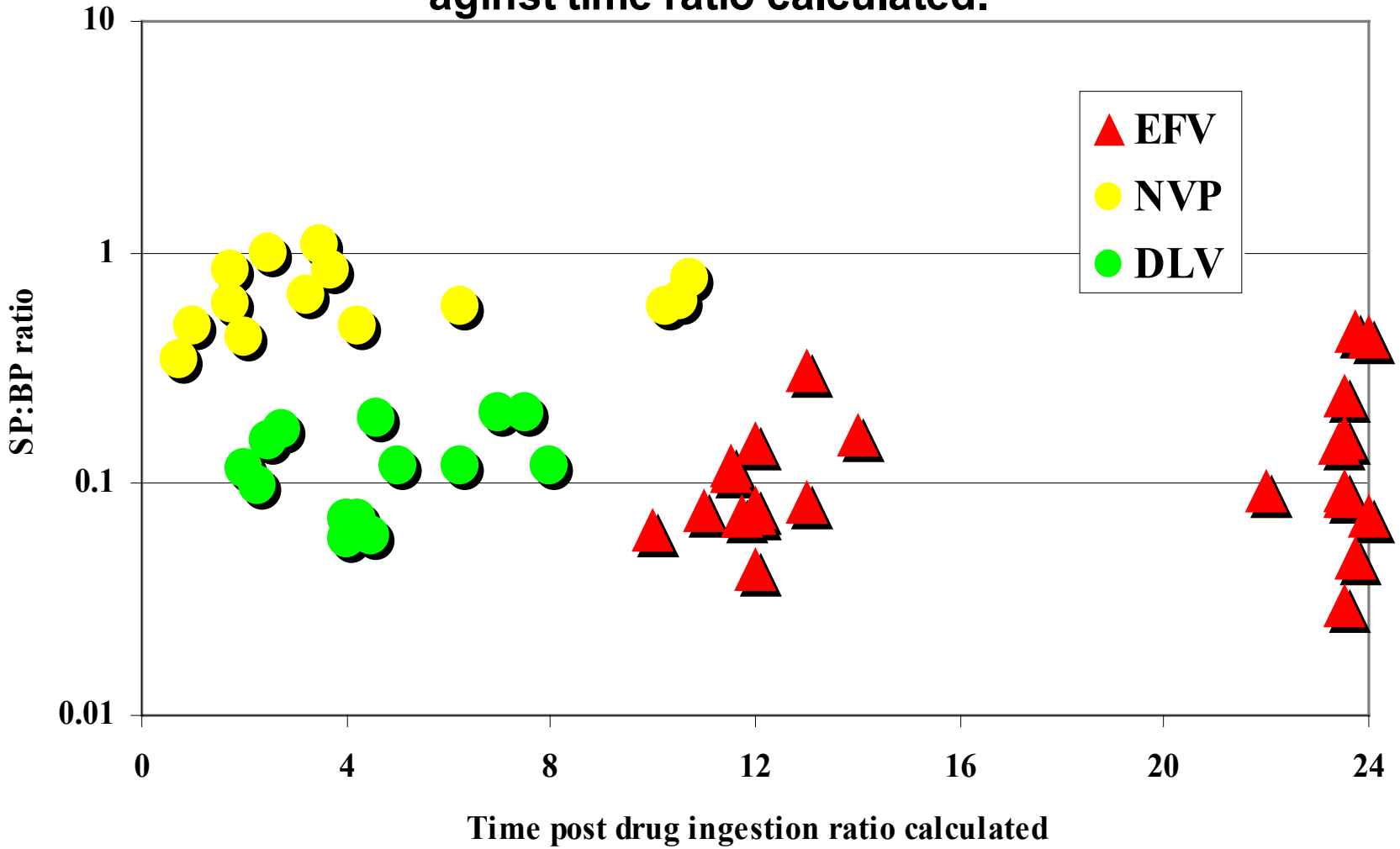
Efavirenz concentrations in blood plasma and seminal plasma at specific times post drug ingestion



AIDS 2001;15:2051-2053

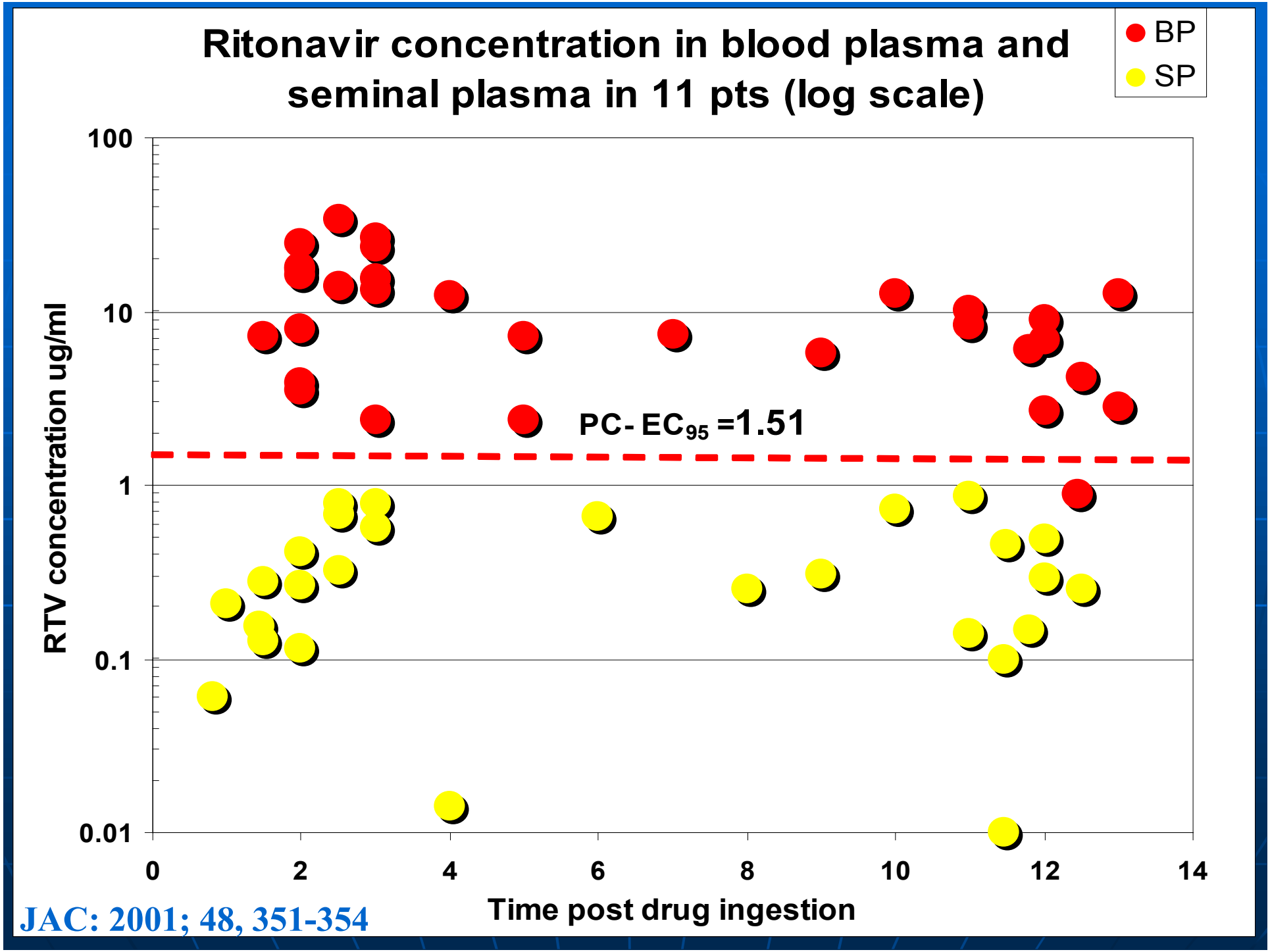
n=19

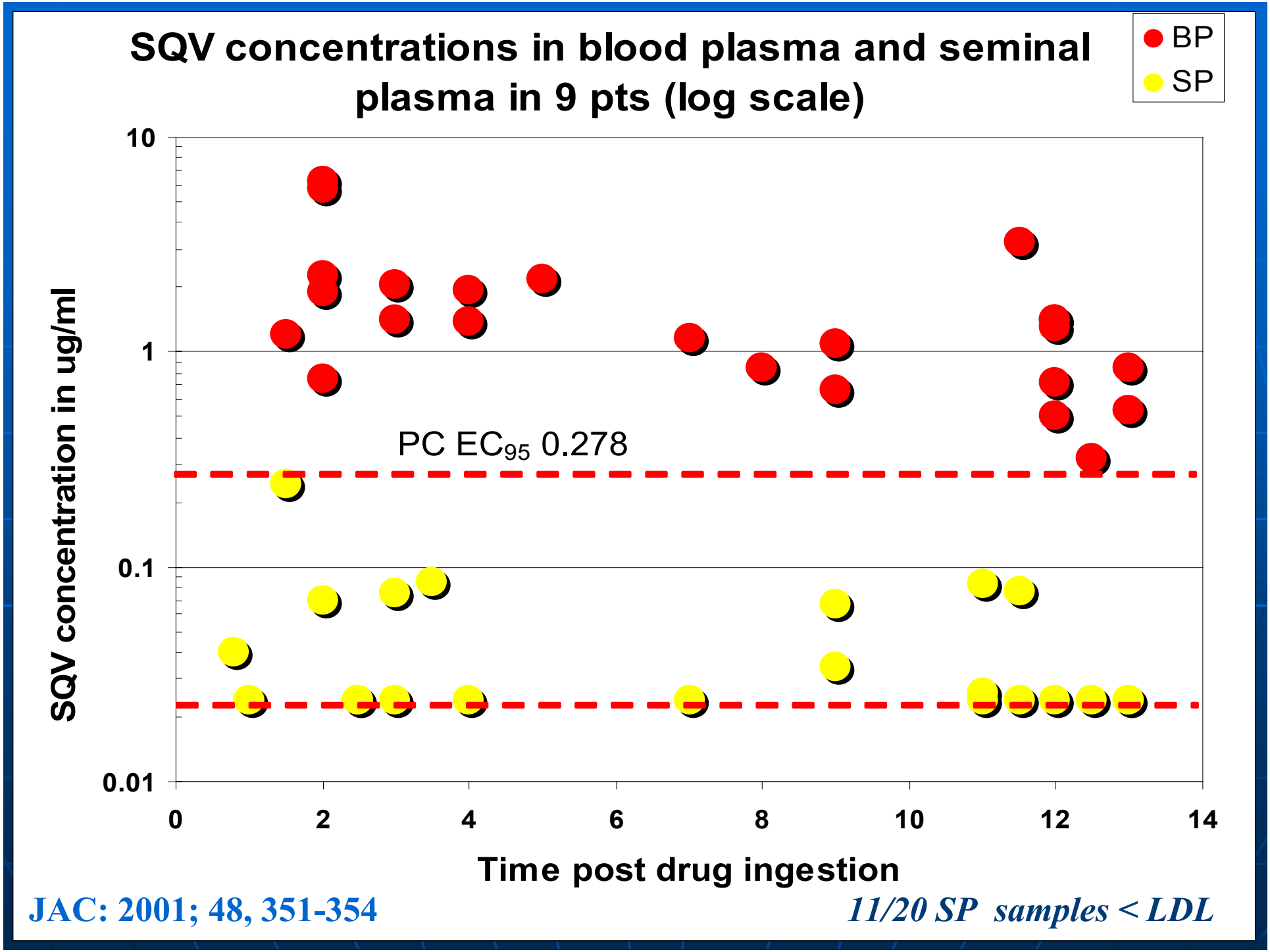
Seminal plasma to blood plasma ratios fot the three NNRTIs nevirapine, delavirdine and efavirenz plotted aginst time ratio calculated.



NVP ***AIDS 2000, 14:1979-1984, , EFV AIDS 2001;15:2051-2053, DLV NOORDWIJK 2001***

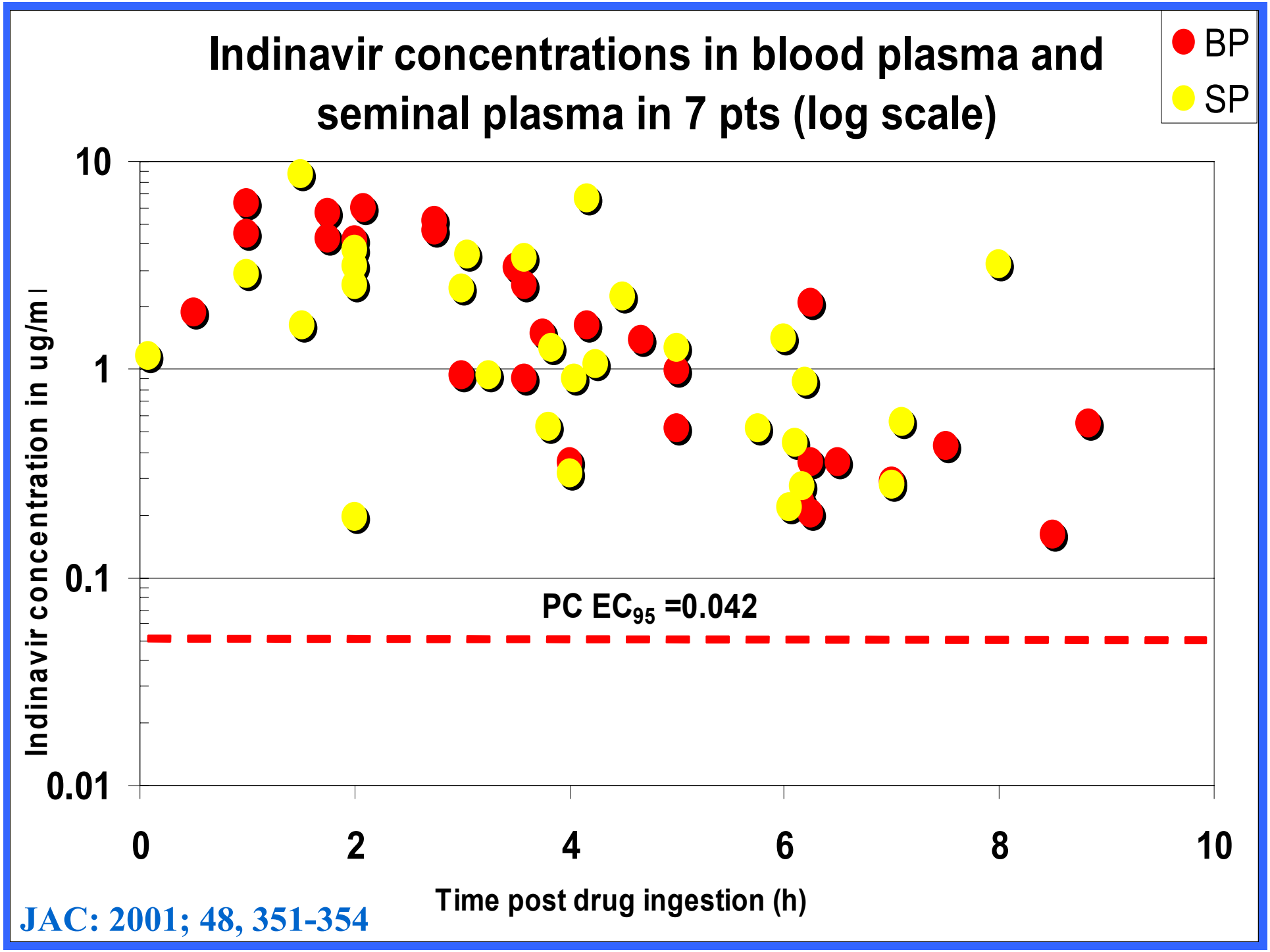
PROTEASE INHIBITORS


Ritonavir concentration in blood plasma and seminal plasma in 11 pts (log scale)
BP
SP
100
10
1
0.1
0.01
RTV concentration ug/ml
PC- EC95 =1.51
0
2
4
6
8
10
12
14
Time post drug ingestion
JAC: 2001; 48, 351-354

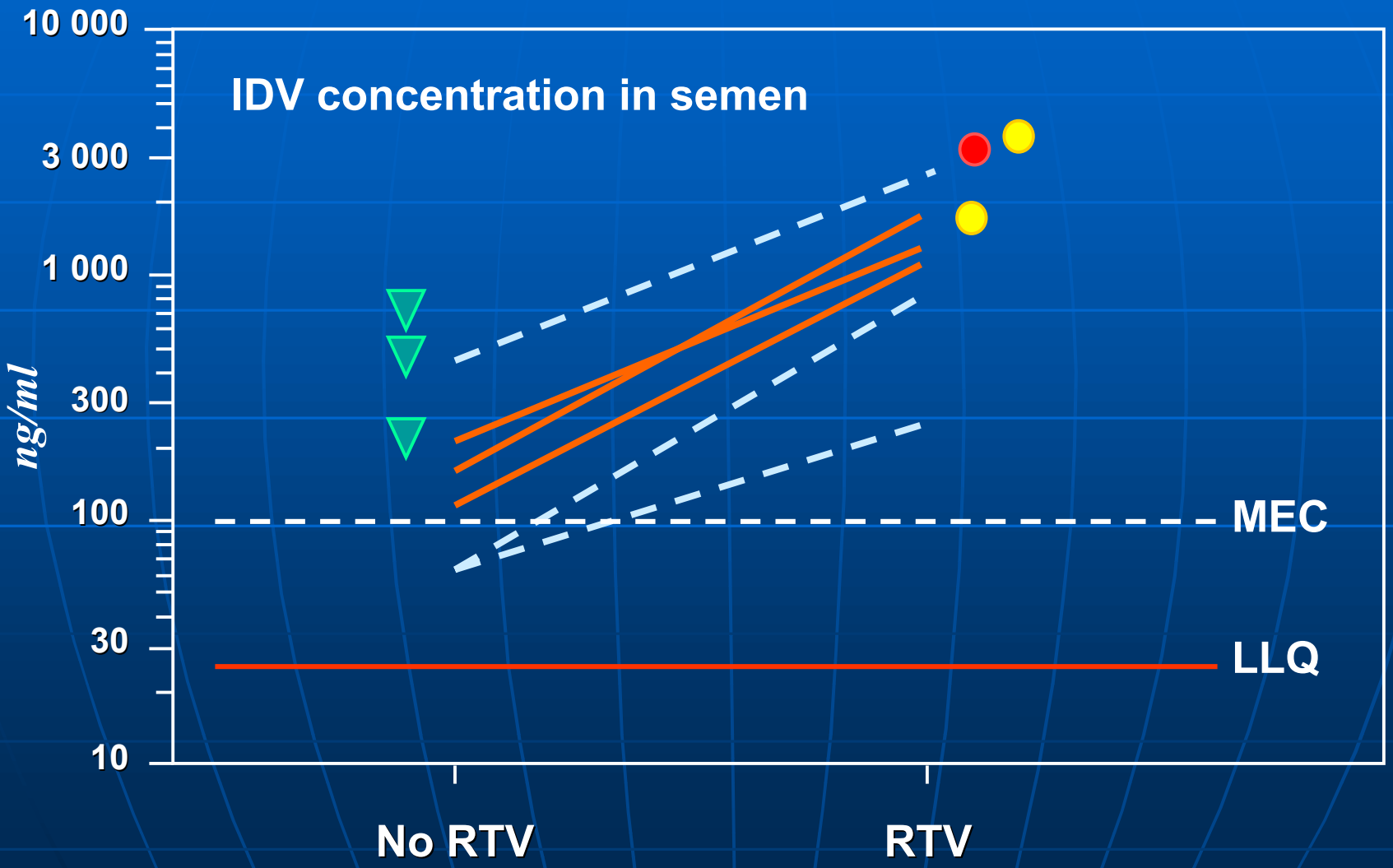


JAC: 2001; 48, 351-354

11/20 SP samples < LDL


Indinavir concentrations in blood plasma and seminal plasma in 7 pts (log scale)
BP
SP
10
1
0.1
0.01
Indinavir concentration in ug/ml
PC EC95 =0.042
0
2
4
6
8
10
Time post drug ingestion (h)
JAC: 2001; 48, 351-354

RTV Increases SP IDV Concentrations



Van Praag et al AIDS June 2000

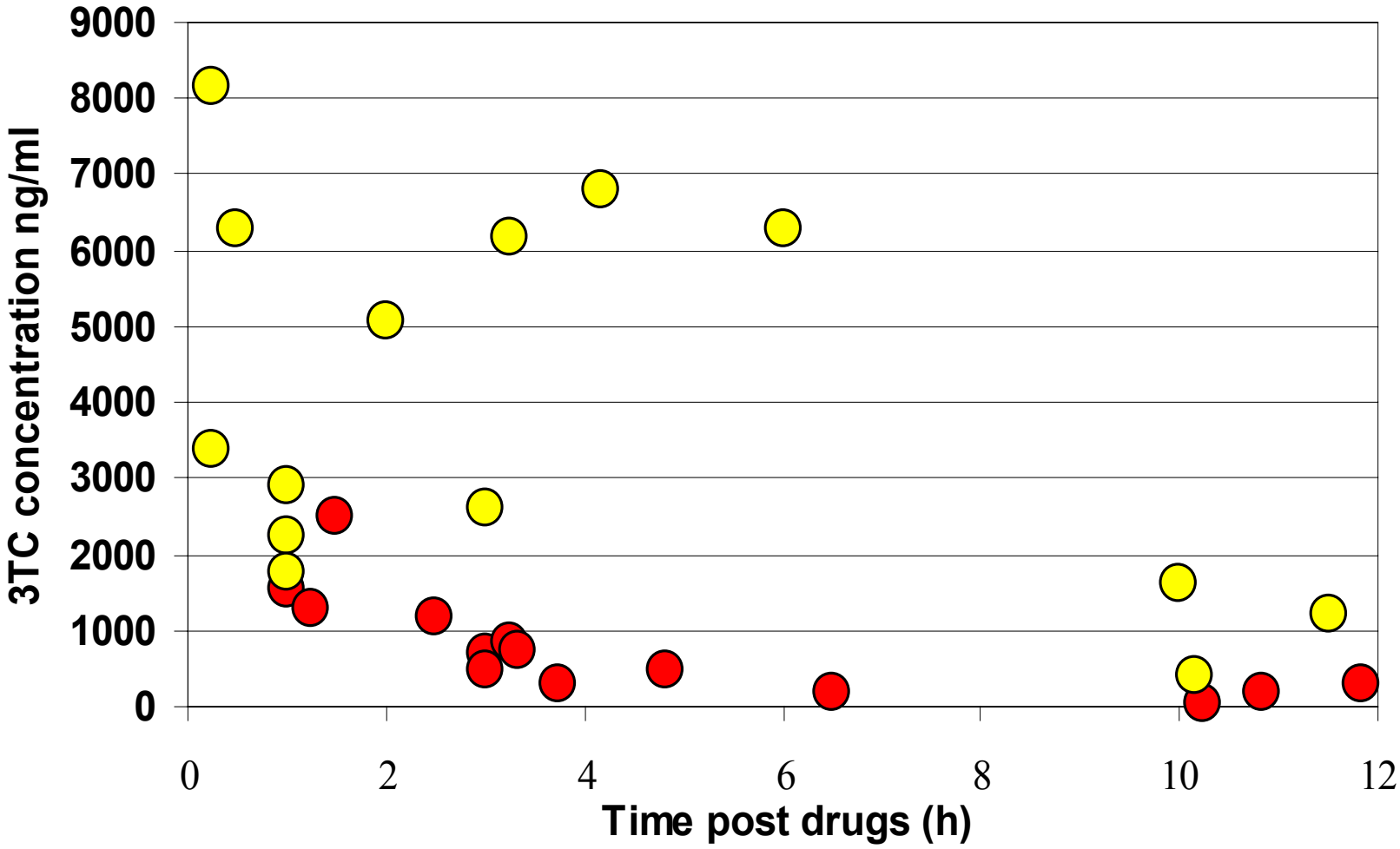
Protease Inhibitor Penetration into Semen

PI	SP / BP	
Indinavir	✓ ✓ (0.6 -1.4)	(1,2,3,4)
Indinavir + RTV	✓✓ (>2)	(2, 4)
Amprenavir	✓ (0.2)	(5)
Lopinavir/RTV	X (0.04)	(3,6)
Nelfinavir	X (0- 0.06)	(3,8)
Ritonavir	X (0.01-0.04)	(1,7)
Saquinavir	X (0-0.04)	(1,7,8)

1. Taylor et al JAC 2001
2. Van Praag et al AIDS 2000
3. Lafeuillade Clinical trials 2002
4. Taylor et al Glasgow 2000
5. Periera et al 7th CROI
6. Sankatsing et al CROI 2002
7. Taylor et al AIDS 1999
8. Reijers et al 7th CROI

Nucleoside Analogues

Lamivudine (3TC) concentration in blood plasma and semen plasma in 8 patients



AIDS 2000, 14:1979-1984

Nucleoside Analogues Concentrations in Semen

Drug	SP / BP	
Zidovudine ✓Π	(~ 5)	(1,2,3)
Lamivudine ✓Π	(3 - 5)	(2,4)
Stavudine ✓	(~ 1)	(4,5)
Abacavir ✓	(~ 1)	(6)
Didanosine ✓	(> 1)	(7)

1. Henry et al JAMA 1988
2. Periera et al JID 1999
3. Anderson et al Pharmacotherapy 2000
4. Taylor et al AIDS 2000
5. Liuzzi et al Glasgow 2000
6. Van Praag et al CID 2002
7. Gatii 8th ECCAT 2001

The Impact of Antiviral therapy on Seminal Shedding is Improving with more Potent HAART Regimens

- Poor response
- Hamed '93 (azt, ddI)
- Kreiger '95 (azt, ddI)
- Liuzzi '96 (azt)
- Kalichman '01 (various)

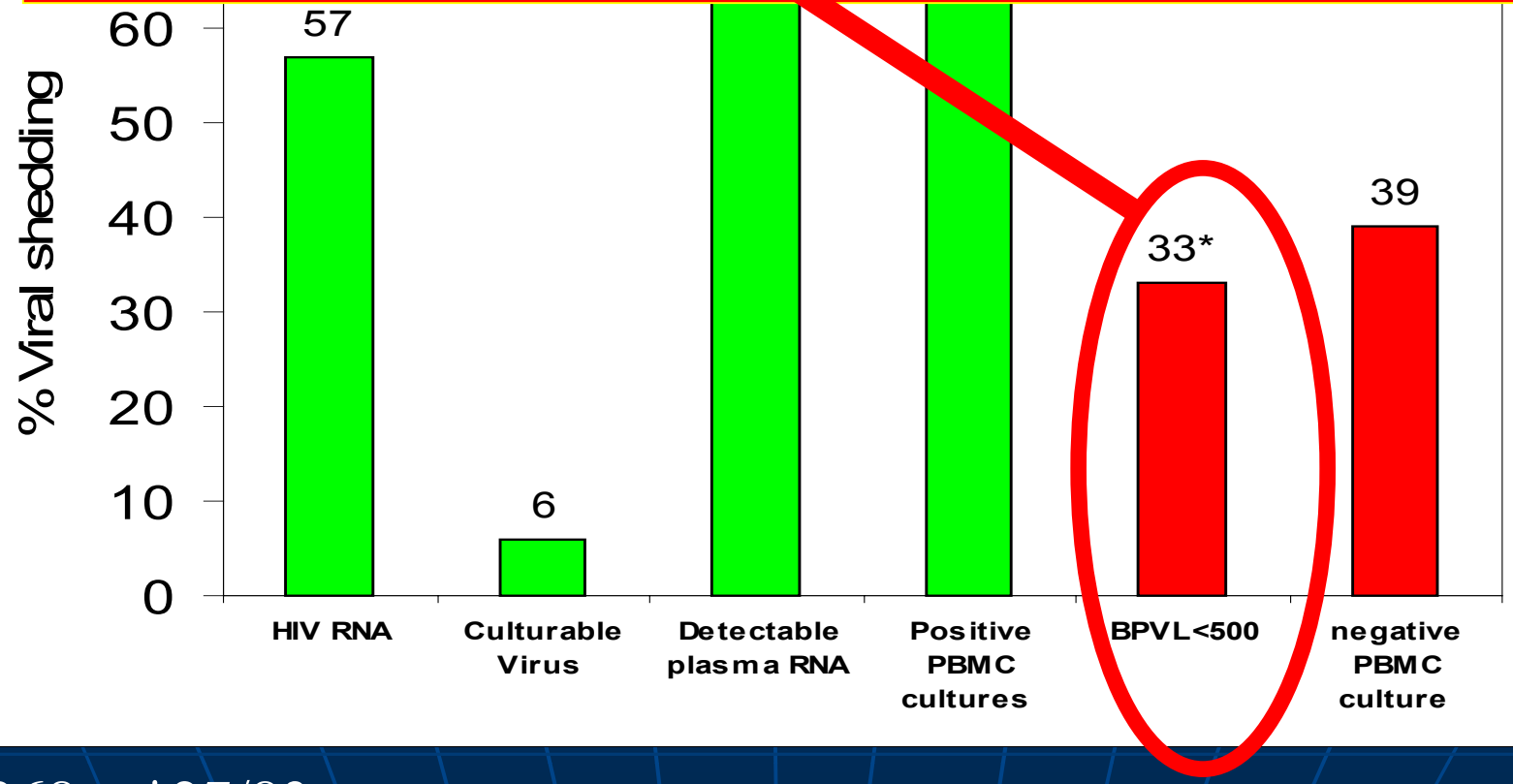
- Good response
- Boswell '97 (IDV,RTV,+NA)
- Gilliam '97
- Vernazza '97, '98, '00 (Triple)
- Gupta '97 (IDV, EFV)
- Eron '00 (APV)
- Liuzzi '00 (Triple)
- Quest '00 (APV,ABC,3TC,AZT)
- Tachet '00 (Triple)
- Taylor '00,'01 (NVP+NAs, IDV+NAs RTV,SQV+NAs, EFV+NAS)
- Coombs '00 (Triple)
- Sadiq '02 (Triple)

Despite HAART there is evidence of viral escape in semen despite low or undetectable viral load in blood plasma.

- Winter et al: STI 1999; 75(4):261-3
- Ball et al: STI 1999; 75(5):337-9
- Mayer et al: C.I.D 1999; 28(6):1252-9
- Tachet et al: AIDS 2000; 13:823-831
- Eron et al: JID 2000;181:1622-8
- Pilcher et al: AIDS 2001;15:837-845
- Kalichman et al: ARHR 2001; 1695-1703
- Sadiq et al: AIDS 2002 16;219225

Determinants of Shedding in the Female

74% were receiving Antiretroviral therapy
52% were receiving Antiretroviral therapy with a protease inhibitor



n=268 *27/83

Kovacs et al Lancet Nov 2001

“Seminal Super Shedders”

Patient	*BPVL*	*SPVL*	*Treatment*
• GL	1,600,000	>2,000,000	none
• AS	92,000	550,000*	none
• PH	200,000	460,000*	none
• MJ	18,000	190,000*	none
• JB	54,000	130,000	none
• MG	69,000	100,000*	NVP,ABC,d4T
• KH	13,000	60,000	RTV,SQV,d4T
• MH	540	23,000*	RTV, SQV,d4T
• LF	2,300	11,000*	NFV/SQV/ddI/d4T

STI's appear to increase seminal shedding in patients not on therapy

- Fluctuations of HIV Seminal DNA with newly acquired STD's (Atkins et al: BMJ 1996)
- SPVL 8 x higher in men with STD's: Reduced by antibiotic treatment. (Cohen et al: Lancet 1997)
- 4 x reduction in SPVL post antibiotic treatment of STD's (Dyer et al: JID 1998)
- Asymptomatic Urethritis independent risk factor for seminal shedding (Winter et al: STI 1999)

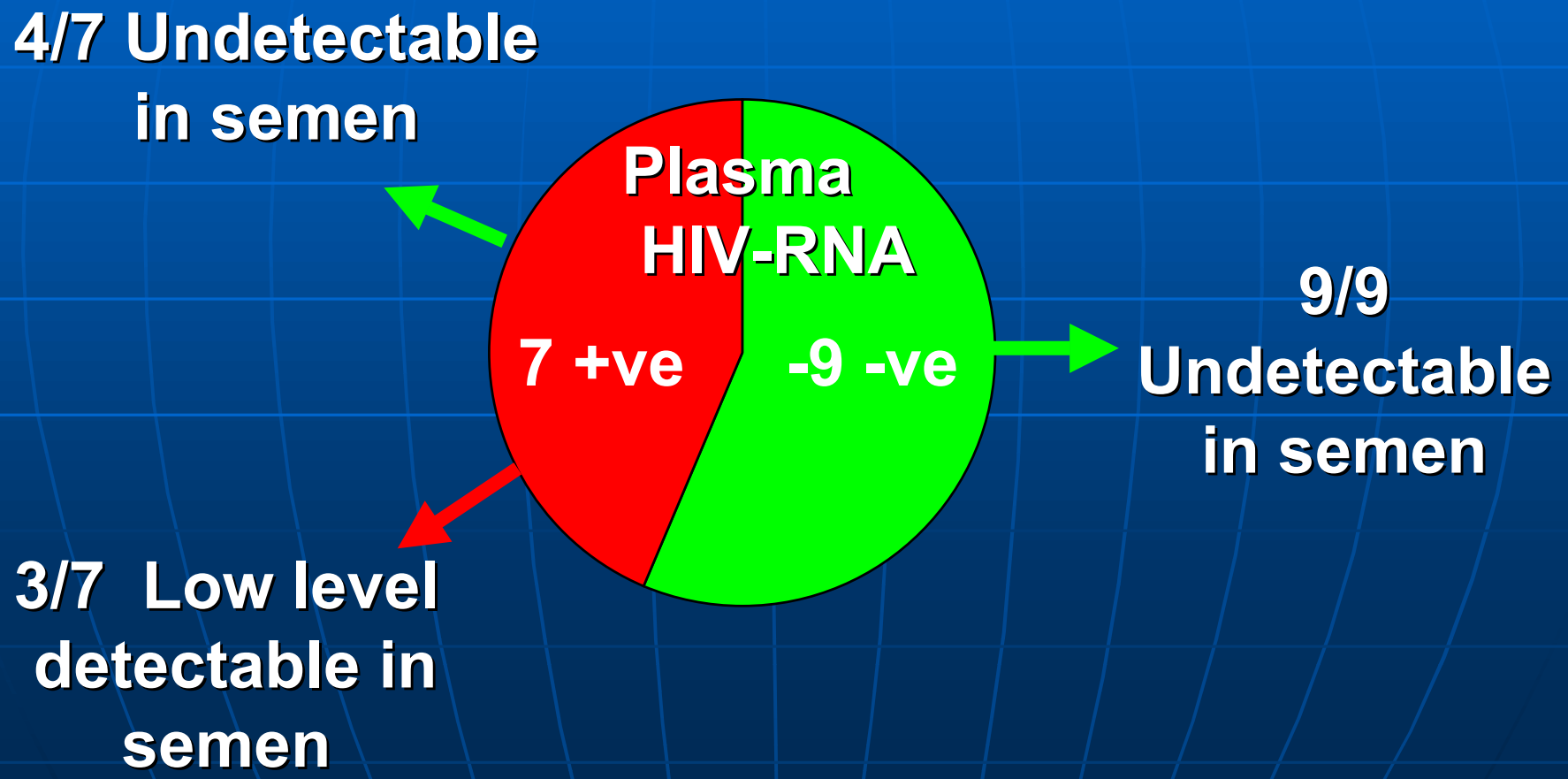
- How do STIs effect seminal shedding in patients taking ART?

Pilot Study: Key Findings

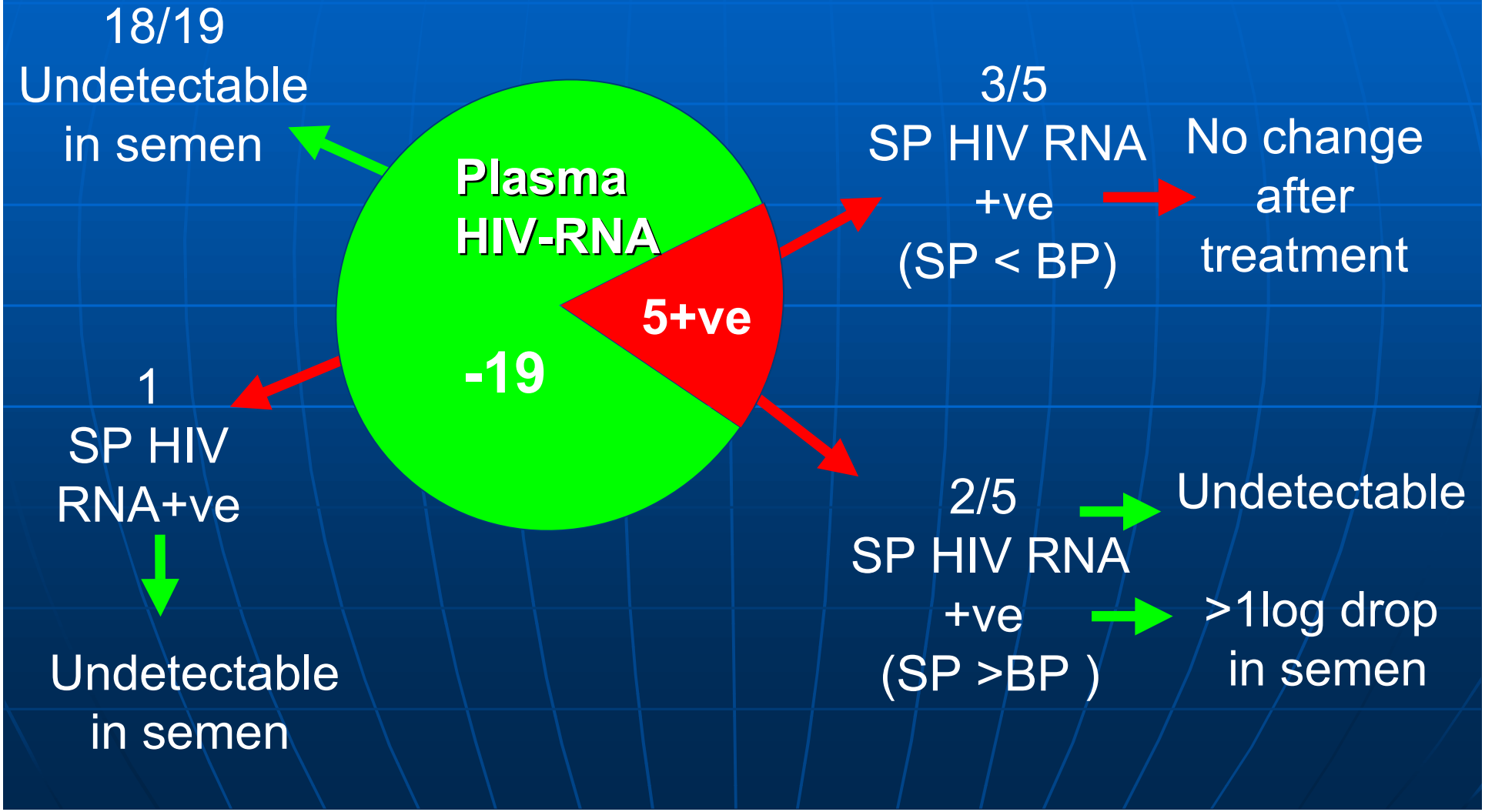
- 24 cases with STI's on ART, 16 controls.
  - (10 GC, 6 C4A, 8 NGU)
  - Produced semen and blood at BL and 1 & 2 wks post antibiotic treatment.
- Results
  - Good correlation between BPVL and SPVL
  - Undetectable in BP = Undetectable in SP
  - Low BPVL ~ low / undetectable SPVL
  - Despite undetectable SPVL RNA >1yr, proviral DNA could still be detected in some patients

Sadiq et al AIDS 2001

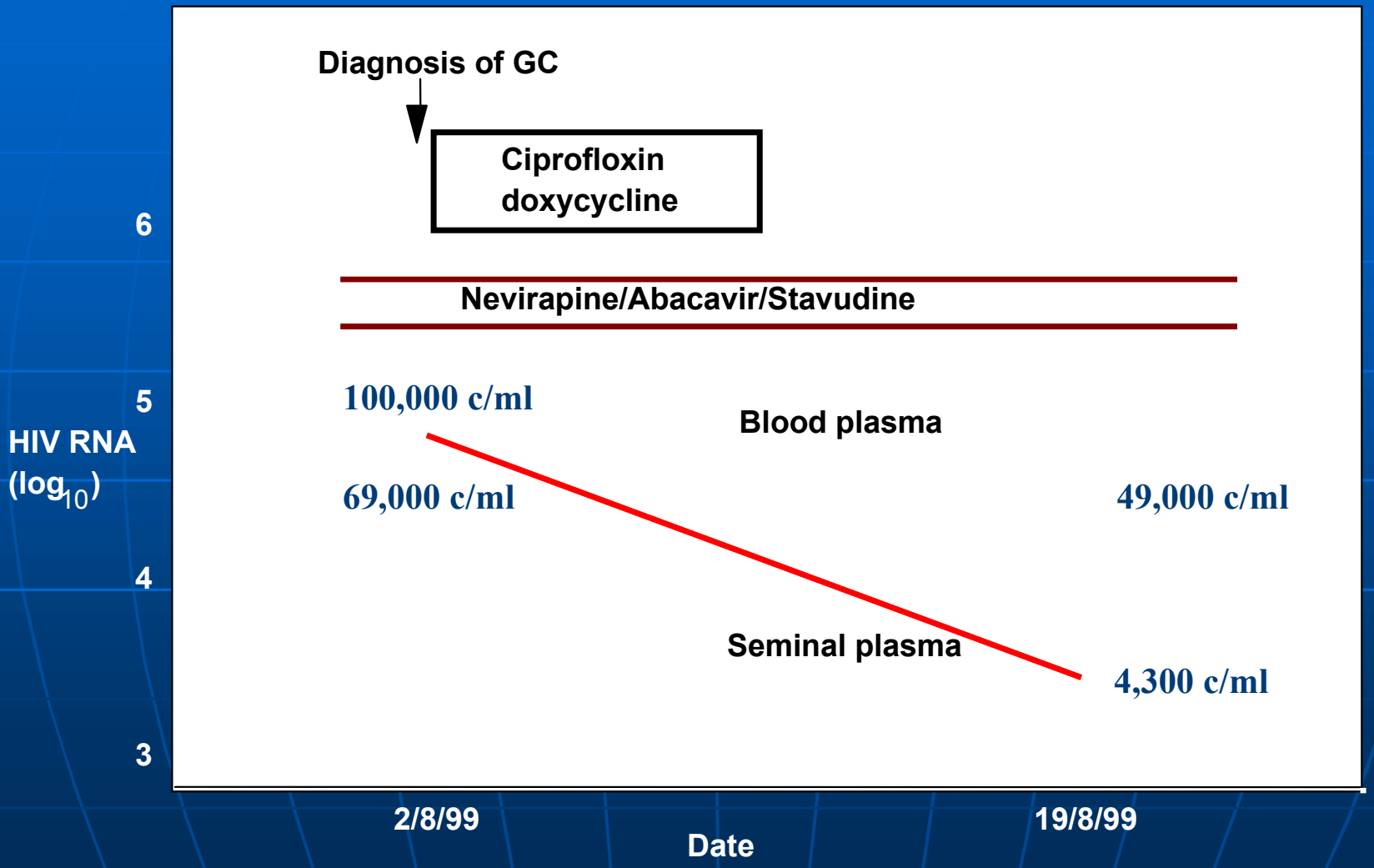
Detection of SP HIV-1 during ART (n=16) Controls



Detection of SP HIV-1 during *ART and Urethritis* (n=24) Cases



Reduction of seminal plasma viral load after treatment of urethritis



Semen/blood genotype : K65R, K103N, Y181C

VIRAL LOADS AND RESISTANCE MUTATIONS IN BLOOD PLASMA AND SEMEN PLASMA IN MEN TAKING ANTIVIRALS AT THE TIME OF SYMPTOMATIC URETHRITIS

PRE TREATMENT AT TIME OF URETHRITIS						POST ANTIBIOTIC TREATMENT		
Case	Treatment	STI	BPVL Visit 1	SPVL Visit 1	Resistance Mutations in blood plasma (BP) and seminal plasma (SP) Visit 1	BPVL Visit 2	SPVL Visit 2	Resistance Mutations
19								
20								
21								
22								
23								
24	d4T, 3TC, NVP	NSU	<500	1,512	No Amp	<1000	<1000	No Amp

4-6 Men on ART with Urethritis and detectable HIV RNA in semen had multiple drug resistance associated mutations in both blood and semen

TAYLOR, SADIQ et al POSTER 373 9th CROI

Conclusions from Pilot Study

- Good news
  - HAART may suppress the replicative bursts associated with STIs, IF viral replication is optimally suppressed.
- Bad news
  - In those who have sub-optimal therapy STIs may enhance the transmission of resistant HIV.

Hypothetical Outcomes

- Best case scenario
  - All antivirals penetrate into the genital tract
  - Genital tract replication stops
  - STIs no effect
  - The sexual transmission of HIV reduced
- Worst case scenario
  - Partial penetration of ARV to the genital tract
  - STIs enhance genital tract replication
  - Evolution and spread of resistant HIV

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IDV, RTV, SQV, EFV, DLV studies

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NVP, 3TC, D4T, ABC studies.

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