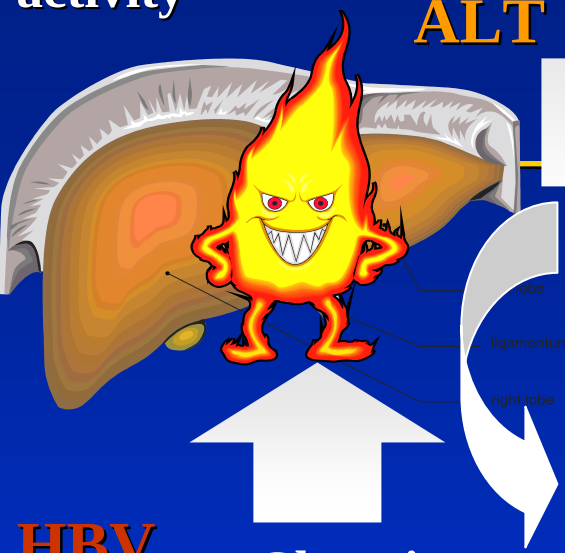
Coinfezione HIV-HCV
e
HIV- HBV
Quando trattare?

Nicola Boffa
Salerno

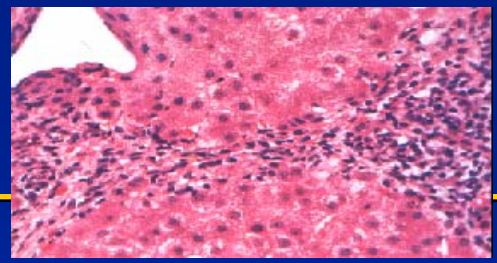
1st INFECTIVOLOGY TODAY
PAESTUM 13-14-15 MAGGIO 2004

Necroinflammatory activity

ALT



Fibrosis



10-40 yrs

Asympt. Cirrhosis

Histology:
Necoinflammatory activity
Fibrosis

HBV DNA

Chronic Hepatitis B

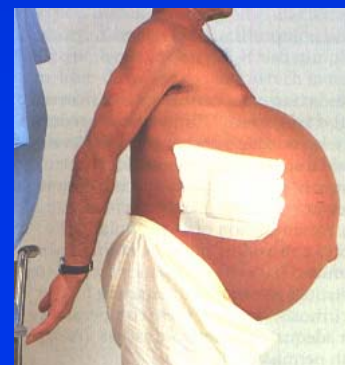
↑Cell proliferation
↓Apoptosis

3-6% x yr.

HCC

2-15 yrs

ESLD



Viral Replication

HBeAg/HBeAb
HBcAbIgM

Immune Response

HBcAb
Occult

Insertional mutagenesis
epigenetic alterations

Death

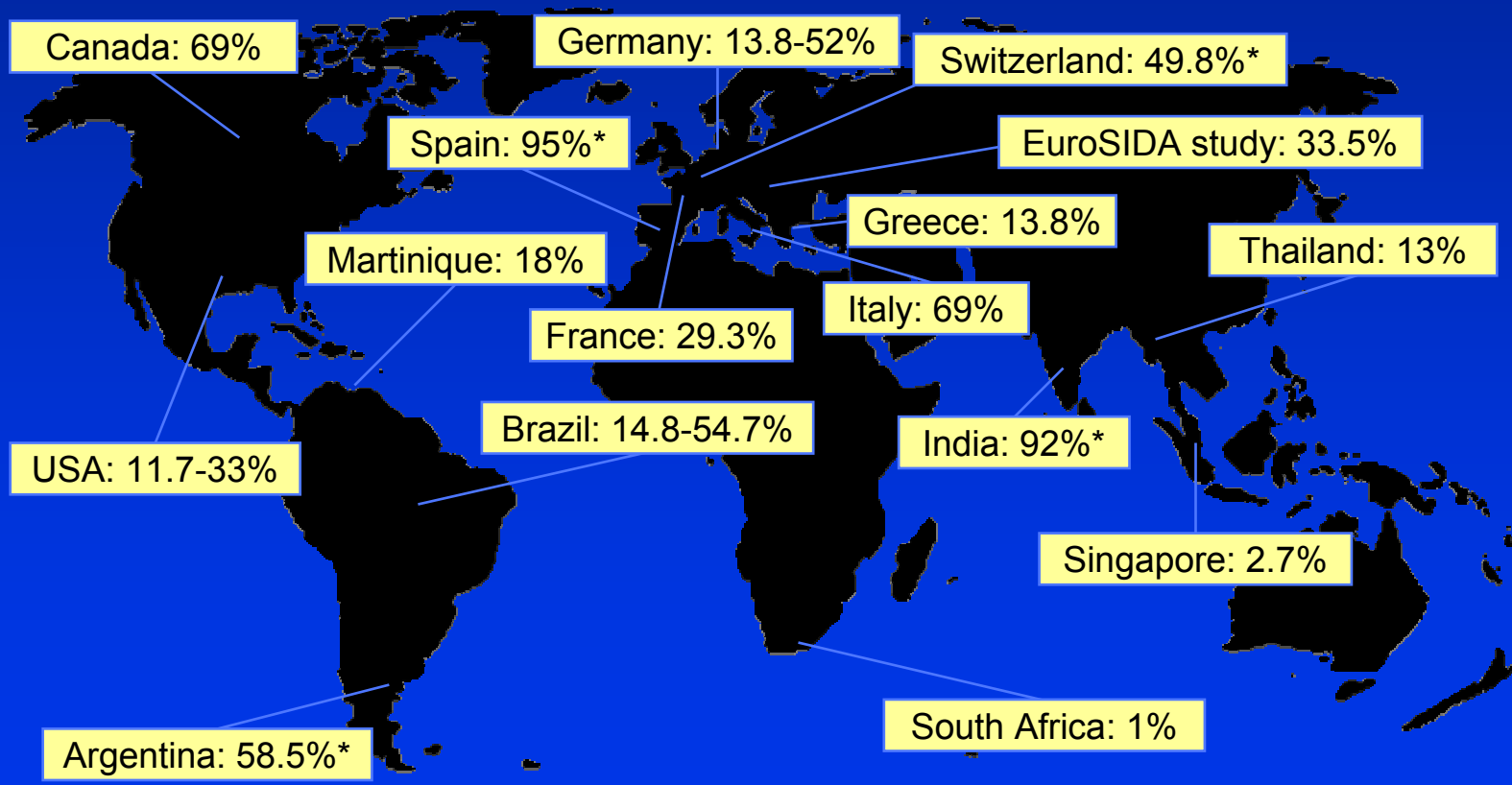
EXPOSURE TO HBV

HCV and HIV Infection

- HCV and HIV have emerged as important and prevalent viral infections worldwide
- Estimated prevalence of HCV in HIV infected patients
  - 30 - 40% of all HIV-infected
  - 60 - 85% of hemophiliac patients
  - 52 - 90% of IDU
  - 4 - 8% of MSM

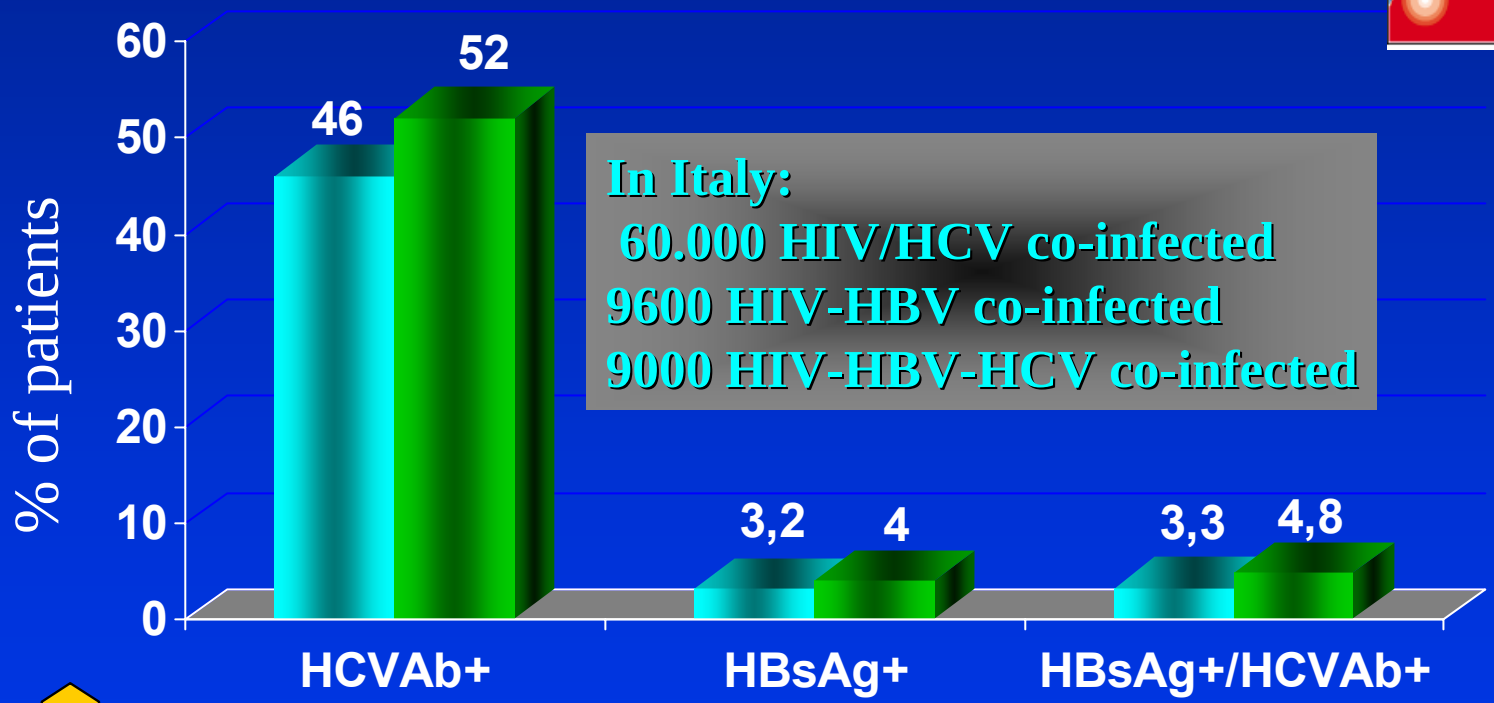
HCV/HIV Co-infection: Geographical Variation

Prevalence of HCV Among Populations of HIV-infected Patients, Published or Presented 1990-2001



*All or a high proportion of the patients were intravenous drug users (IDUs)

Prevalence of HCV and HBV co-infection in Italian HIV+ from cohort and observational databases



In Italy:
60.000 HIV/HCV co-infected
9600 HIV-HBV co-infected
9000 HIV-HBV-HCV co-infected

THE MASTER PROJECT
Standardized management of antiretroviral therapy

Bergamo
Brescia1-2
Busto
Cremona
Ferrara
Firenze
Lecco
Pavia
P. Ligure
Verbania

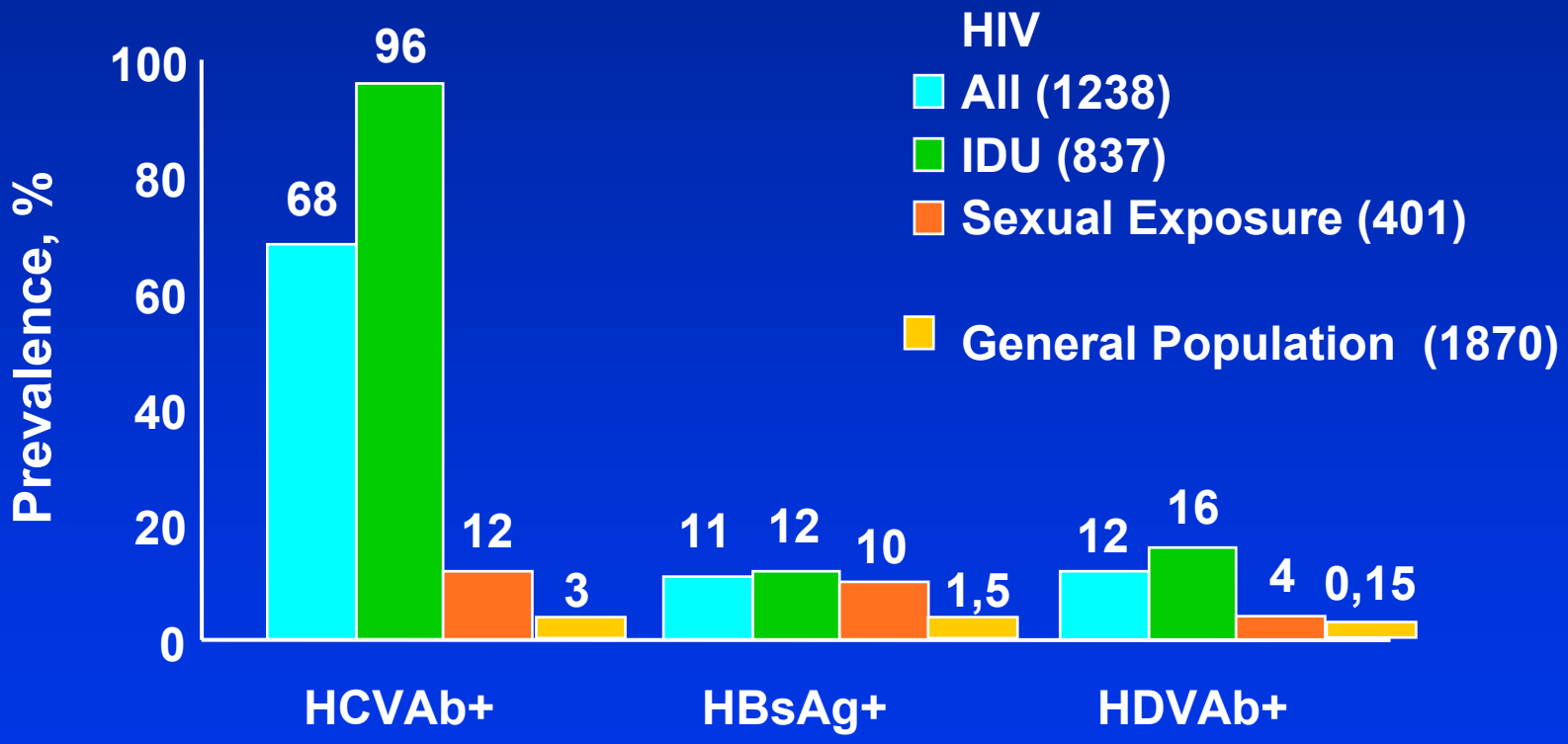
Italian Cohort Naive Antiretroviral — I C O N A

I.Co. N.A. 3917 pz. MASTER DBASE 8183 pz.

ICONA, Bari 12-13 giugno 2002

Prevalence of Hepatitis Viruses infection in 1238 HIV+ and in 1870 HIV-

Infectious Diseases Department .- University of Brescia



THE MASTER PROJECT
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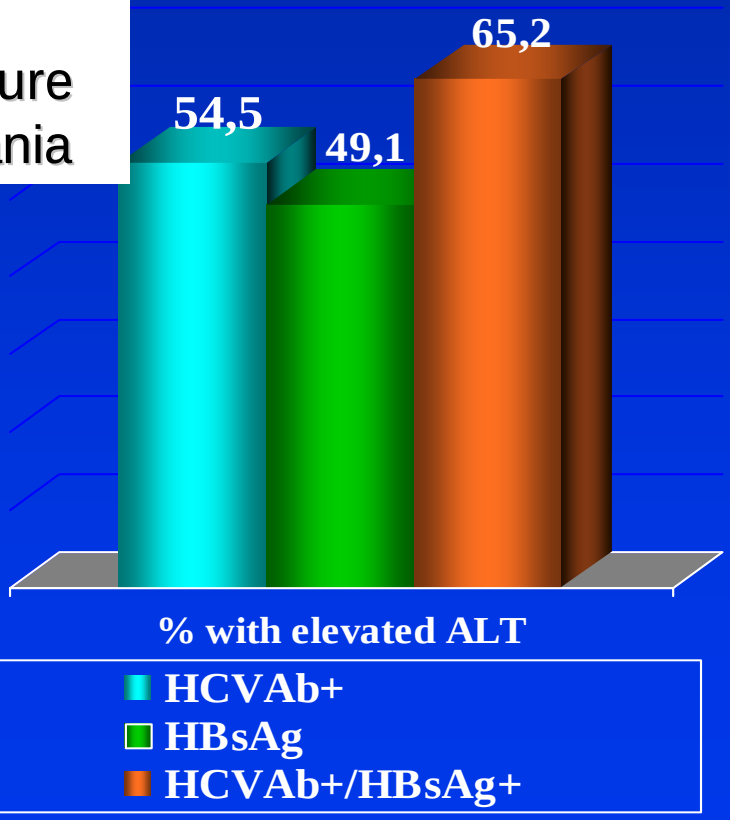
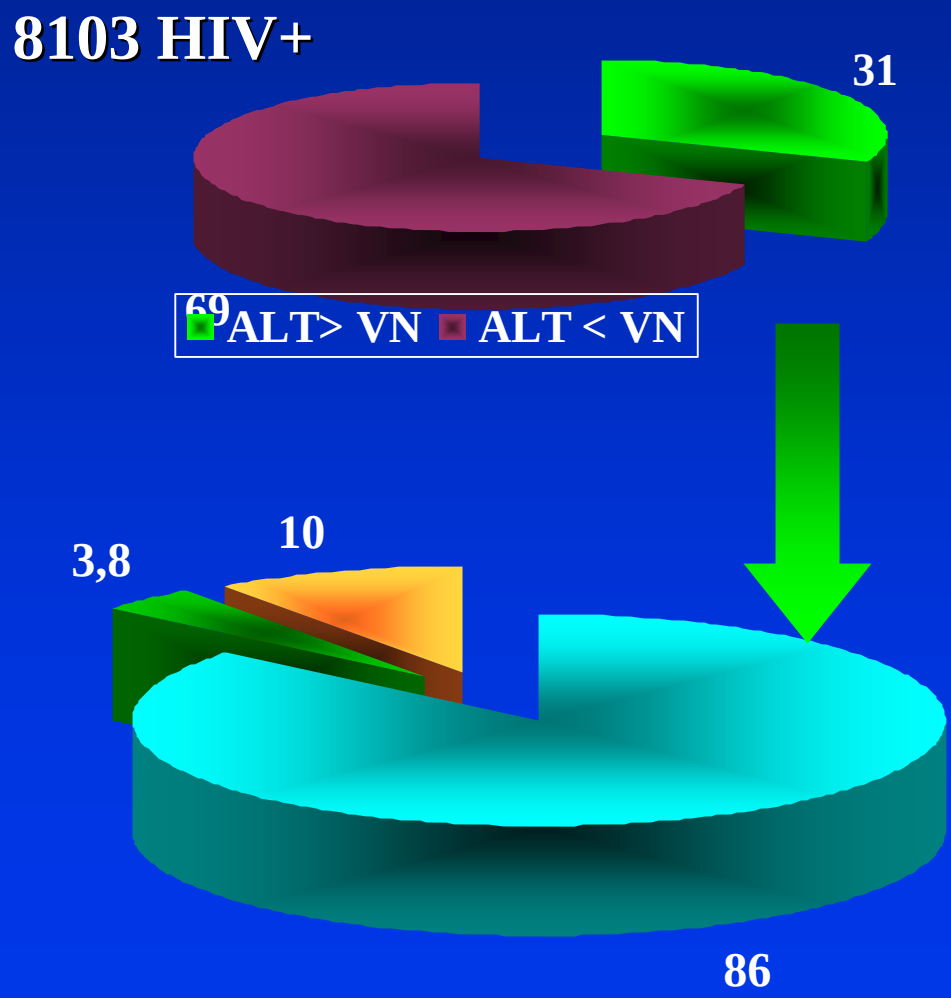
Verbania

MASTER observational DBASE: % HIV+ with hypertransaminasemia stratified according to etiology



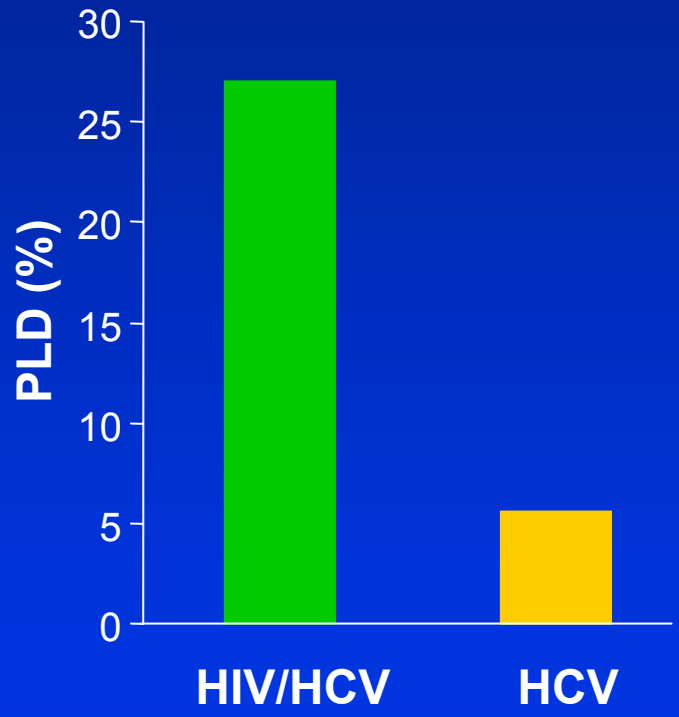


HIV/HCV Co-infection

- HIV infected patients have prolonged life expectancy due to availability of highly active antiretroviral therapy
- Hepatitis C is a leading cause of morbidity and mortality
- Compared with HCV mono-infection
  - Higher HCV RNA titers
  - More rapid progression to cirrhosis and end stage liver disease ∴ more urgency to treat

Impact of HIV Coinfection HCV-Related Clinical Outcomes

- Montreal hemophilia cohort
  - 154 patients (81 HIV+)
- Risk PLD
  - Odds ratio 7.4
  - Mean duration between HCV and PLD: 17.2 years
- Survival after PLD
  - Mean: 3.2 years
  - 73% developed AIDS

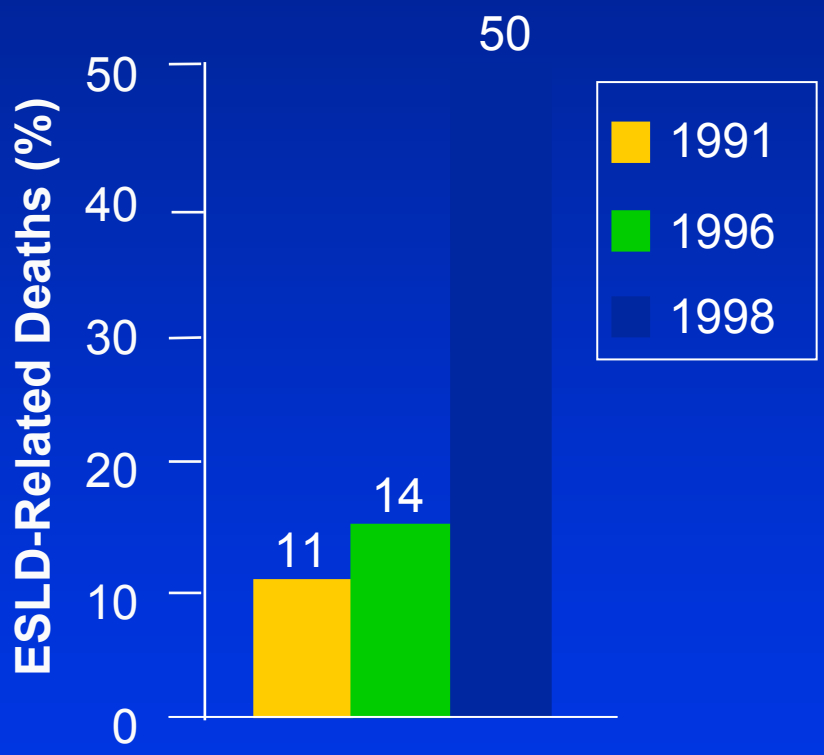


HCV = hepatitis C virus; HIV = human immunodeficiency virus; PLD = progressive liver disease.

Lesens et al. *J Infect Dis*. 1999;179:1254-1258.

Increasing Mortality From ESLD in Patients With HIV

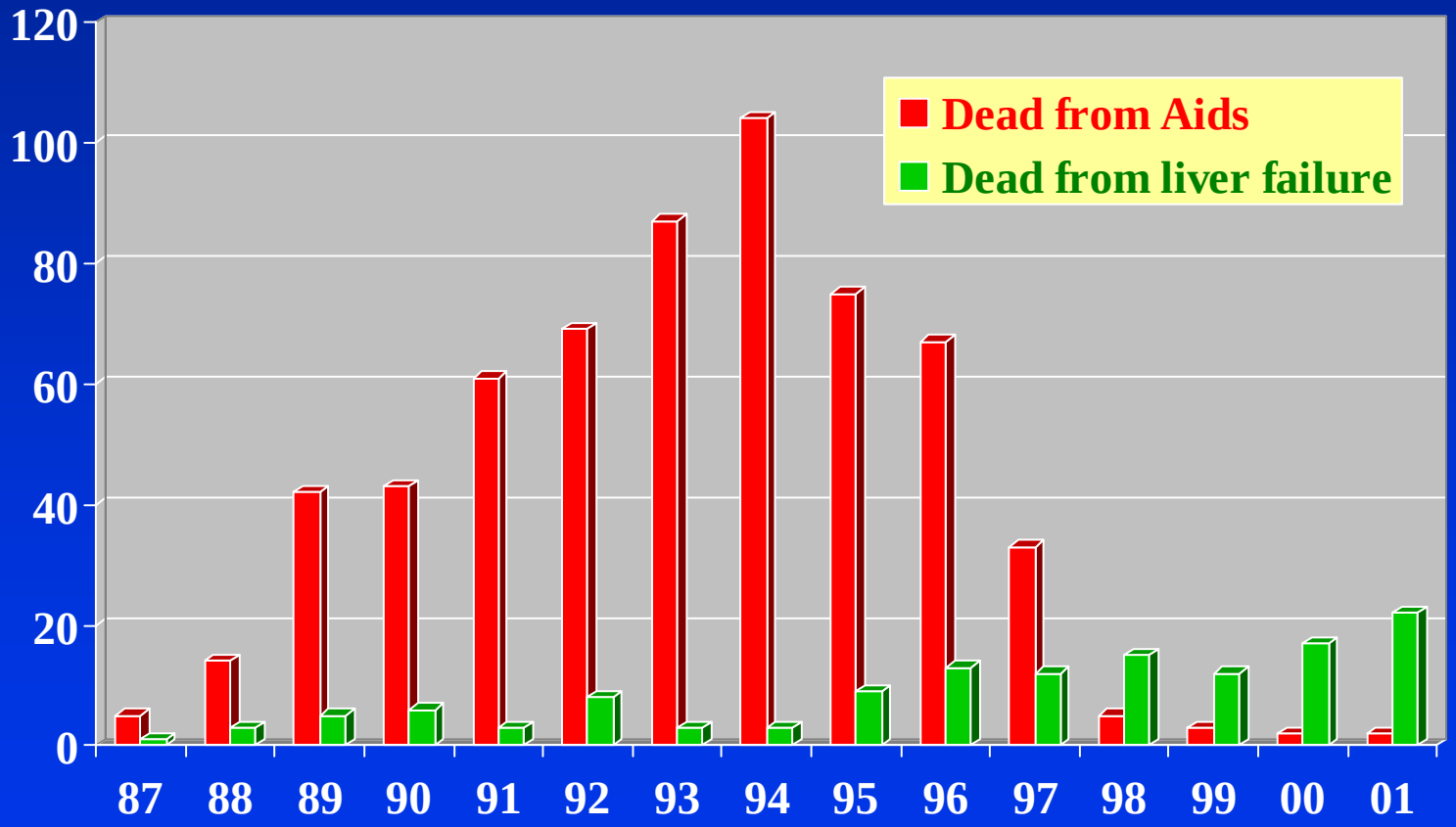
- One third of 1998 cohort had recent history of discontinuing HAART secondary to hepatotoxicity
- More than 1/2 who died with ESLD had either NDVL or CD4 >200/mm^3 6 months prior to death



ESLD = end stage liver disease; NDVL = no detectable viral load.

Bica et al. *Clin Infect Dis.* 2001;32:492-497.

Mortalità per AIDS ed insufficienza epatica (ESLD) in una coorte di pazienti di Torino e Verona, 1987-2001



Di Perri G. *et al.*, 2001

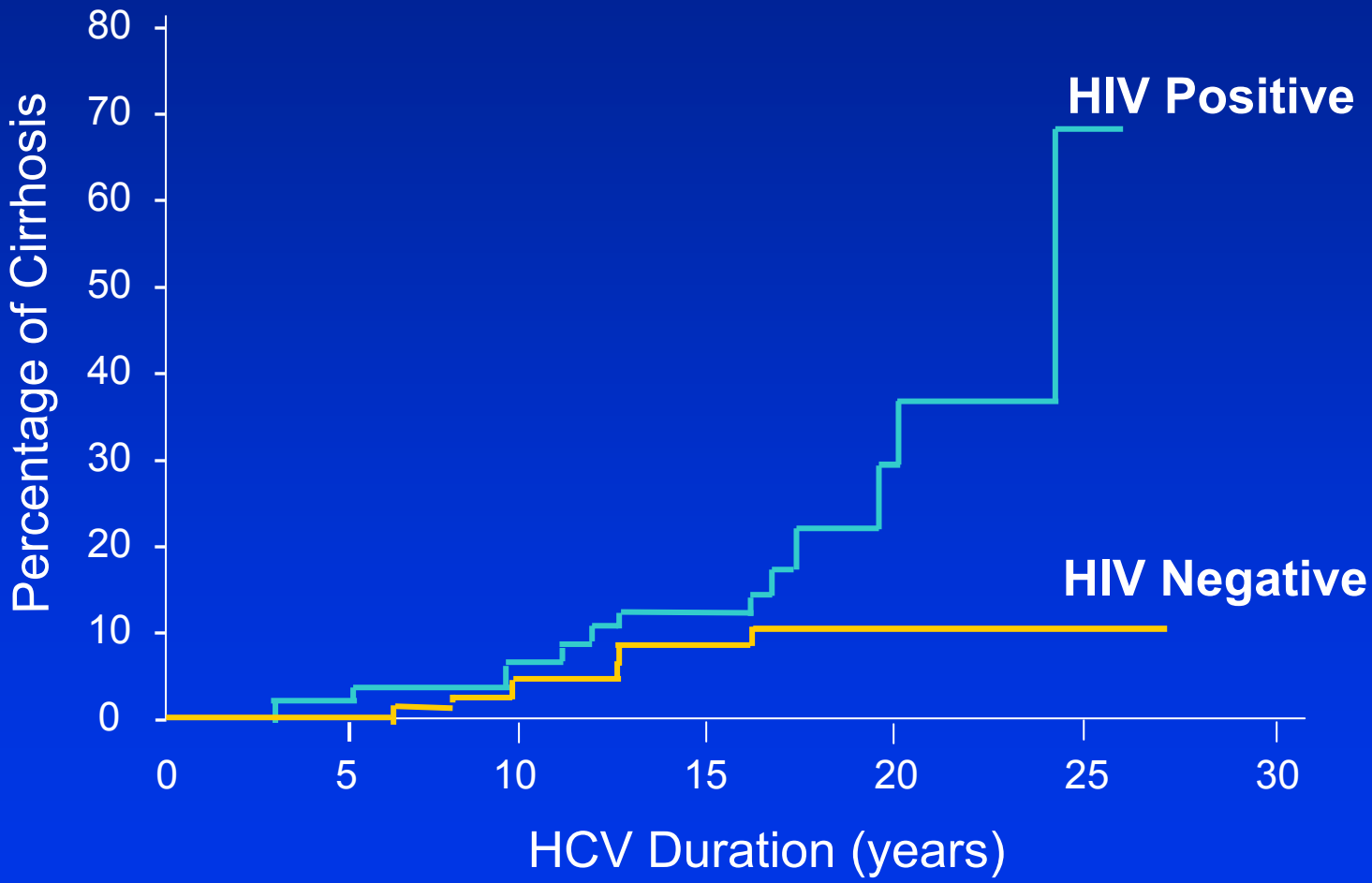
Trend dei tassi di mortalità per ESLD

Anno	*ESLD*	*P-Y*	*ESLD per 1000 P-Y*	*Rate ratio*	*95% CI*
1987-95	41	6094	6.7	1	-
1996	13	893	14.6	2.1	1.16-4.04
1997	12	853	14.1	2.1	1.09-3.98
1998	15	764	19.6	2.9	1.61-5.27
1999	12	672	17.8	2.7	1.39-5.05
2000	17	744	22.8	3.4	1.93-5.98
2001	22	828	26.6	3.9	2.35-6.63

Poisson regression analysis: p = 0.002

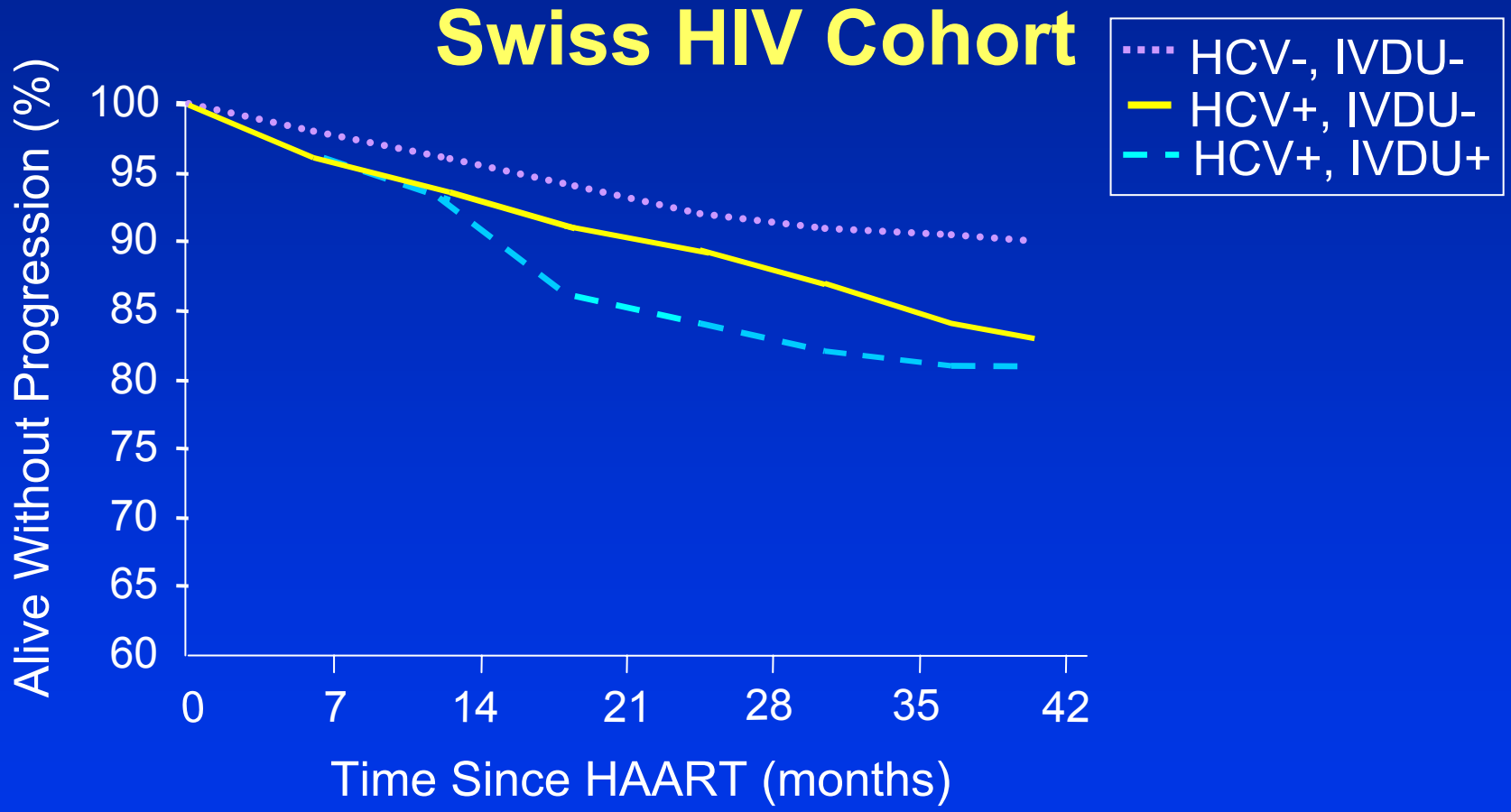
Di Perri G. *et al.*, 2001

Update 2002
Morbidity/Mortality in HIV/HCV



P=.04.
HCV = hepatitis C; HIV = human immunodeficiency virus.
Di Martino et al. *Hepatology.* 2001;34:1193-1199.

Outcomes After HAART According to HCV Status and IVDU



HAART= highly active antiretroviral therapy; HCV = hepatitis C virus; IVDU = intravenous drug use.

Greub et al. *Lance*t. 2000;356:1800-1805.

Effect of HAART on Hepatitis C

- Haart is associated with a substanzial improvement in survival and this incluted a significant improvement in liver-related deaths attibuited to HCV

Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet. 2003;362:1708-1713

Why treat HCV infection in patients with HIV?

- In patients infected with HIV, HCV clearly has a worse prognosis
- Evidence is mounting that HCV worsens the prognosis of HIV (Swiss cohort study)
- In patients infected with HIV, HCV may soon be the leading cause of death
- HAART hepatotoxicity may necessitate HCV treatment in order for patients to tolerate HIV medications

Obstacles in the Treatment of HIV/HCV Patients

- Higher degrees of fibrosis at baseline
- Higher baseline levels of HCV RNA
- Pre-existing cytopenias
- Mental health and substance abuse issues
- Drug interactions
  - Potentiation of drug-induced toxicities
  - Potential negative impact on HIV control

RIBAVIRINA

inibizione della fosforilazione di timidina

in vitro

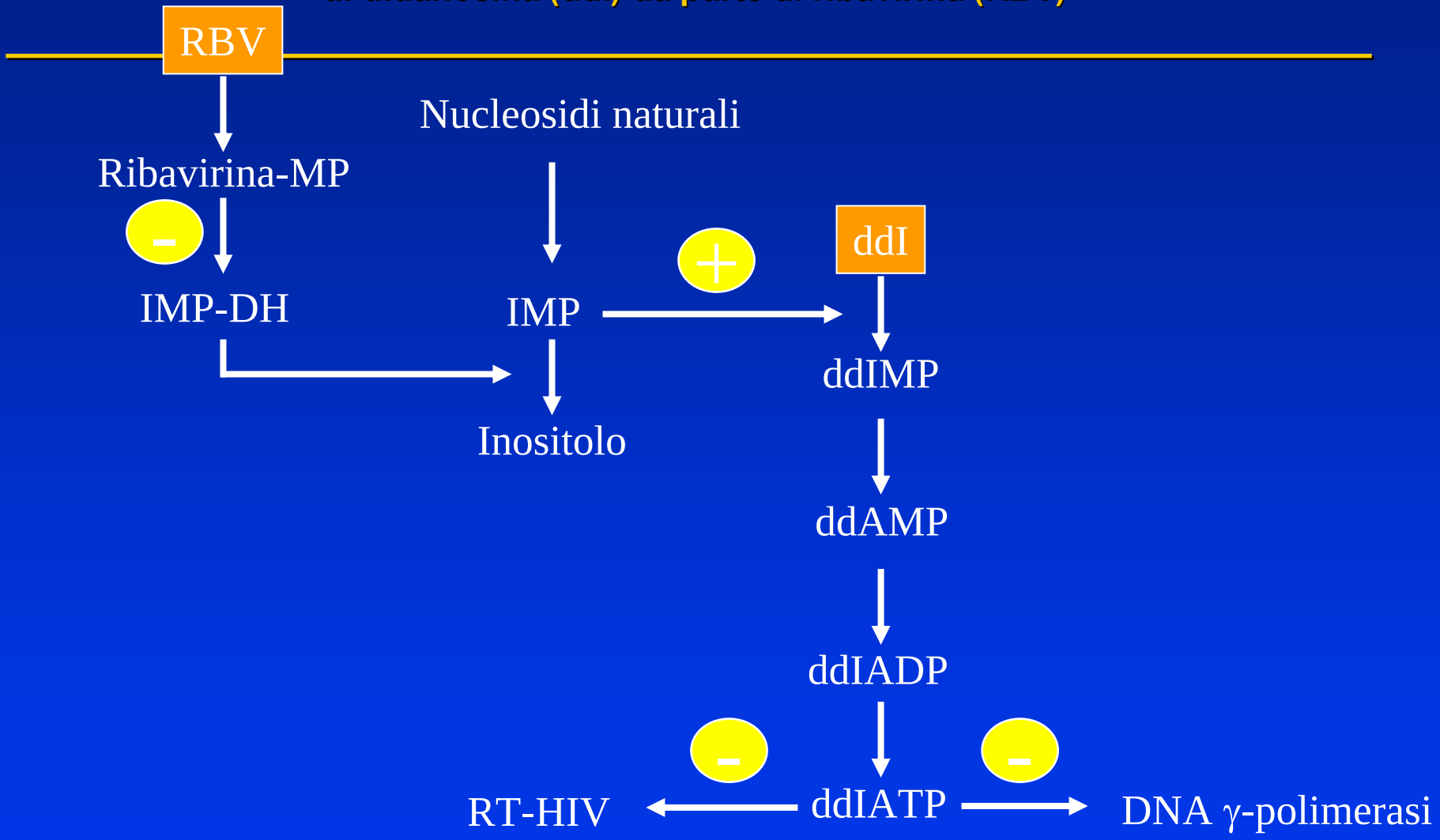
ZDV
ddC
3TC
d4T

ddI

in vivo

- nessuna interazione con HAART
- acidosi lattica (ddI ?)

Pathway metabolico che conduce al potenziamento di didanosina (ddI) da parte di ribavirina (RBV)



Question about use of IFN/RBV in HIV-Infected Patients

- Will HIV control wane?
- Will CD4 counts decline?
- Will pre-existing anemia be exacerbated by use of RBV?
- Will DDI-associated toxicities increase with the use of RBV?
- Will treatment be safe and effective?

Treatment of HIV/HCV With PEG-IFN α-2b + RBV

- 68 patients naïve to IFN
- 73% on ART; CD4 >300
- HIV RNA <5,000 copies/ml
- 50% with high HCV RNA; 35% with genotype 3
- Only 17% with liver biopsy
- Duration of treatment dependent on genotype

Perez-Olmeda, M. *AIDS* 2003;17(7):1023-28.

Treatment of HIV/HCV With PEG-IFN α-2b + RBV

- ETR: 40%
- SVR: 28% (intention to treat)
- 30% relapsed off therapy
- No adverse effect on HIV control

Perez-Olmeda M. *AIDS*. 2003;17(7):1023-28.

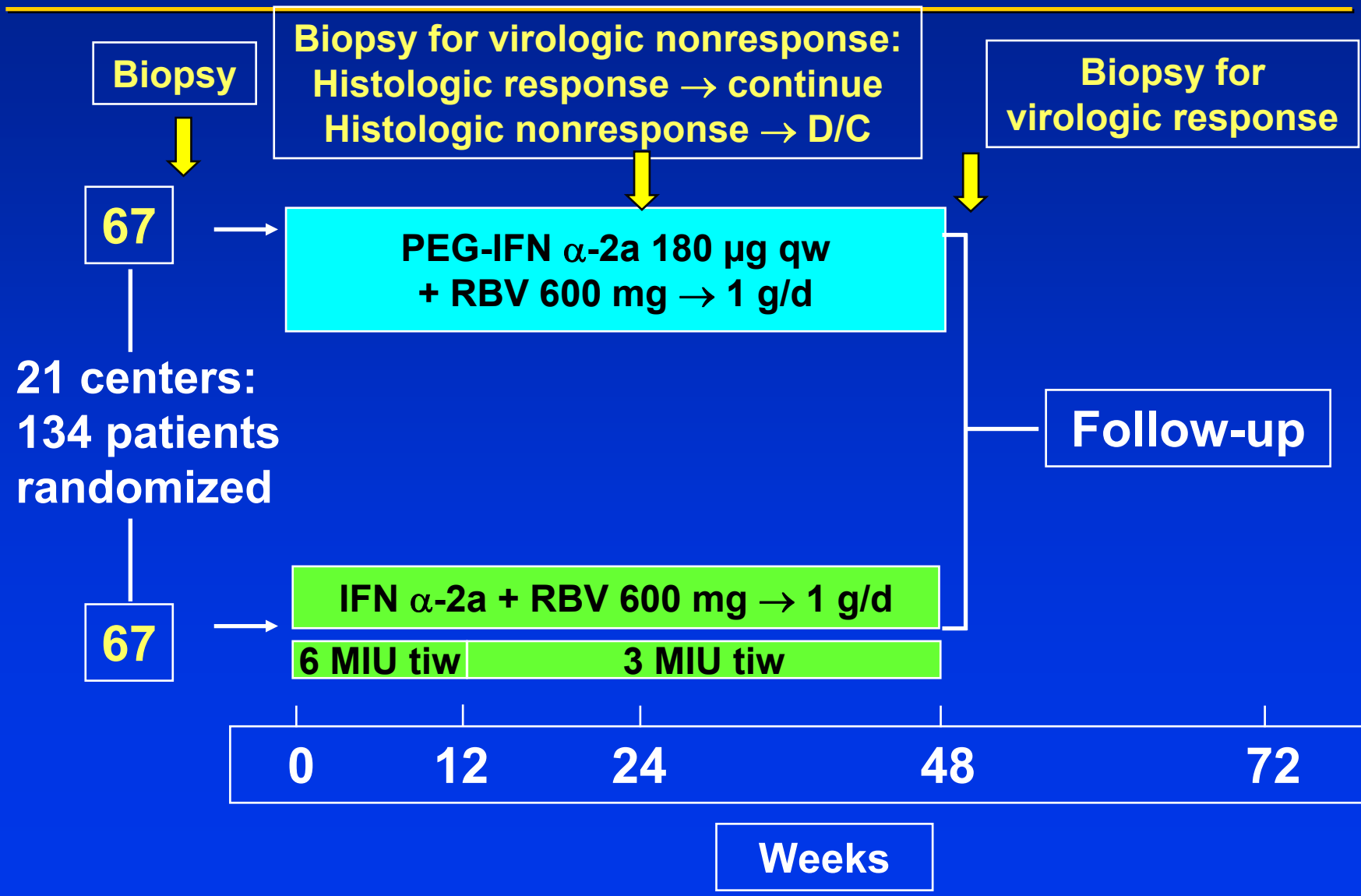
Treatment of HIV/HCV With PEG-IFN α-2b + RBV

Predictors of Virological Response to HCV Therapy—Multivariate Analysis of SVR

Parameter	OR	*P*
HCV genotype 3	3.5	0.052
HCV RNA <800,000 IU/mL	5.5	0.009

Perez-Olmeda M. *AIDS* 2003;17(7):1023-28

ACTG A5071: Study Design



ACTG-A5071

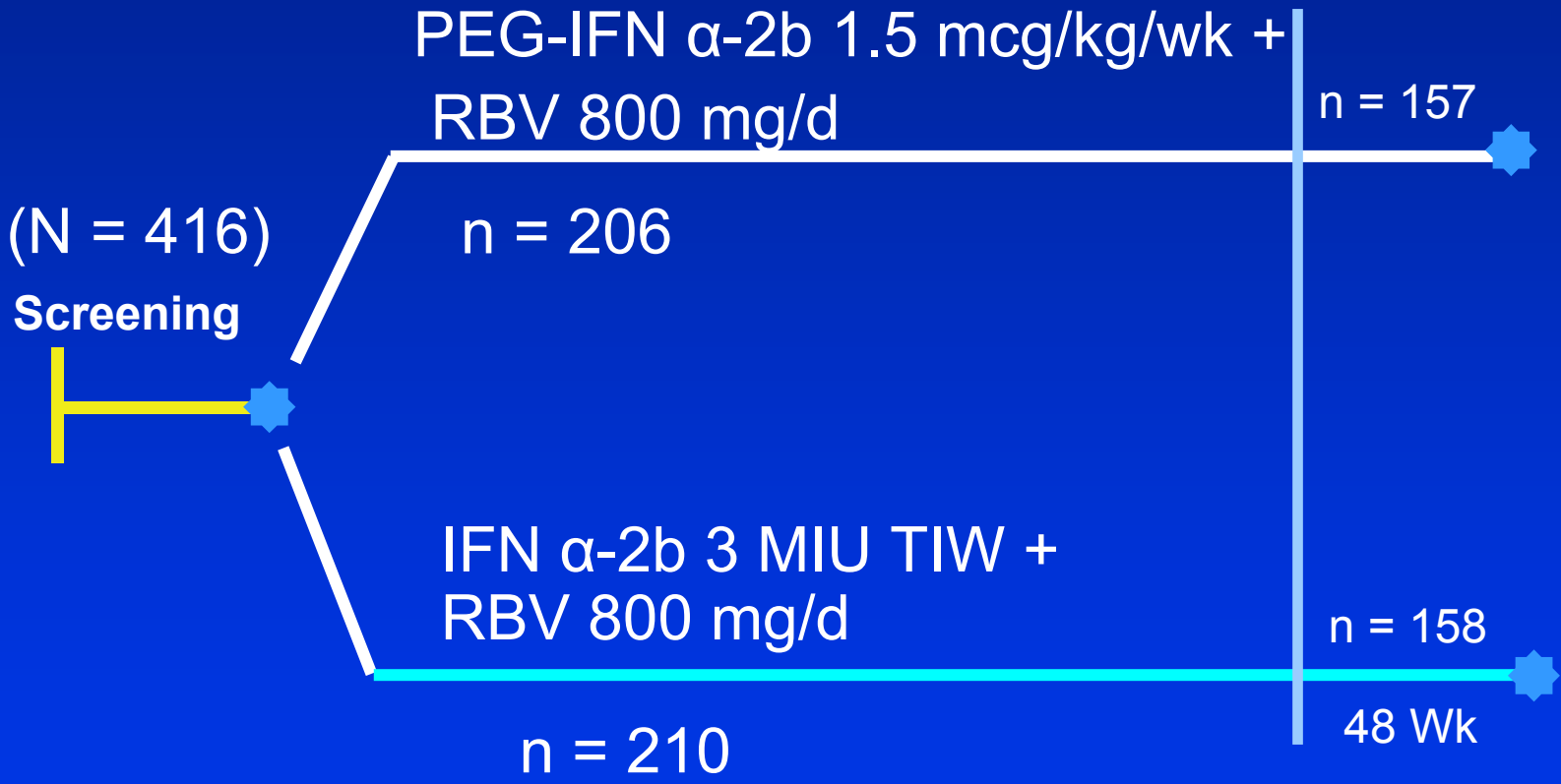
Baseline	IFN-RBV (n = 67)	PEG-RBV (n = 66)
CD4+ cell count, median cells/mcL	444	492
Genotype 1	78%	77%
Fibrosis (median)	2.0	2.0
Results SVR -- 72 weeks		
All patients	8 (12%)	18 (27%)*
Genotype 1	* 3/52 (6%)	7/51 (14%)
Other genotypes	5/15 (33%)	11/15 (73%)
Premature discontinuation		
For adverse reactions	8 (12%)	8 (12%)

P </= .05

ACTG A5071: Histologic Response (HR) in Virologic Non-responders (NR) (24 sett)

	IFN + R n=67	PEG-IFN + R n=66
NR	57 (85%)	37 (56%)
Wk 24 bx obtained	37	23
Histologic response	15 (40%)	6 (26%)
VR + HR	25 (37%)	35 (53%)

RIBAVIC (ANRS HCO2): PEG-IFN α-2b/RBV



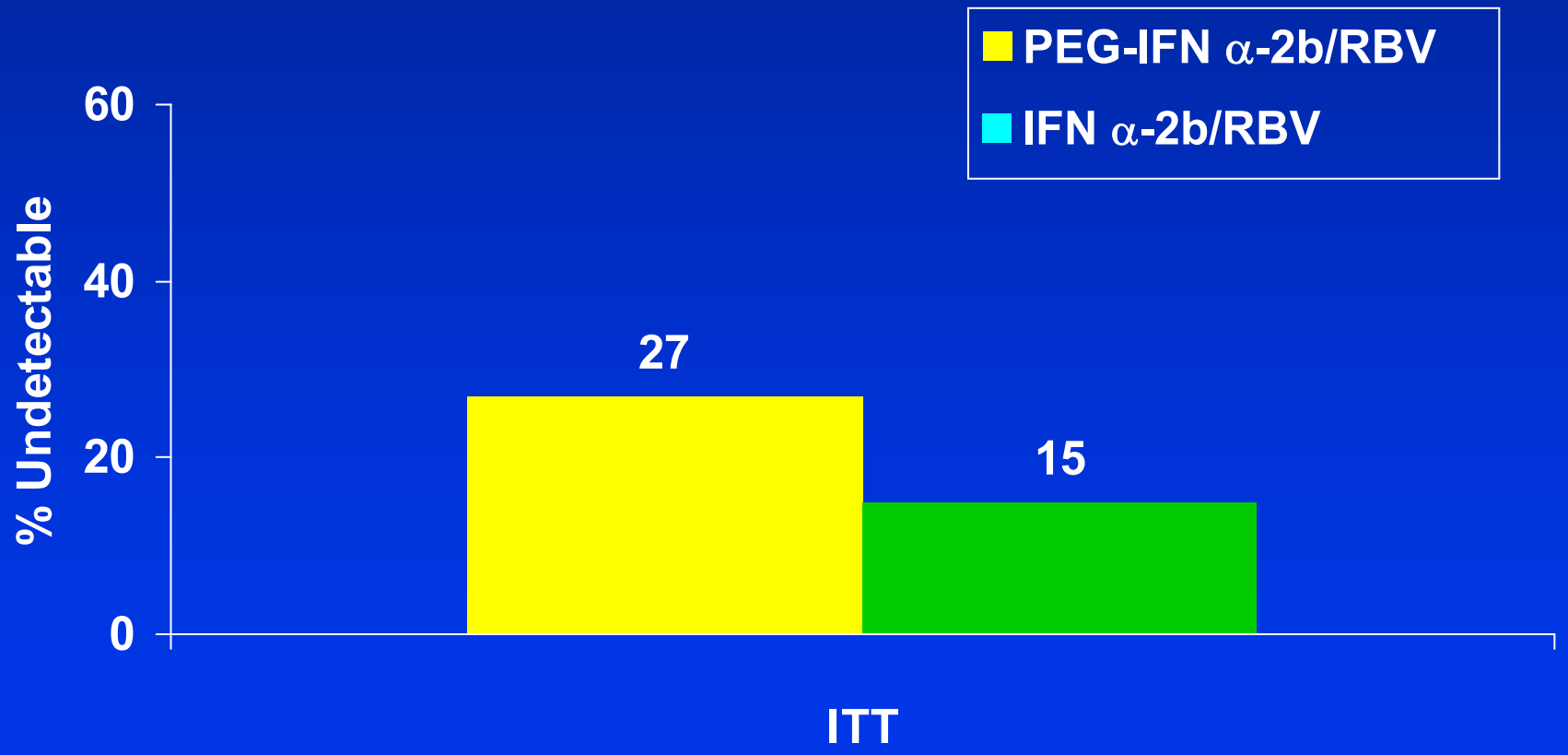
Pol et al. *J Hepatology* 2003;38:92A

RIBAVIC: Patient Demographics

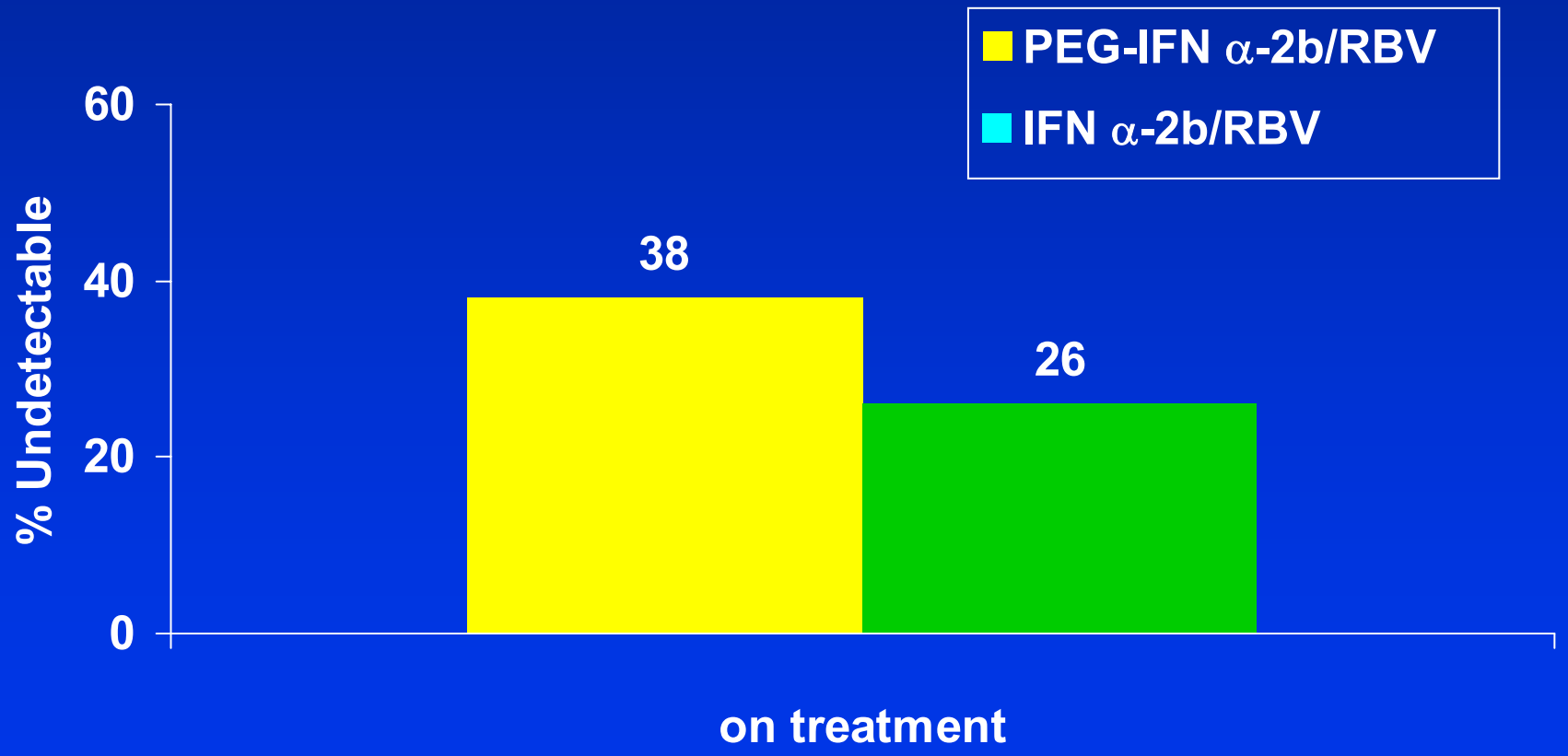
- 80% on HAART
- Mean CD4 = 515
- 60% HIV <200, Mean HIV RNA = 3.48 $\log_{10}$
- F3-4 = 39%, normal ALT = 16%

Pol et al. *J Hepatology* 2003;38:92A

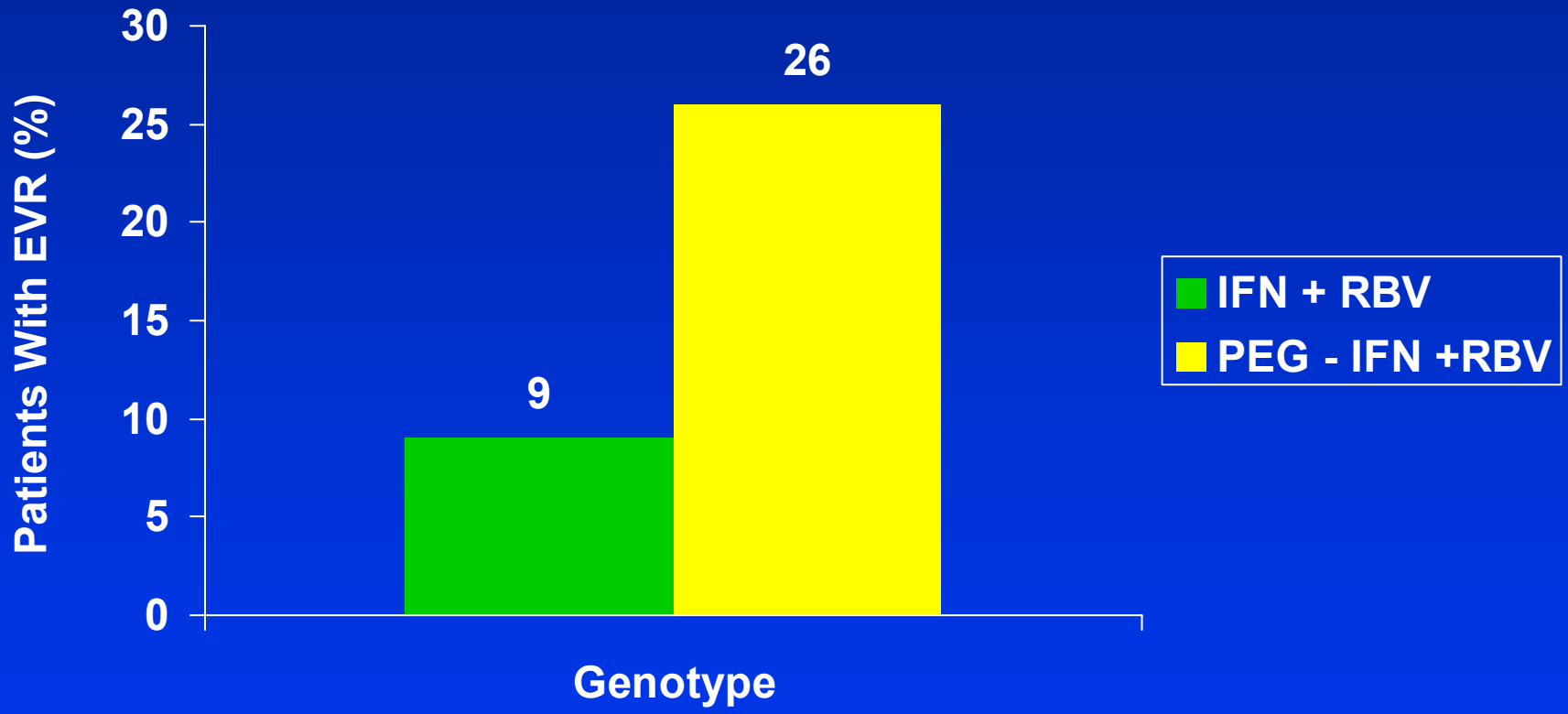
RIBAVIC: SVR (412 Patients) – ITT analysis



RIBAVIC: SVR for those who completed therapy



RIBAVIC: ETR in Genotype 1/4



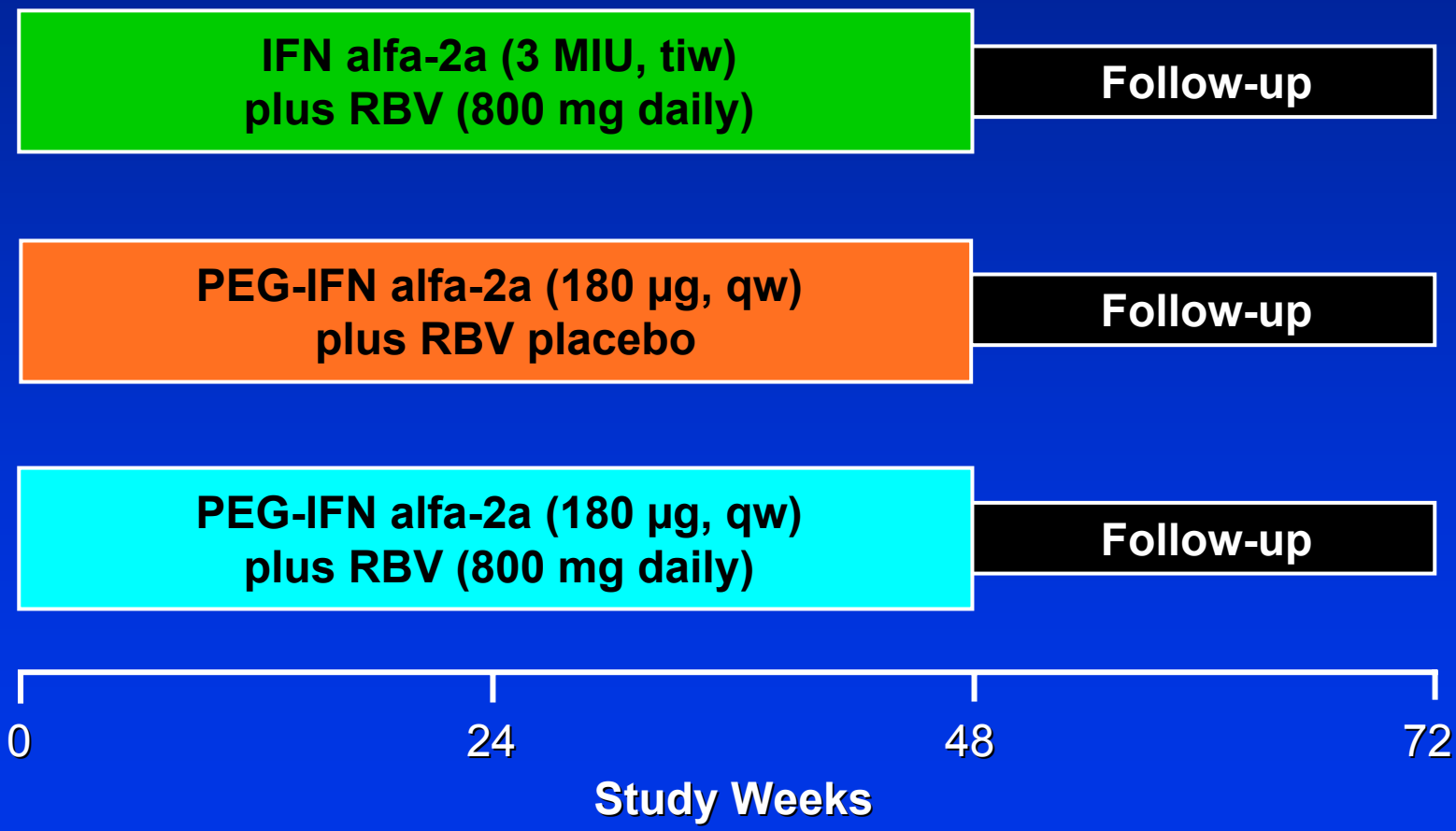
Pol et al. *J Hepatology* 2003;38:92A

RIBAVIC: Safety and Tolerability

- High rate of SAEs, resulting in therapy discontinuations (34% PEG; 36% std IFN)
  - Psychiatric, 21 events
  - Infections, 12
  - Hematologic, 9
  - Liver failure, 10
  - Hyperlactatemia, 8
    - Association with ddI (OR ~ 23)

Pol et al. *J Hepatology* 2003;38:92A

APRICOT Study Design



Key Inclusion Criteria

- HCV criteria
  1. Liver biopsy (≤15 months) consistent with
  2. HCV infection, If cirrhotic Child-Pugh Grade A

- HIV criteria
  1. HIV antibody or quantifiable HIV RNA
  2. $CD4^+$ cell count
     - ≥200/µL *or*
     - ≥100/µL to <200/µL with <5000 copies/mL HIV RNA
  3. HIV disease stable with or without anti-retroviral treatment

Baseline Characteristics: HCV

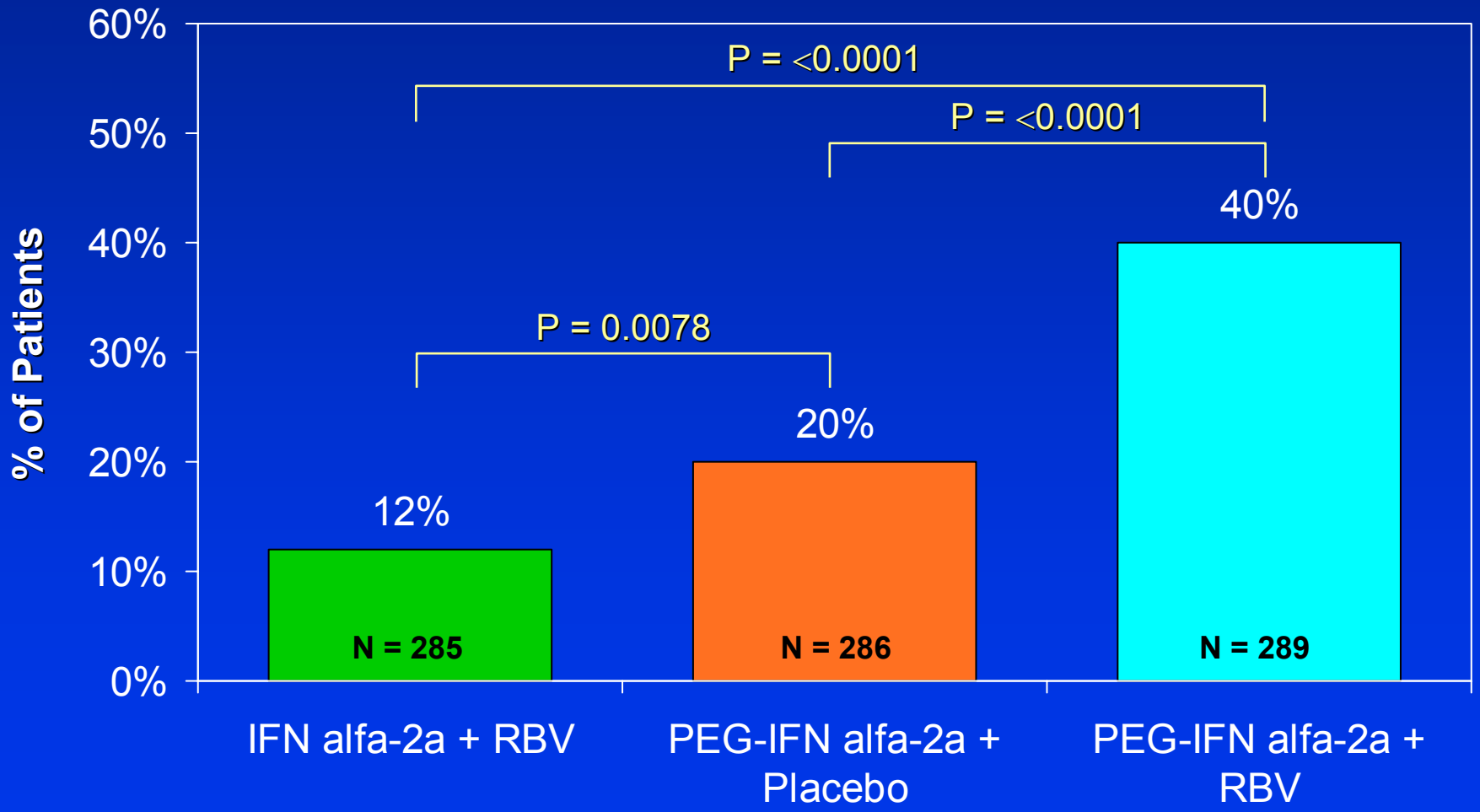
	IFN alfa-2a + RBV (N = 285)	PEG-IFN alfa-2a + Placebo (N = 286)	PEG-IFN alfa-2a + RBV (N = 289)
HCV RNA (IU/mL x 10^6)			
Mean	5.2	6.3	5.6
Median	3.6	4.6	3.5
Range	0.006 - 44	0.006 - 30	0.006 - 44
HCV Genotype (%)			
Type 1	60	61	61
Type non-1	40	38	38
2	5	6	4
3	26	26	28
4	8	7	6
Other	<1	<1	<1

Baseline Characteristics: HIV

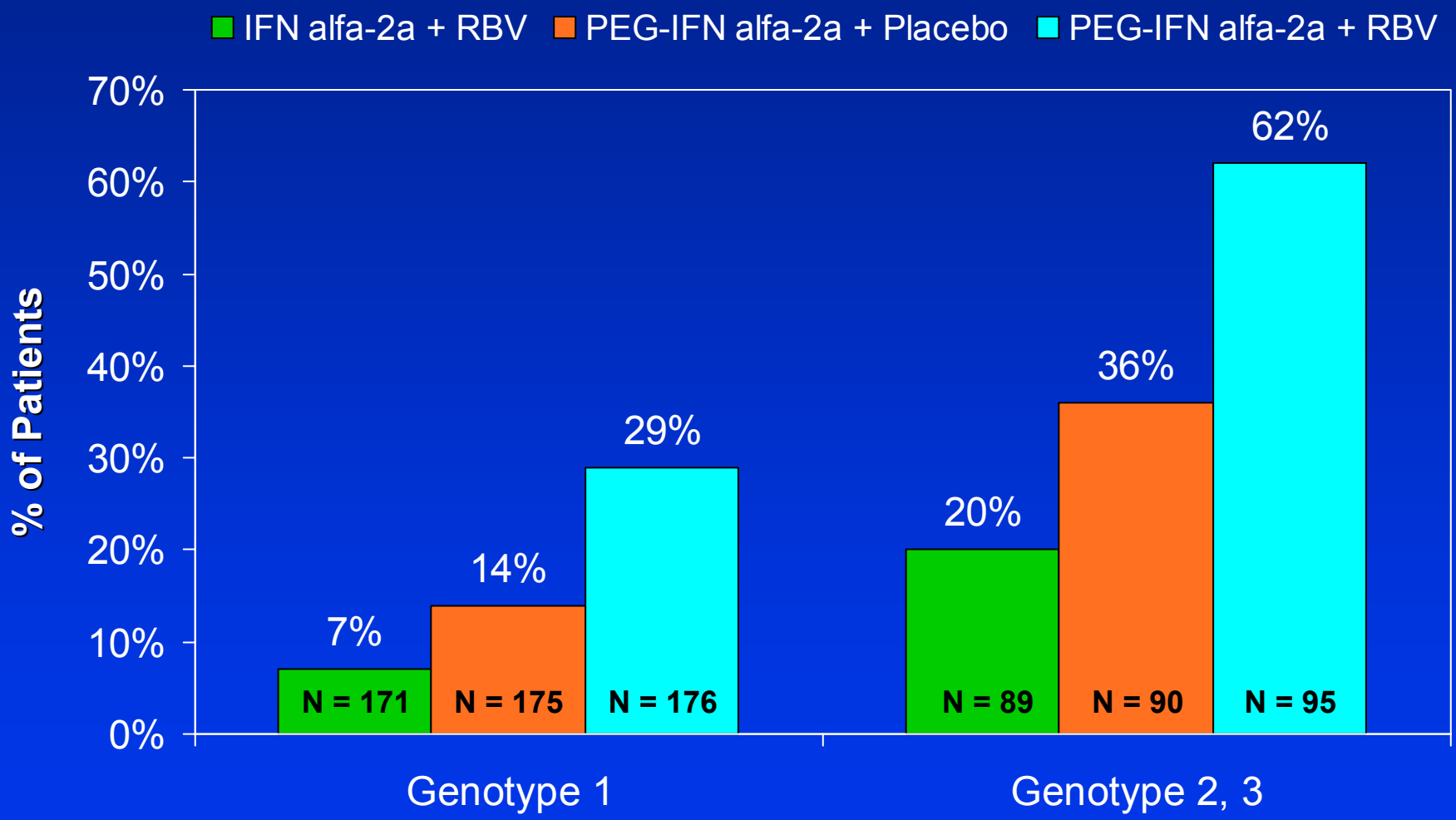
	IFN alfa-2a + RBV (N = 285)	PEG-IFN alfa-2a + Placebo (N = 286)	PEG-IFN alfa-2a + RBV (N = 289)
ART* (%)	84	85	84
HIV RNA			
Median	<50	<50	<50
Range	<50 - 640,622	<50 - 490,625	<50 - 580,679
$CD4^+$ Counts (cells/μL)			
Mean	542	530	520
<200 (%)	7	5	6

*Any treatment used as antiretroviral therapy

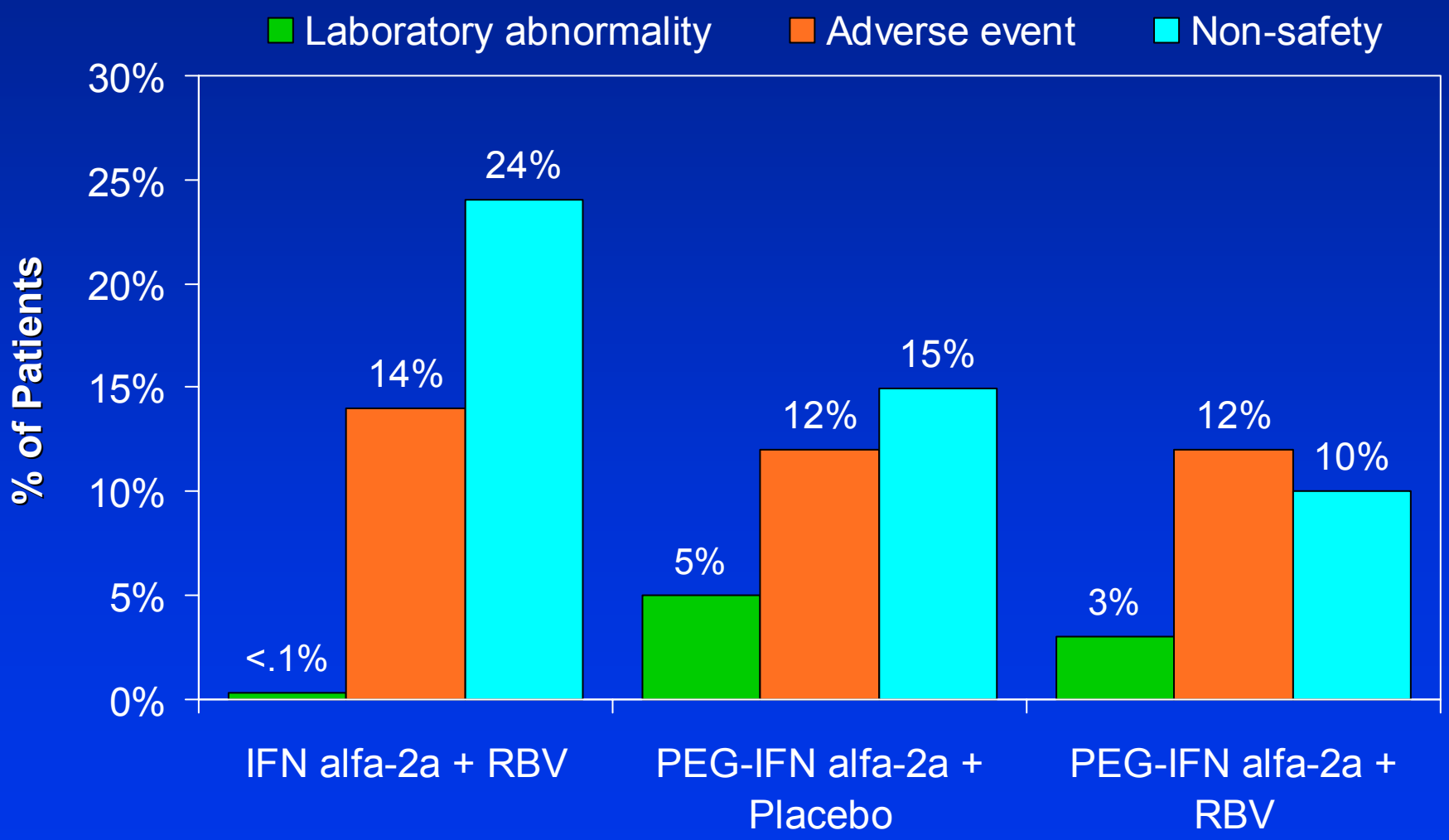
Sustained Virologic Response



Sustained Virologic Response by Genotype



Withdrawal from Treatment



Adverse Events ≥20%

	IFN alfa-2a + RBV (N = 285)	PEG-IFN alfa-2a + Placebo (N = 286)	PEG-IFN alfa-2a + RBV (N = 288)
Fatigue	40%	41%	44%
Pyrexia	35%	43%	44%
Headache	41%	38%	39%
Myalgia	29%	33%	36%
Nausea	25%	27%	30%
Diarrhea	24%	26%	28%
Insomnia	29%	21%	26%
Asthenia	24%	22%	28%
Depression	22%	20%	26%
Arthralgia	18%	20%	20%
Weight decreased	14%	18%	20%

Incidence of Laboratory and Clinical Events Associated with HCV Treatment

	IFN alfa-2a + RBV (N = 285) N (%)		PEG-IFN alfa-2a + Placebo (N = 286) N (%)		PEG-IFN alfa-2a + RBV (N = 289) N (%)	
ANC <0.5 x10^9/L	1	(<1)	37	(13)	31	(11)
Platelets <20 x10^9/L	0	(0)	1	(<1)	1	(<1)
Hemoglobin <8.5 g/dL	4	(1)	10	(3)	11	(4)
Triglycerides >1200 mg/dL	10	(4)	16	(6)	16	(6)
Weight decrease of >10%	75	(26)	70	(25)	72	(25)
Serious depression	2	(<1)	4	(<1)	3	(<1)

Impact of HCV Treatment on Absolute $CD4^+$ Count and $CD4^+$%*

	IFN alfa-2a + RBV	PEG-IFN alfa-2a + Placebo	PEG-IFN alfa-2a + RBV
Baseline**			
$CD4^+$ cells/μL	512	481	476
$CD4^+$%	26	25	25
Change from baseline at week 48**			
$CD4^+$ cells/μL	-99	-115	-140
$CD4^+$%	+2.3	+2.1	+3.9

* Patients who completed 48 weeks of treatment

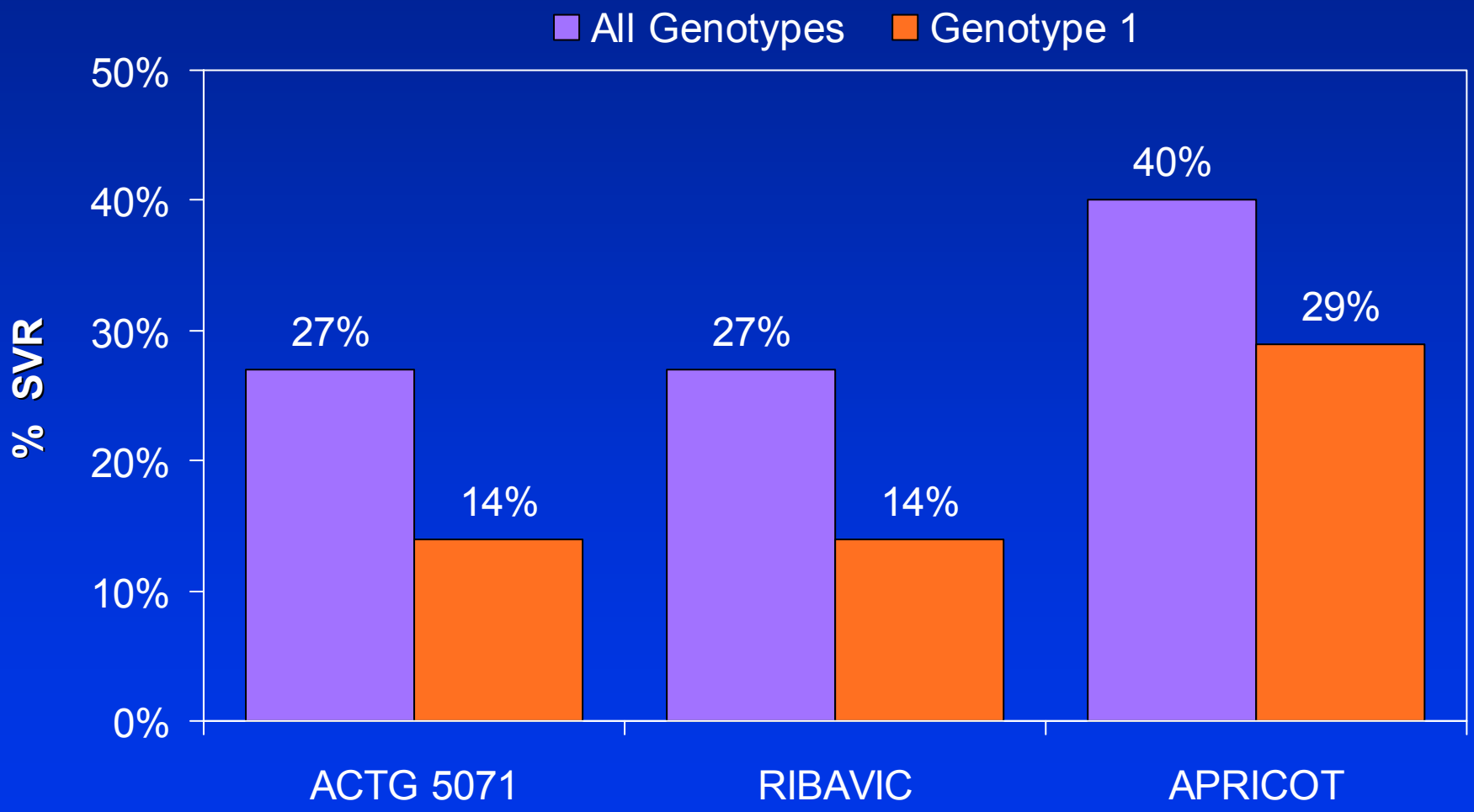
** Median

Impact of HCV Treatment on HIV-1 RNA

Median Log_{10} HIV RNA (copies/mL)

	Baseline	Δ from Baseline at End of Treatment	Δ from Baseline 4 Weeks after End of Treatment
Patients receiving ART at baseline			
IFN alfa-2a + RBV	1.699	0.000	0.000
PEG-IFN alfa-2a + Placebo	1.699	0.000	0.000
PEG-IFN alfa-2a + RBV	1.699	0.000	0.000
Patients not receiving ART at baseline			
IFN alfa-2a + RBV	3.852	0.000	0.414
PEG-IFN alfa-2a + Placebo	4.061	-0.983	0.055
PEG-IFN alfa-2a + RBV	3.947	-0.894	0.056

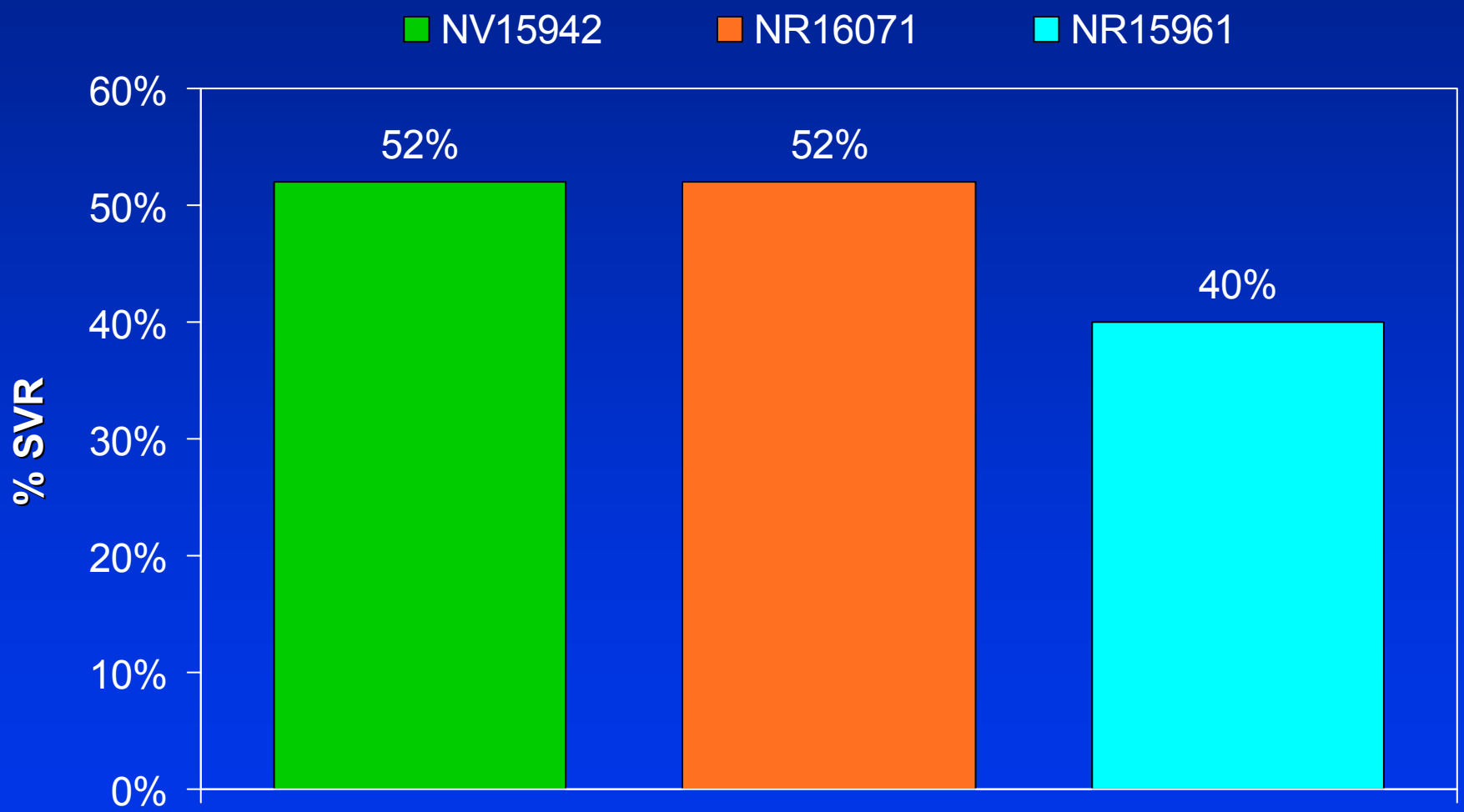
PEG-IFN SVR: All Genotypes and Genotype 1 (ACTG 5071 vs RIBAVIC vs APRICOT)



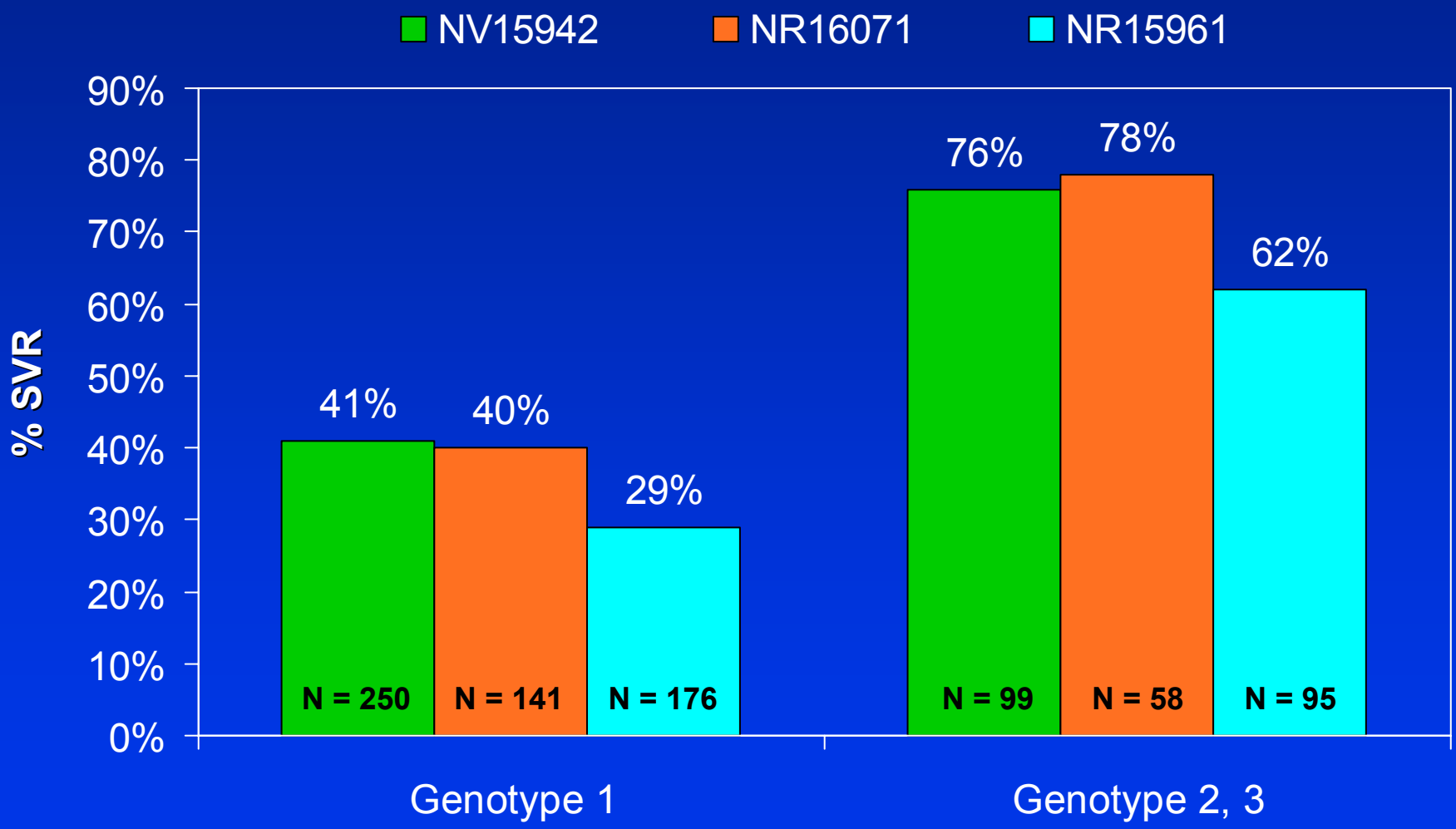
Comparison of Mono-infection Results (NV15942 and NR16071) with Key Co-infection Results (NR15961)

Peg-ifn alfa2a 180 μg +
RBV 800 mg, 48 weeks

Sustained Virological Response – All Genotypes (Peg-ifn alfa-2a 180 μg + RBV 800 mg)



Sustained Virological Response – By Genotype (Peg-ifn alfa-2a 180 μg + RBV 800 mg)



ACTG-A5071,RIBAVIC, APRICOT
permit the following conclusions for HIV/HCV coinfection

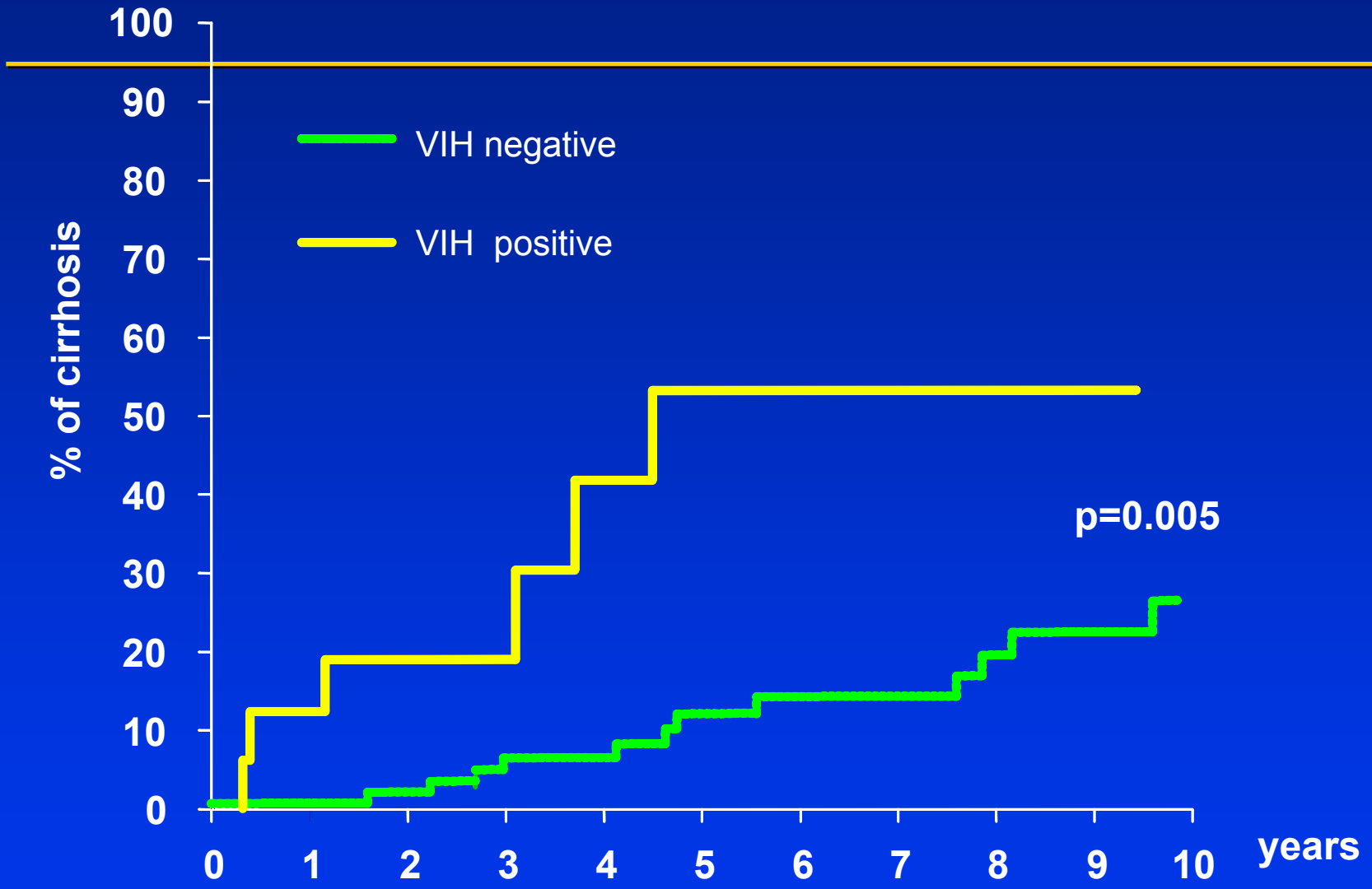
1. The combination of PEG and ribavirin x 48 weeks in patients with virologic response at week 12 appears to be the standard.
2. The rates of SVR reported were 27% to 40% for all patients and 14% to 29% for genotype 1.
3. These rates are significantly lower than those reported for patients with HCV monoinfection.
4. HCV RNA virologic response with < 2 log10 IU/mL at 12 weeks predicts SVR but not necessarily histologic response.
5. The treatment is generally well tolerated and has no significant impact on HIV, although CD4+ cell counts decrease temporarily during therapy with PEG.
6. PEG may have significant anti-HIV activity in those with HIV viremia at baseline

Chronic hepatitis B in patients co-infected with HIV

- HBsAg seropositivity : 10%
- Higher prevalence of cirrhosis than HIV negative HBV-infected patients
- Decrease survival of HIV-HBV co-infected individuals compared to HIV mono-infected

Rustgi VK et al. Ann Intern Med. 1984;101:795-7.
Colin JF et al. Hepatology. 1999;29:1306-10.
Gilson RJC et al. AIDS. 1997;11:597-606.

HIV/HBV co-infection: Natural history



Adapted from Di Martino V et al. Gastroenterology 2002; 123: 1812-1822

HIV/HBV co-infection: Natural history (MACS)

Liver-related mortality, in a cohort of 5293 patients, 1984 /1987 - 2000

N	Viral status HIV	Viral status HBsAg	Liver-related mortality (n)	Liver death (1000 pers/yr)	p
3093	-	-	0	0.0	
139	-	+	1	0.8	0.04
2346	+	-	35	1.7	<0.0001
213	+	+	26	14.2	<0.0001
5293			62	1.1	

Liver related mortality
X 19 HBV/HIV vs HBV (RR18; 73,1-766,1 - p<0,001)

Thio CL et al. Lancet 2002; 360: 1921-1926.

Treatment of HBV in HIV co-infected patients

- **Interferon**
- ***Lamivudine***
- ***Adefovir dipivoxil***
- ***Tenofovir fumarate disoproxil***
- ***FTC (Emtriva)***

Treatment of HBV in HIV co-infected patients: IFN α2a

HBeAg and HBV DNA negativation (<5 pg/mL) in patients treated with IFN α2a

MIU/TIW	HIV+	HIV-
2.5	0/ 5	1/ 4
5	0/ 4	1/ 5
10	0/ 5	4/ 9
Control	0/ 3	0/ 6

Mac Donald et al. Hepatology. 1987;7:719-23.

Treatment of HBV in HIV co-infected patients: IFN α2

HBeAg and HBV DNA negativation (<5 pg/mL) in homosexual men treated with IFN α2a

	HIV+ (n=25)	HIV- (n=25)
10 MIU/TIW 12 weeks	1/12 (8.3%)	5/13 (38.5%)
Control	0/13 (0%)	1/12 (8.3%)

Wong DK et al. Gastroenterology. 1995;108:165-71.

Treatment of HBV in HIV co-infected patients

- *Interferon*
- **Lamivudine**
- *Adefovir dipivoxil*
- *Tenofovir fumarate disoproxil*
- *FTC (Emtriva)*

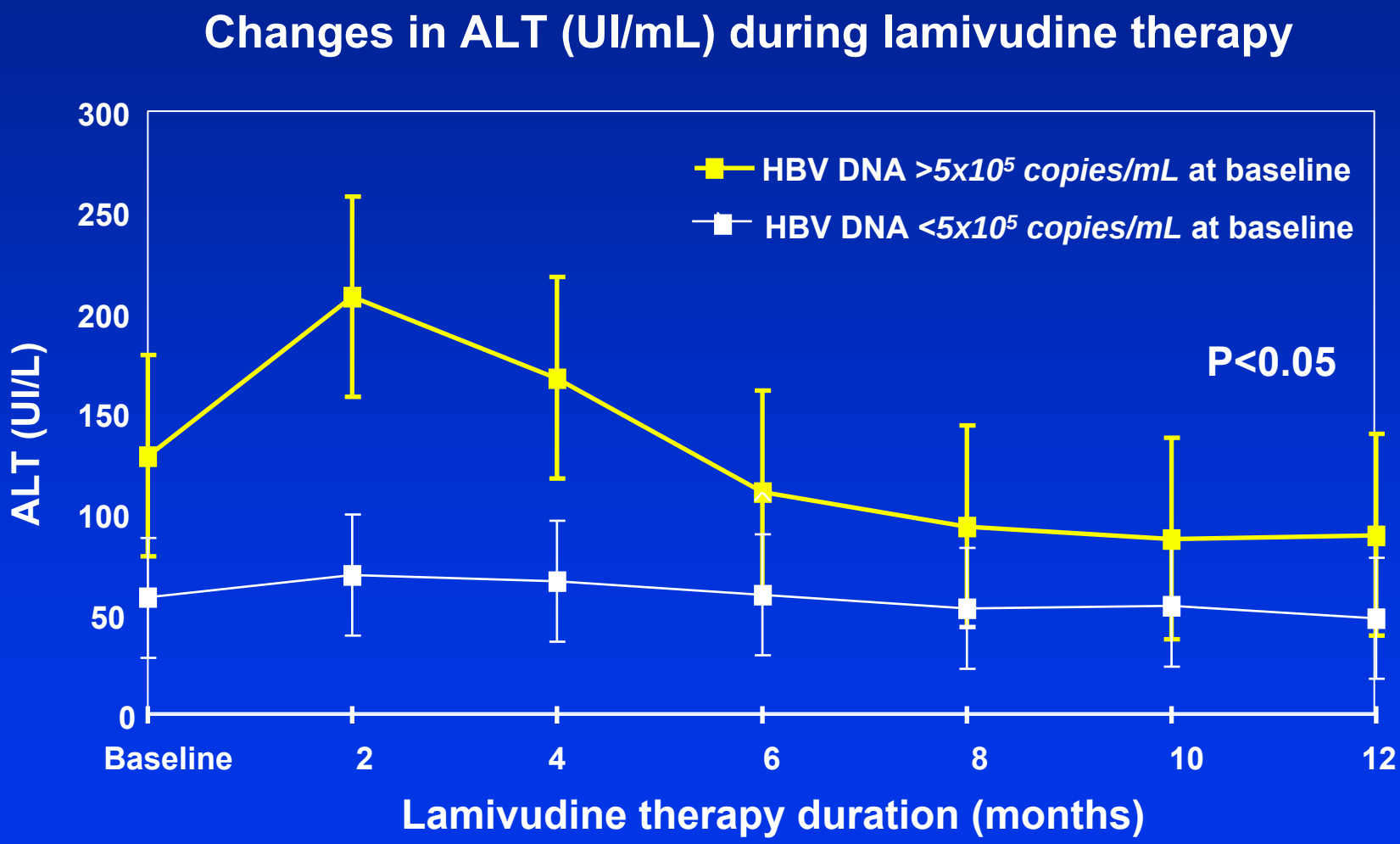
Treatment of HBV in HIV co-infected patients: Lamivudine

One year of lam on HBV serological markers in HIV co-infected patients

	HBV DNA >5 pg/mL n=27	HBV DNA <5 pg/mL n=10
Loss of HBsAg	0 (0%)	3 (30%)
Loss of HBeAg	5 (18.5%)	—
Seroconversion to anti-HBs	0 (0%)	2 (20%)
Seroconversion to anti-HBe	3 (11%)	—
Loss of serum HBV DNA (MH- 1 000 000 copies/mL)	26 (96.3%)	—
Loss of serum HBV DNA (PCR – 1000 copies/mL)	23 (88.5%)	6 (100%)

Y Benhamou et al. Ann Intern Med. 1996;125:705-712.

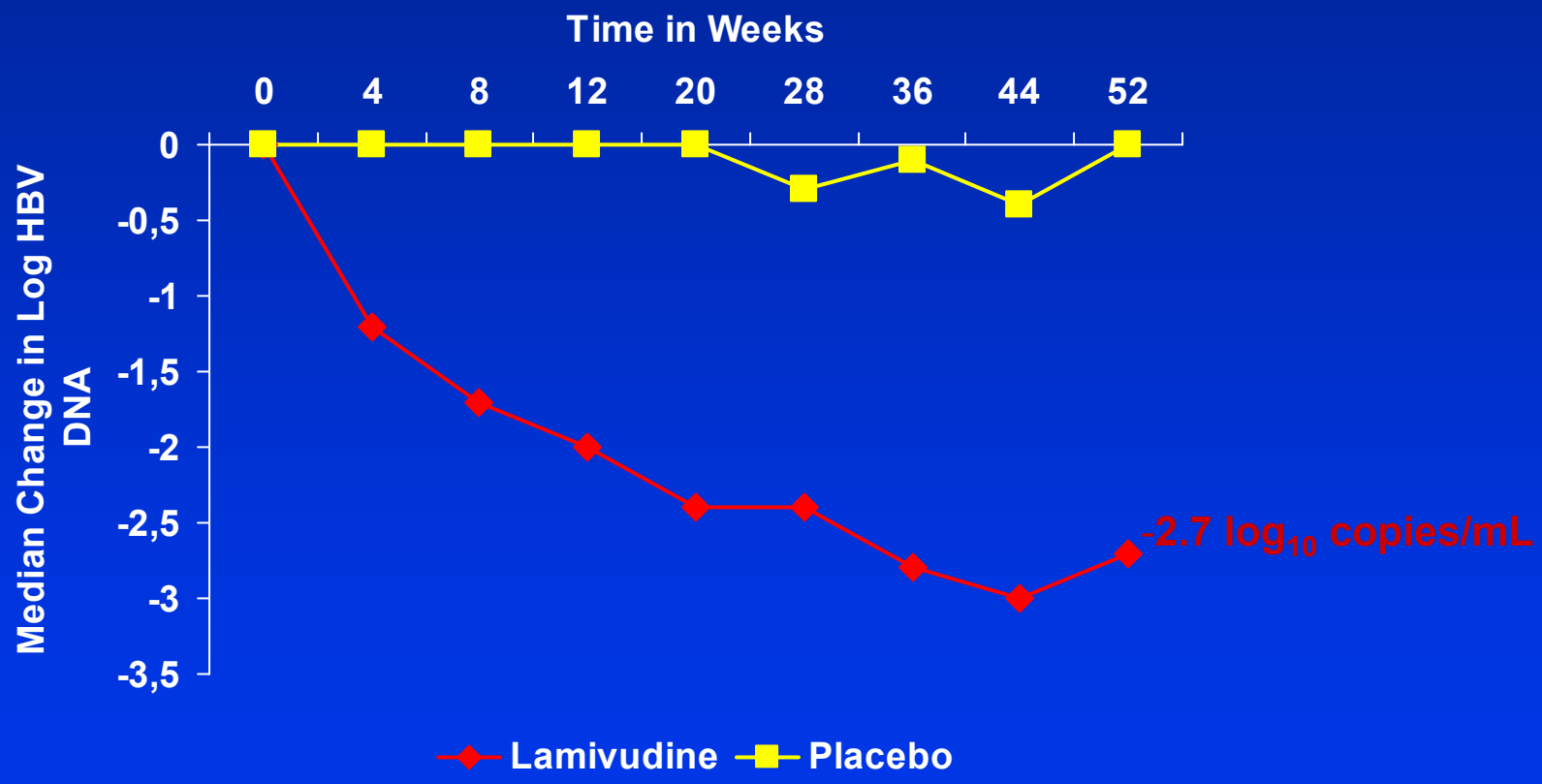
Treatment of HBV in HIV co-infected patients: Lamivudine



Y Benhamou et al. Ann Intern Med. 1996;125:705-712.

Treatment of HBV in HIV co-infected patients: Lamivudine

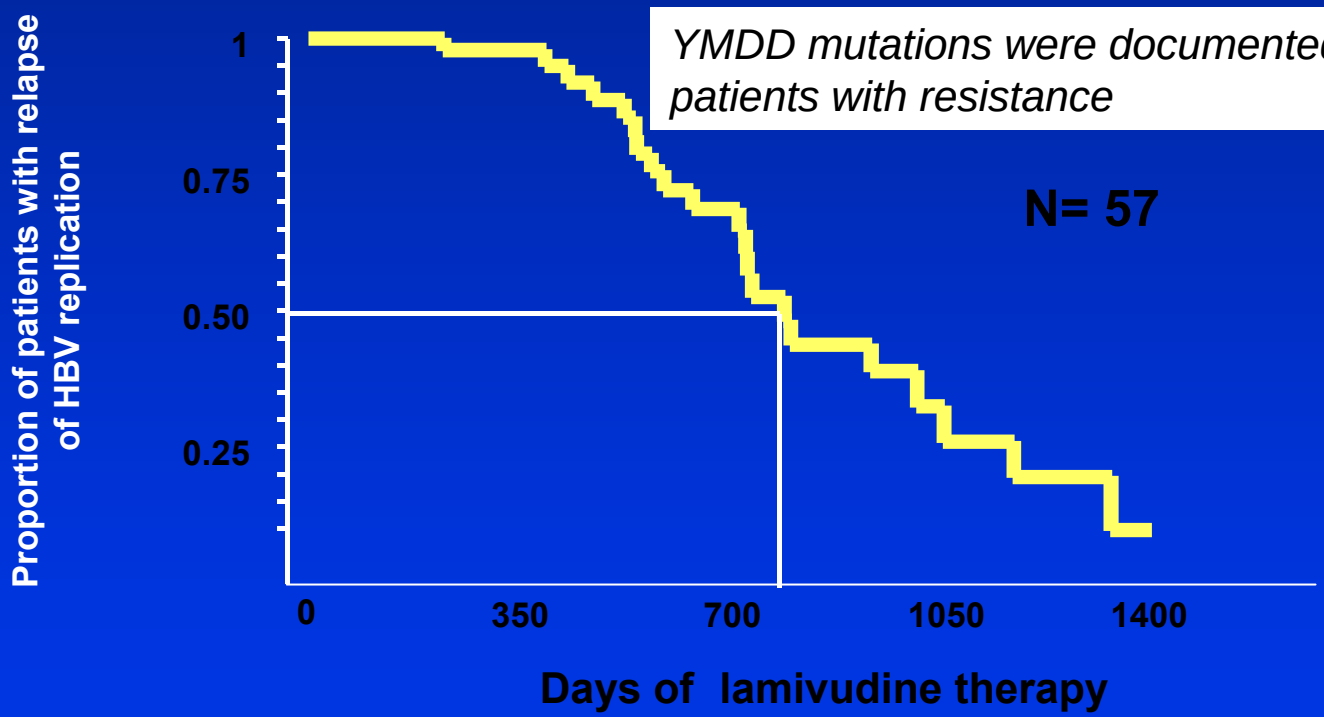
Median change in serum HBV DNA over 52 weeks



Dore GJ et al. J Infect Dis. 1999;180:607-13

Treatment of HBV in HIV co-infected patients: Lamivudine resistance

Cumulative risk for the development of HBV resistance to lamivudine



Number of patients under observation	57	32	13	6	3

Benhamou Y, et al. Hepatology 1999; 30:1302-06.

Treatment of HBV in HIV co-infected patients

- *Interferon*
- *Lamivudine*
- **Adefovir dipivoxil**
- *Tenofovir fumarate disoproxil*
- *FTC (Emtriva)*

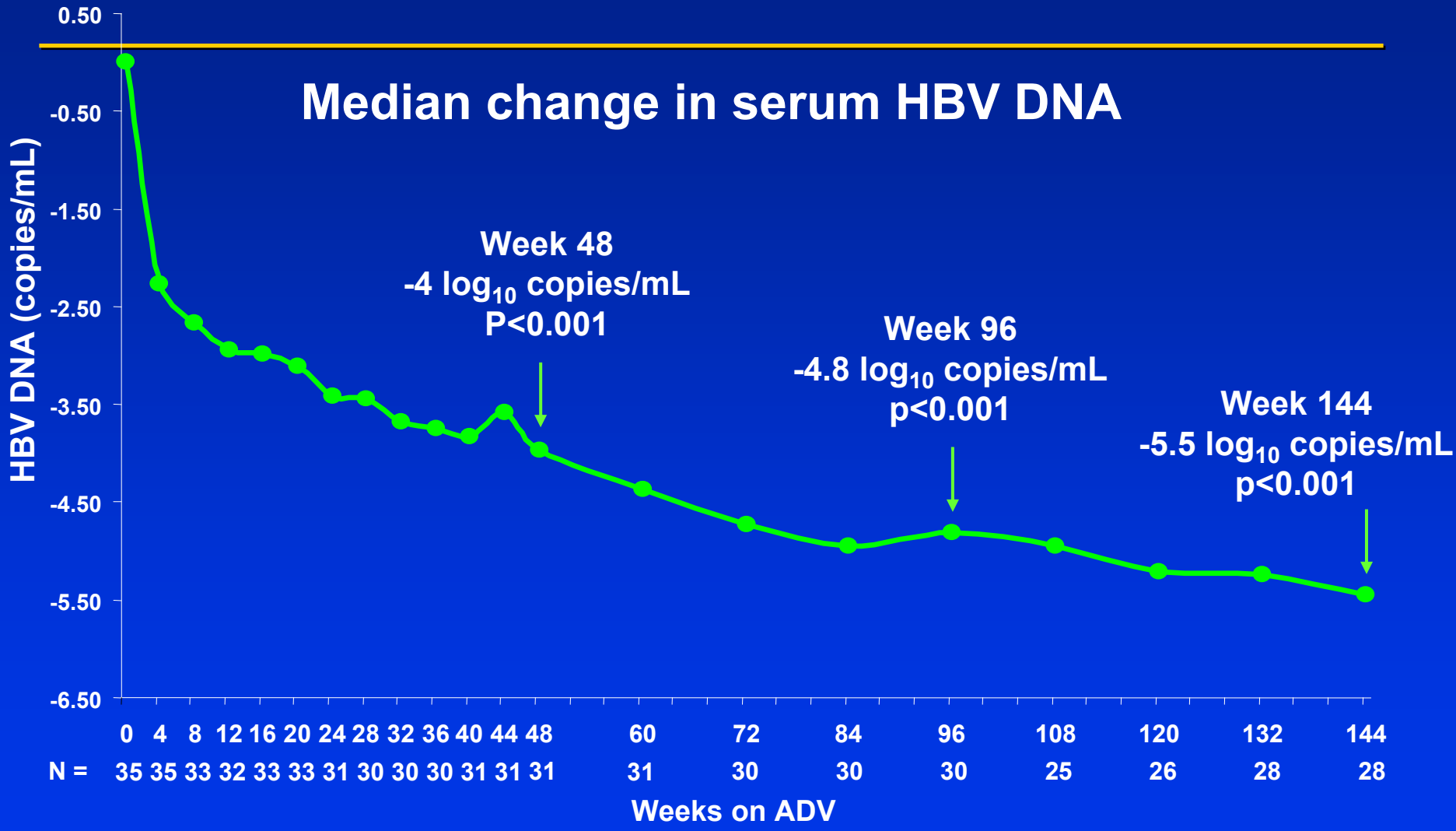
Treatment of LAM-R HBV in HIV co-infected patients: Adefovir

Baseline HBV characteristics

	n=35
Median HBV DNA (log_{10} copies/mL)	8.75
Median ALT (IU/L)	81
HBeAg positive	33
Liver Histology (METAVIR)	**n=23**
- Mean (±SEM) Activity	1.52 ± 0.15
- Mean (±SEM) Fibrosis	2.04 ± 0.24
- Cirrhosis	22%
HIV RNA (log10 copies/mL) Mean (±SEM)	2.88 ± 0.13
CD4 cell count (cells/mm3) Mean (±SEM)	422 ± 34

Benhamou Y et al. Lancet. 2001. 358:718-23
Benhamou Y et al. AASLD 2003

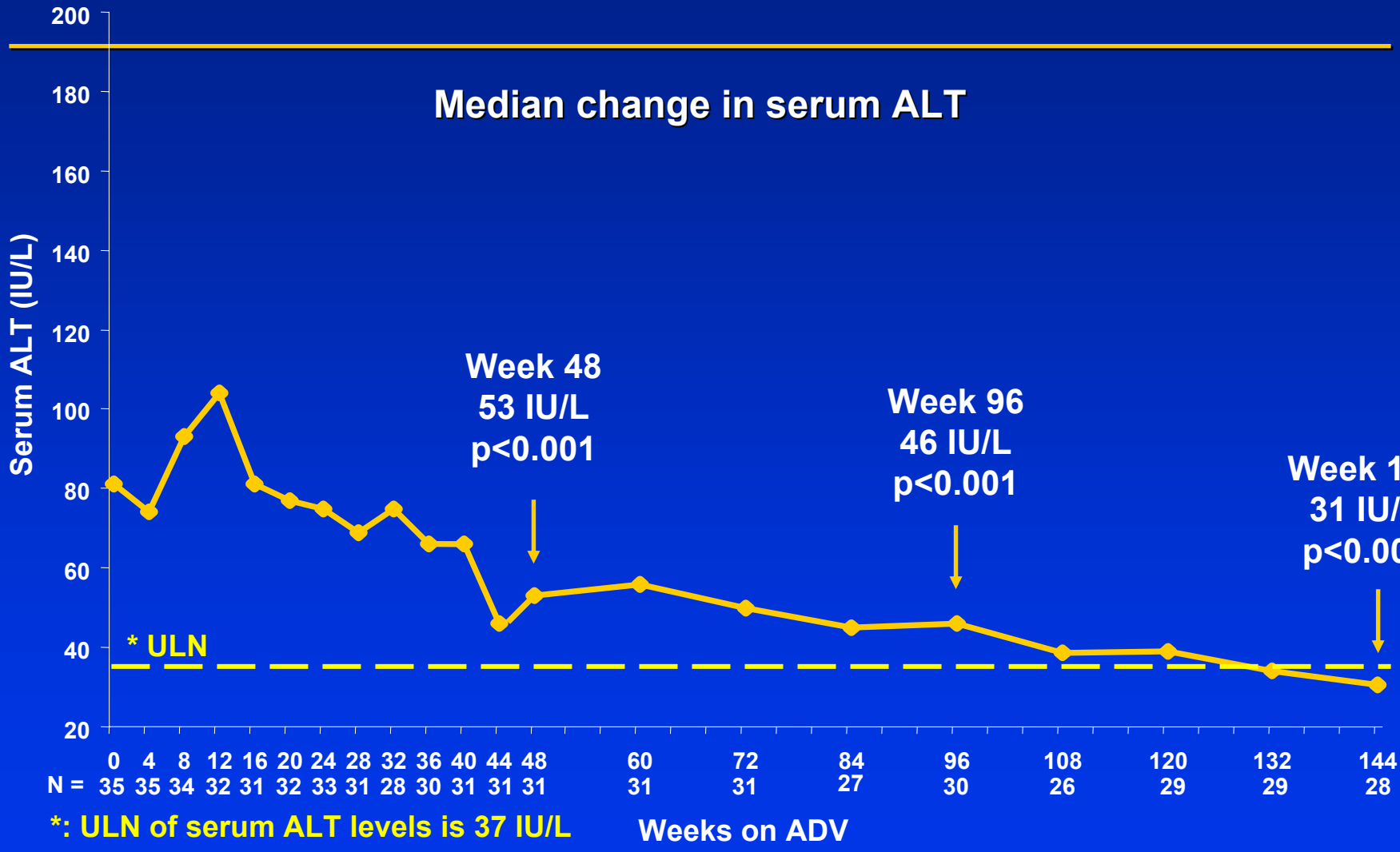
Treatment of LAM-R HBV in HIV co-infected patients: Adefovir



Benhamou Y et al. AASLD 2003

Benhamou Y et al. Lancet. 2001. 358:718-23

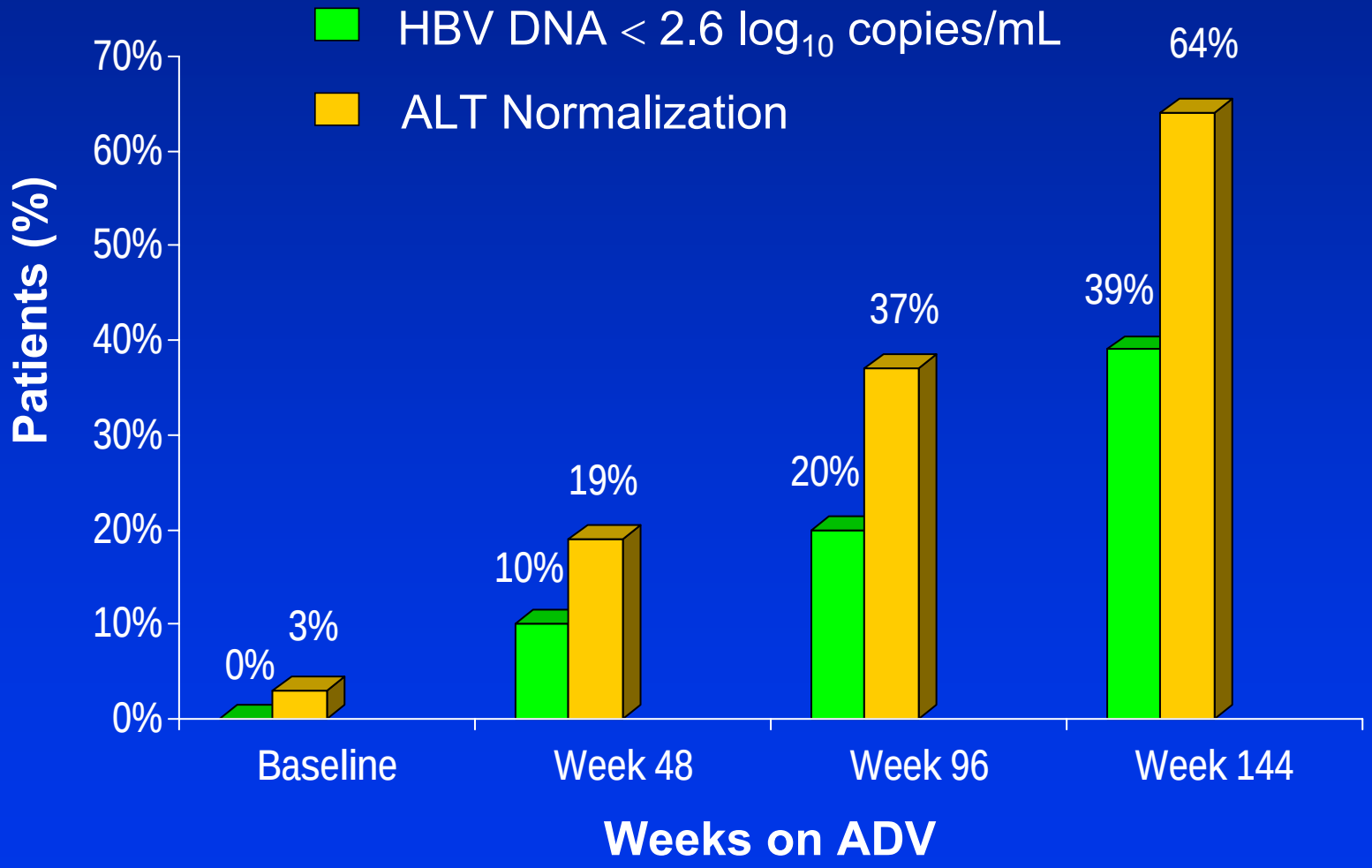
Treatment of LAM-R HBV in HIV co-infected patients: Adefovir



Benhamou Y et al. AASLD 2003

Benhamou Y et al. Lancet. 2001. 358:718-23

Treatment of LAM-R HBV in HIV co-infected patients: Adefovir



Benhamou et al. AASLD 2003

Treatment of HBV in HIV co-infected patients

- *Interferon*
- *Lamivudine*
- *Adefovir dipivoxil*
- **Tenofovir fumarate disoproxil**
- *FTC (Emtriva)*

TDF in HIV/HBV co-infected patients

	N	Wild type/ LAM-R	Duration of TDF (weeks)	Change in HBV DNA (log_{10} copies/mL)
Cooper D	12	5/7	24	-5±0.7*
Nelson M	20	9/11	52	4**
Ristig MB	6	0/6	24	4.3**
Benhamou Y	12	0/12	24	-3.83±0.38*

* Mean. ** Median

Cooper D et al. CID. 2003: 124
Nelson M et al. AIDS. 2003;17:F7-F10
Ristig MB et al. J Infect Dis. 2002;186:1844-7
Benhamou Y et al. N Engl J Med. 2003;348:177-8

TDF in HIV/HBV co-infected patients

Change in HBV DNA during TDF therapy in HIV/HBV co-infected

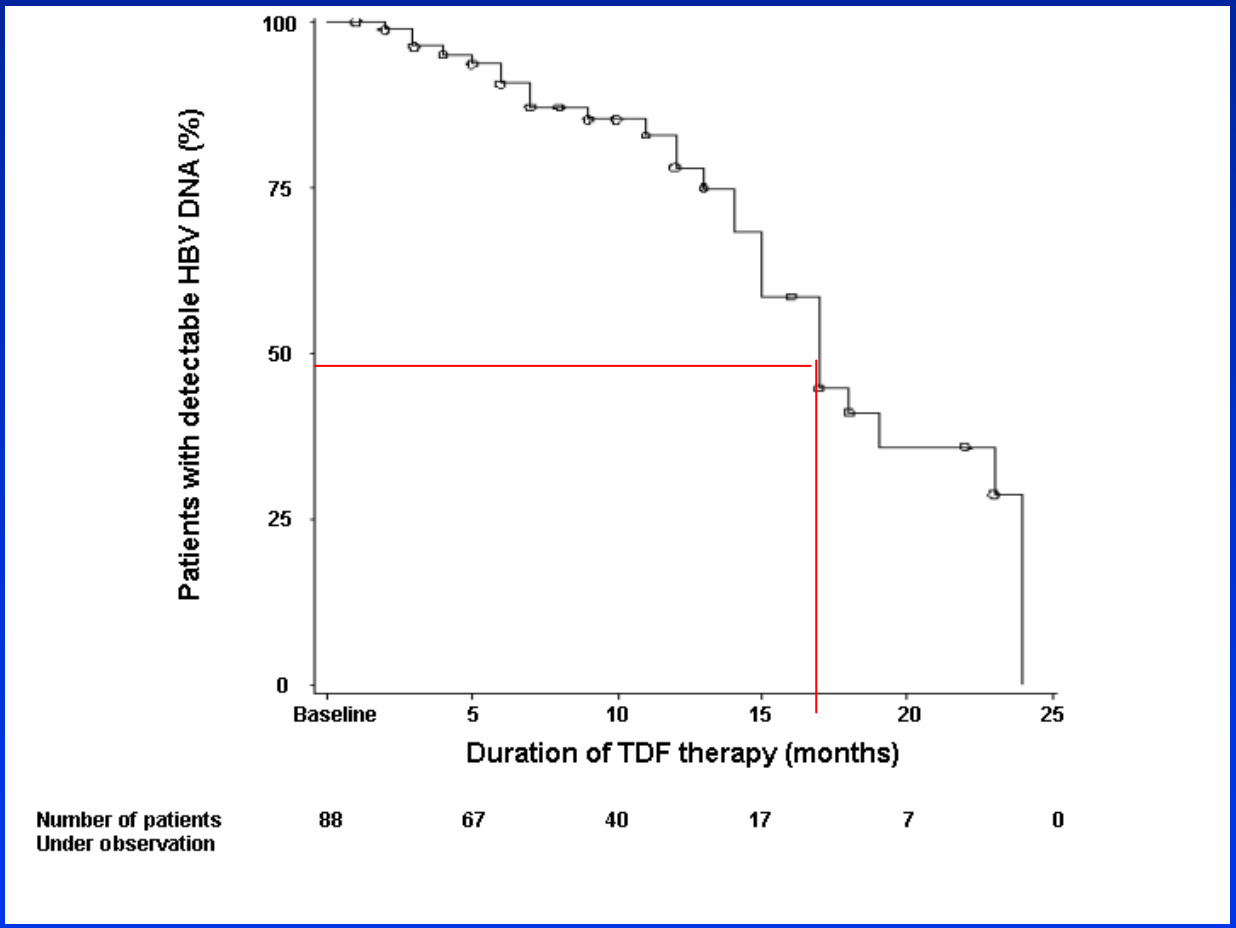
76% of the patients were receiving LAM at TDF initiation (presumed LAM-R)

	N	Median (range) of follow-up (months)	HBV DNA (median; SD) (log_{10} copies/mL) Baseline	End of follow up	Change from baseline	P
- Total	88	8.8 (1.0 – 21.0)	8.02 (1.97)	2.95 (1.54)	-3.82 (2.04)	< 0.001
- HBeAg+	66	8.0 (1.0 – 21.0)	8.17 (1.55)	3.05 (1.67)	-3.68 (2.00)	< 0.001
- HBeAg-	19	6.0 (1.0 – 17.0)	4.84 (2.15)	2.30 (2.15)	-2.54 (1.82)	< 0.001

Benhamou et al. For the TECOVIR Study Group. AASLD 2003

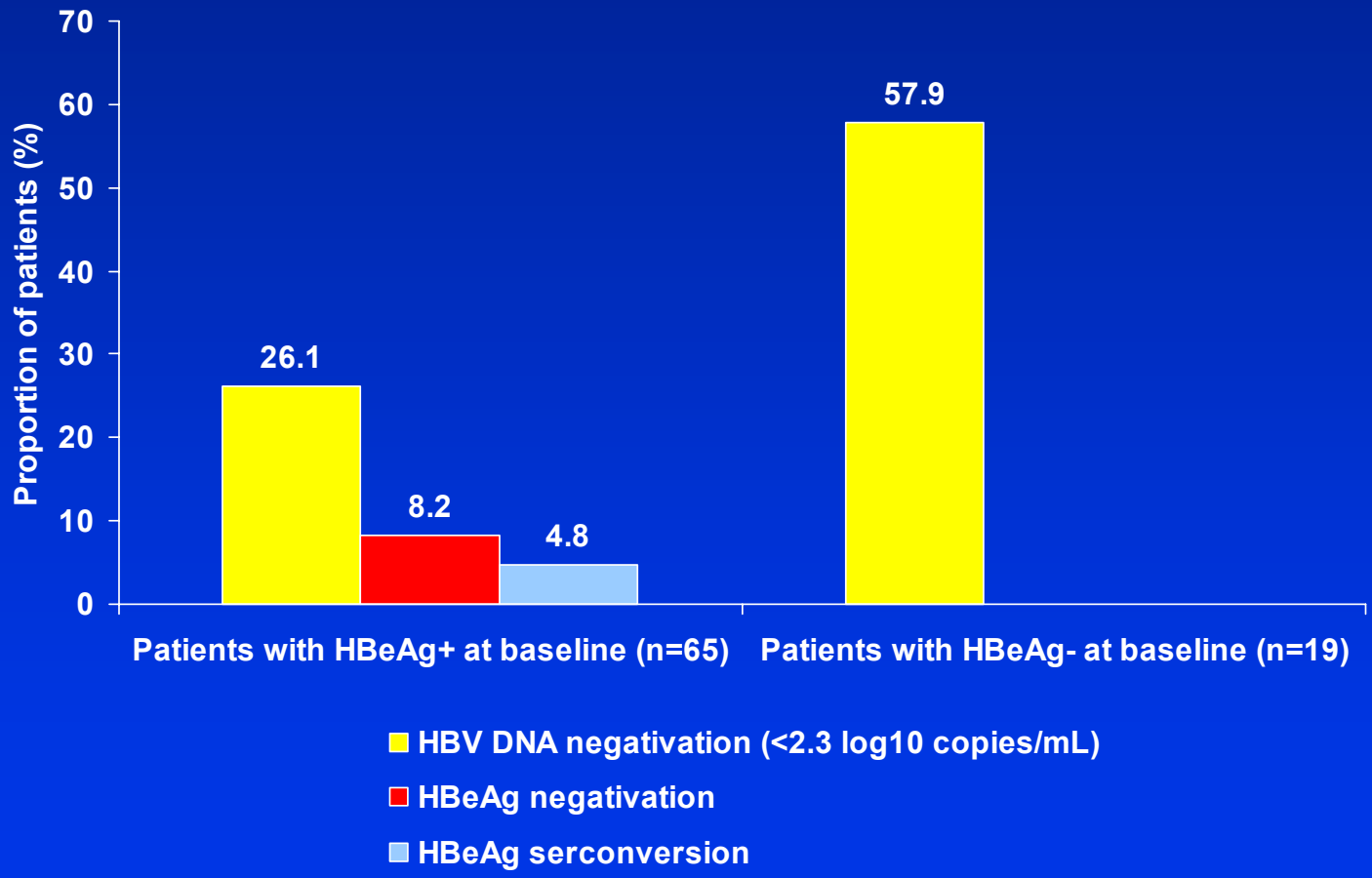
TDF in HIV/HBV co-infected patients

Time to DNA negativation (<2.3 copies/mL)



Benhamou et al. For the TECOVIR Study Group. AASLD 2003

TDF in HIV/HBV co-infected patients

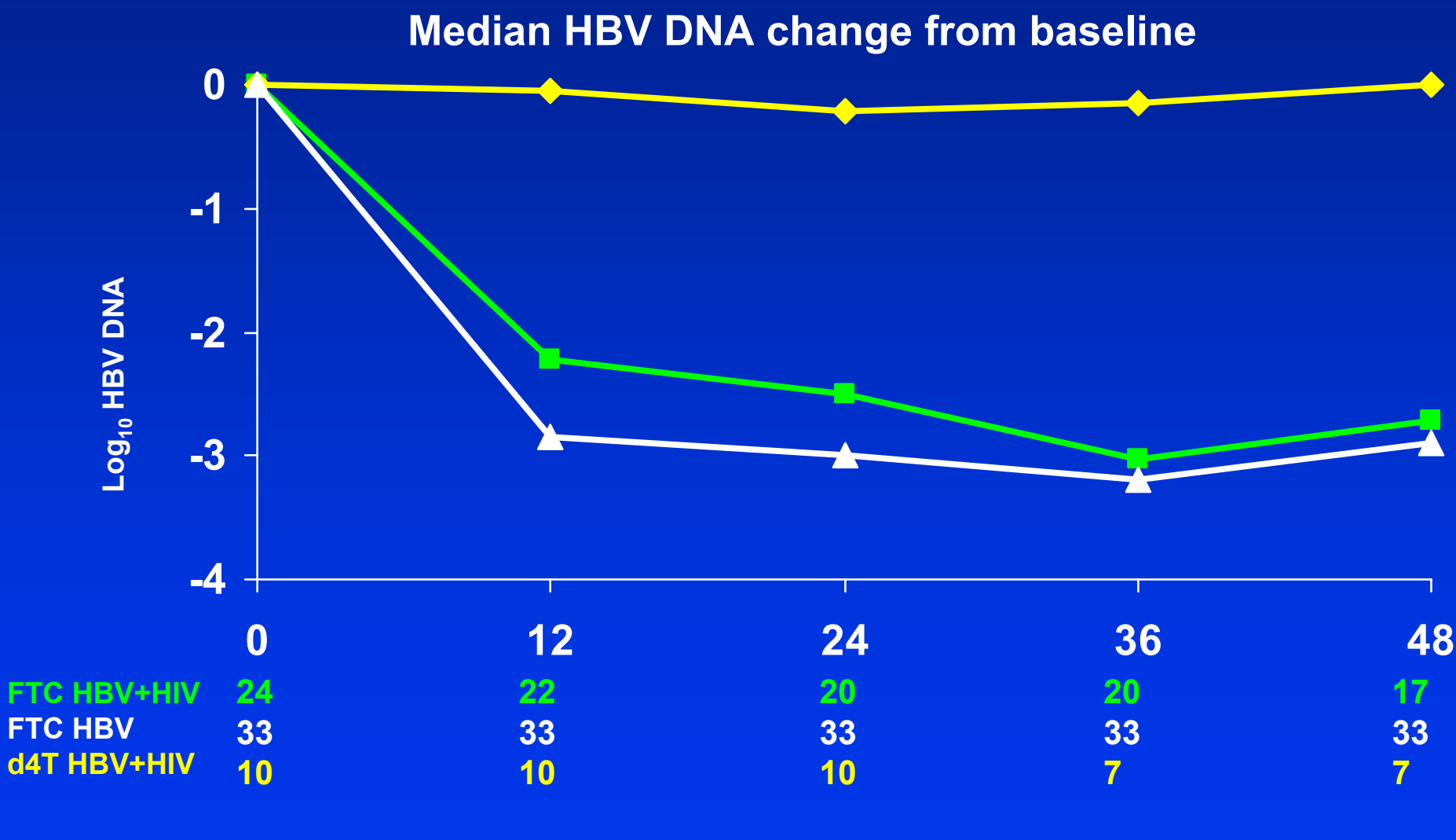


Benhamou et al. For the TECOVIR Study Group. AASLD 2003

Treatment of HBV in HIV co-infected patients

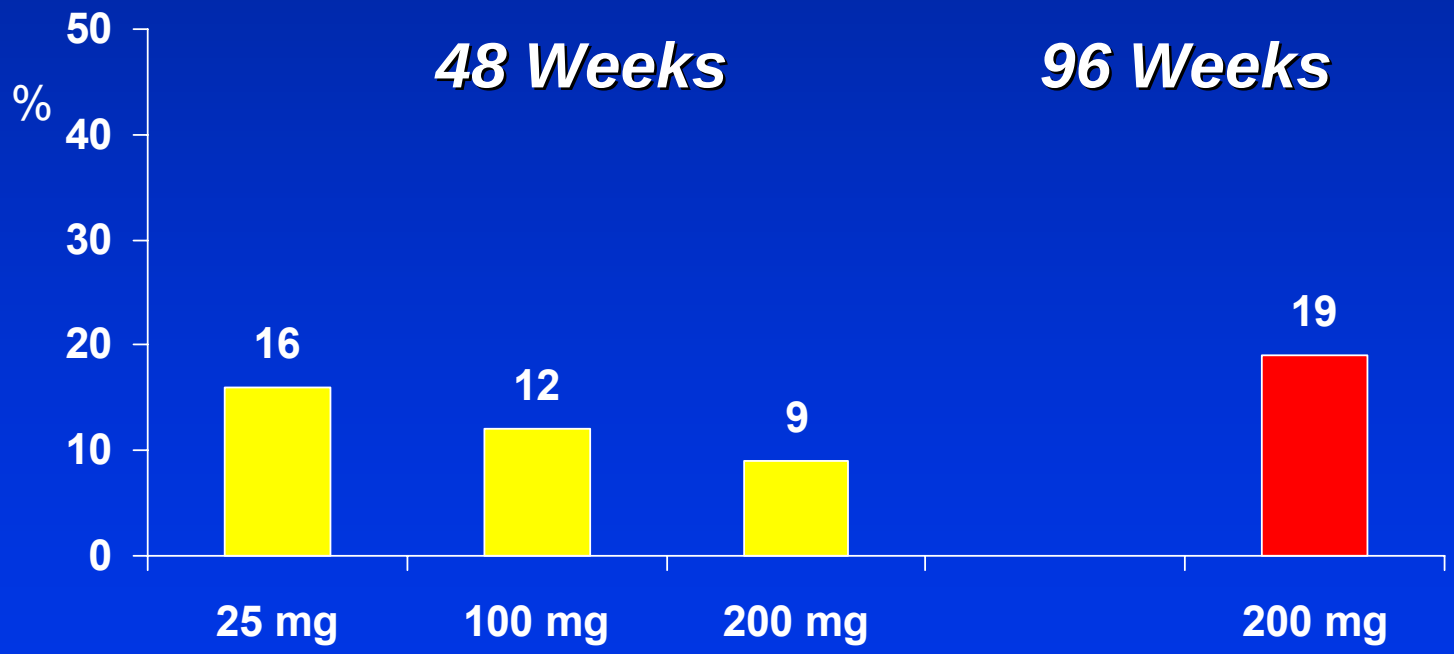
- *Interferon*
- *Lamivudine*
- *Adefovir dipivoxil*
- *Tenofovir fumarate disoproxil*
- **FTC (Emtricitabina)**

FTC in HIV/HBV co-infected patients

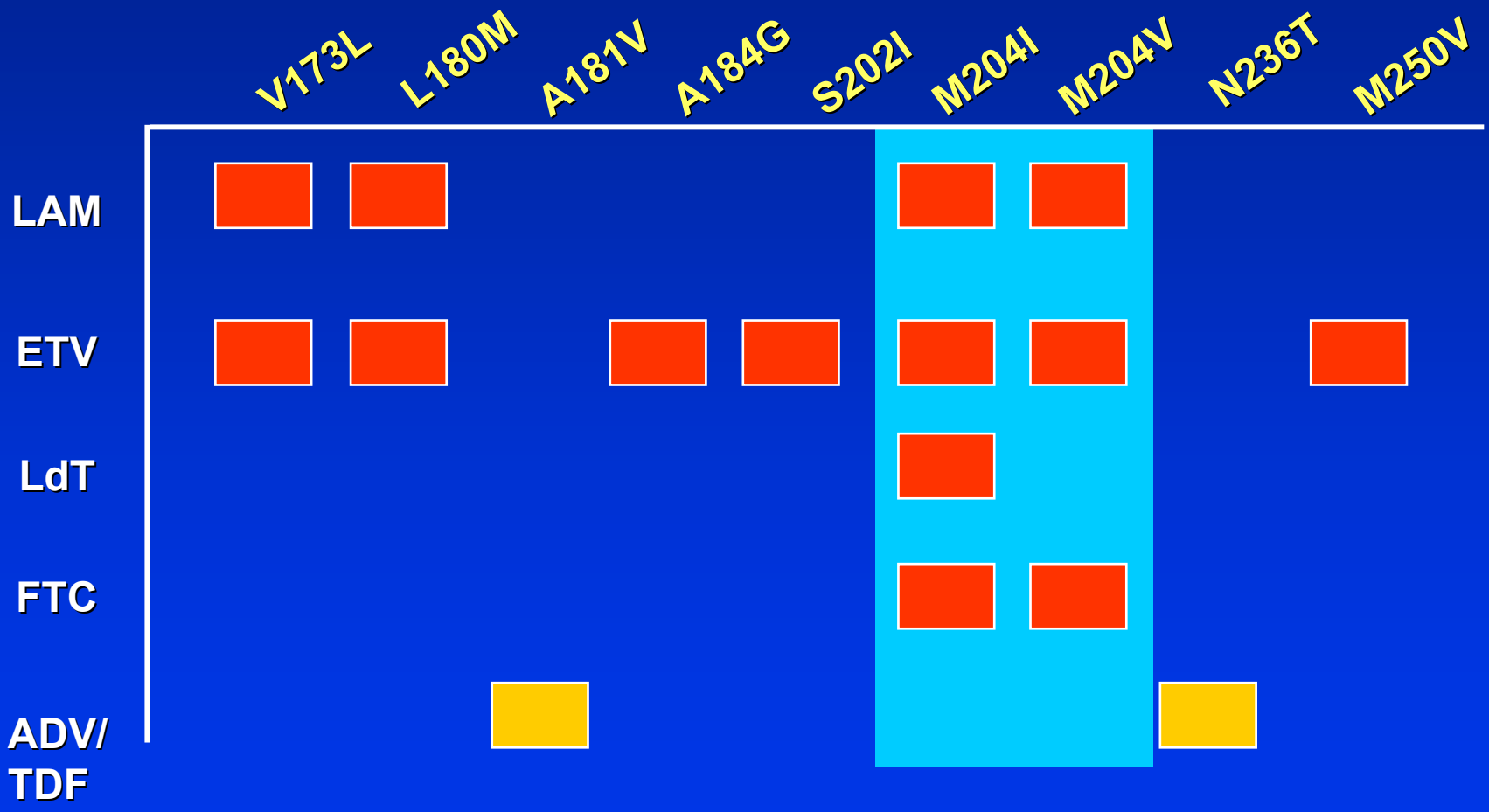


FTC in HIV/HBV co-infected patients

Resistance mutations in non HIV/HBV infected patients



Cross Resistance *in vivo*



Treatment of CHB in HIV co-infected patients

- **If ARV is indicated for HIV**
  - HBV treatment has to be considered : TDF – FTC – LAM in ARV regiment
  - LAM-R patients :
    - TDF or ADV
- **If ARV is not indicated for HIV**
  - ADV
- **Perspectives: combinations**
  - NRTs : Nucleotides (TDF – ADV) + Nucleosides (FTC – LAM)
  - NRTIs/PEG IFN?

HAART Related Hepatotoxicity in HIV/HBV Co-infected Patients

	No.	HAART	HCV/HBV	Incidence	Predictors
Sulkowski M.	211	PI	51%	11%	HCV, **HBV**, ↑CD4, RTV
Saves M.	748	PI	41%	9%	HCV, **HBV** previous cytolysis
Nunez M.	222	PI, NNRTI	40%	9%	HCV, age, alcohol
Sulkowski M.	87	2 NRTI	61%	6%	HCV, **HBV**, ↑ CD4
Saves M.	1249	2 NRTI	44%	6%	HCV, **HBV** previous cytolysis

Sulkowski M et al. JAMA 283:74-80.
Saves M et al. AIDS 1999;13:F115-F121.
Nunez M et al. JAIDS 2001;27:426-31.

Tomba del tuffatore