Do we need new drugs for treatment naïve patients?

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WHO WILL I VOTE FOR IN 2008?

Can we do Better than FDC of EFV + TDF +FTC

- Do we need other naïve treatments with the “Holy Grail” of ARV therapy?
- Should all naïve studies compare the new regimen to EFV + 2 NRTI?

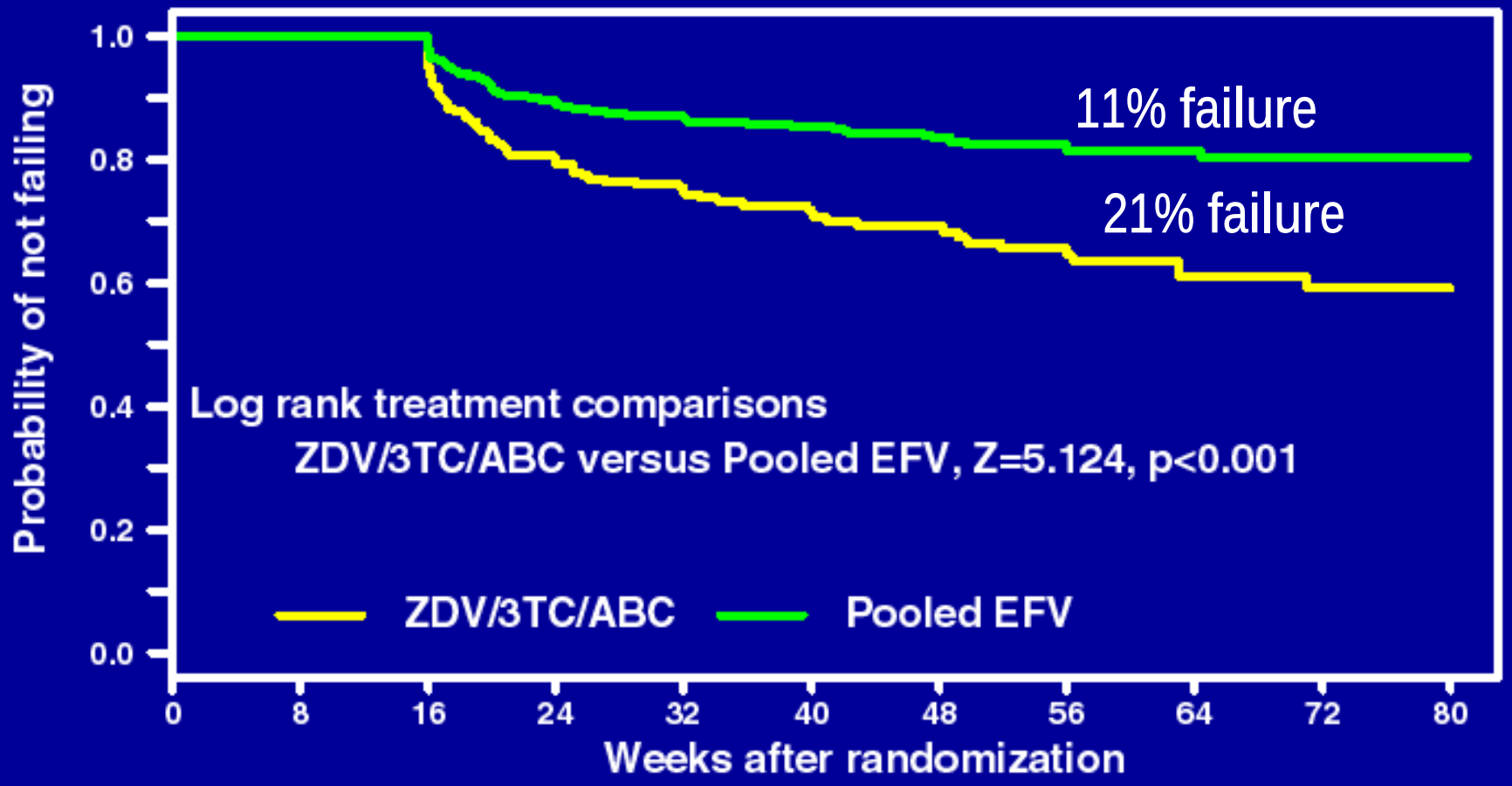
Guideline revisions 2007

- Updated IAS-USA,[1] WHO[2] (July 2006), and HHS Guidelines[3] (Dec 2007)
- What to start?
  - DHHS: two preferred regimens
    - LPVr, FPVr, ATVr + 2NRTI
    - EFV + 2NRTI
    - NRTI = ZDV/3TC or TDF/FTC (FDC)
  - IAS-USA: 2 NRTI + NNRTI or PIr

1. Hammer S, *et al. JAMA* 2006;296:827–43.
2. 2. www.UNAIDS.org.
3. 3. www.hivatis.gov

A5095: Time to first virologic failure

ALL study subjects

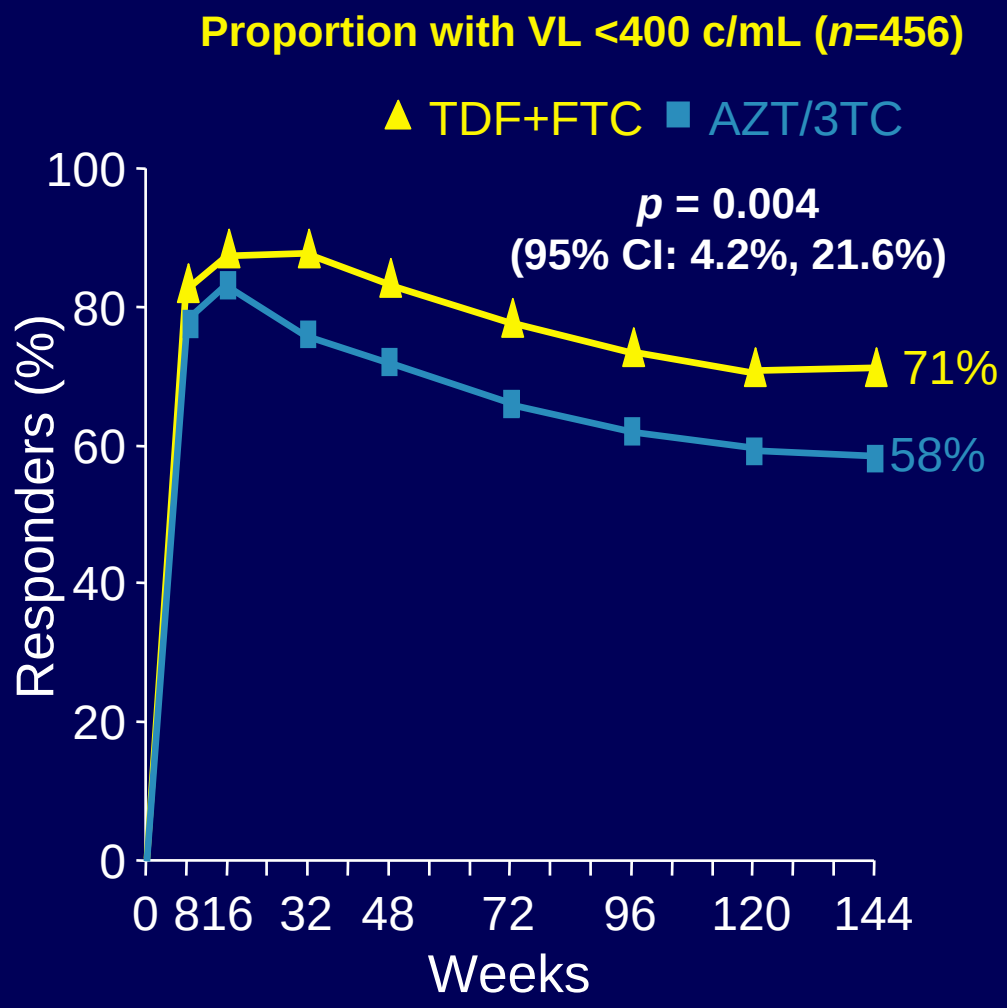


ZDV/3TC/ABC	382	329	282	185	139	109	88	67	46	27	2
Pooled EFV	765	653	576	421	338	279	217	165	102	52	13

Gulcik et al. NEJM 2004; 350:1850

GS 934: TDF/FTC vs AZT/3TC (+ EFV) at final Week 144 (ITT)

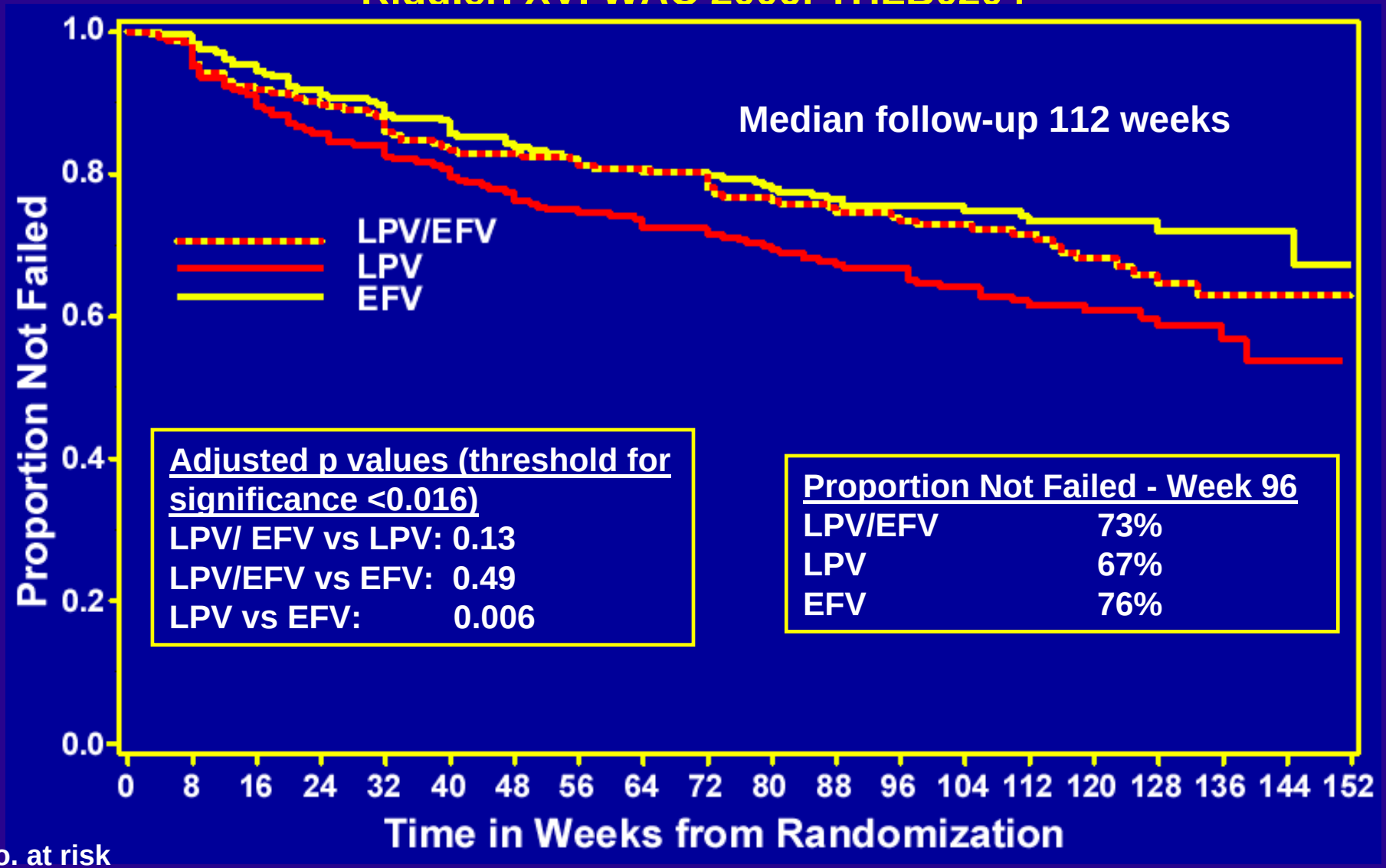
- VL <50 c/mL (TLOVR): 64% (TDF/FTC) vs 56% (AZT/3TC) (*p*=0.08)
- CD4 increases: +312 vs +271 (TDF vs AZT, *p*=0.09)



Arribas JR, *et al.* *4th IAS*, Sydney 2007, #WEPEB029

Time to Virologic Failure

Riddler. XVI WAC 2006: THLB0204



Adjusted p values (threshold for significance <0.016)

LPV/ EFV vs LPV:	0.13
LPV/EFV vs EFV:	0.49
LPV vs EFV:	0.006

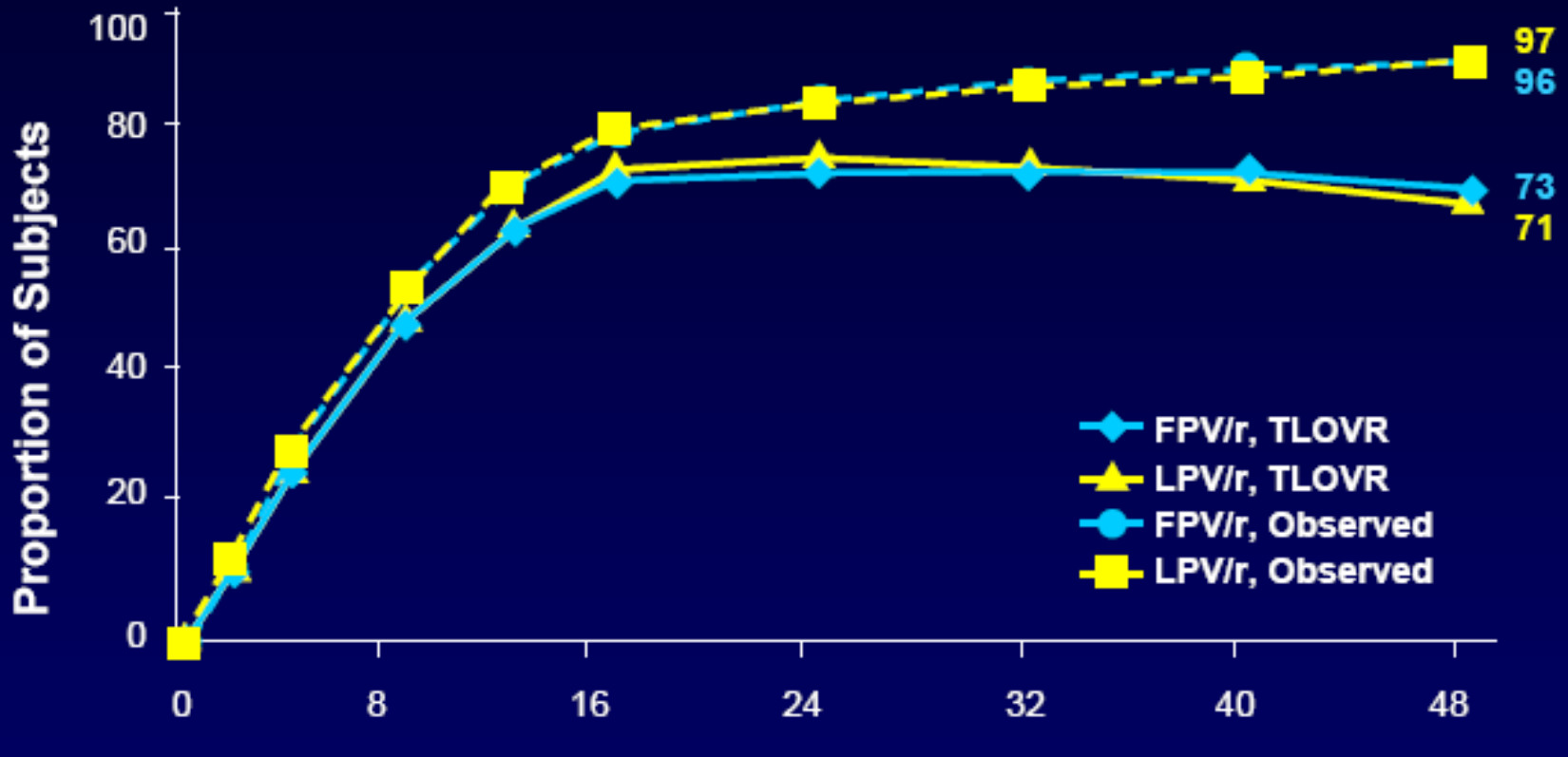
Proportion Not Failed - Week 96

LPV/EFV	73%
LPV	67%
EFV	76%

No. at risk

LPV/EFV	250	215	189	181	149	73	17
LPV	253	210	185	168	140	74	14
EFV	250	210	186	173	142	73	19

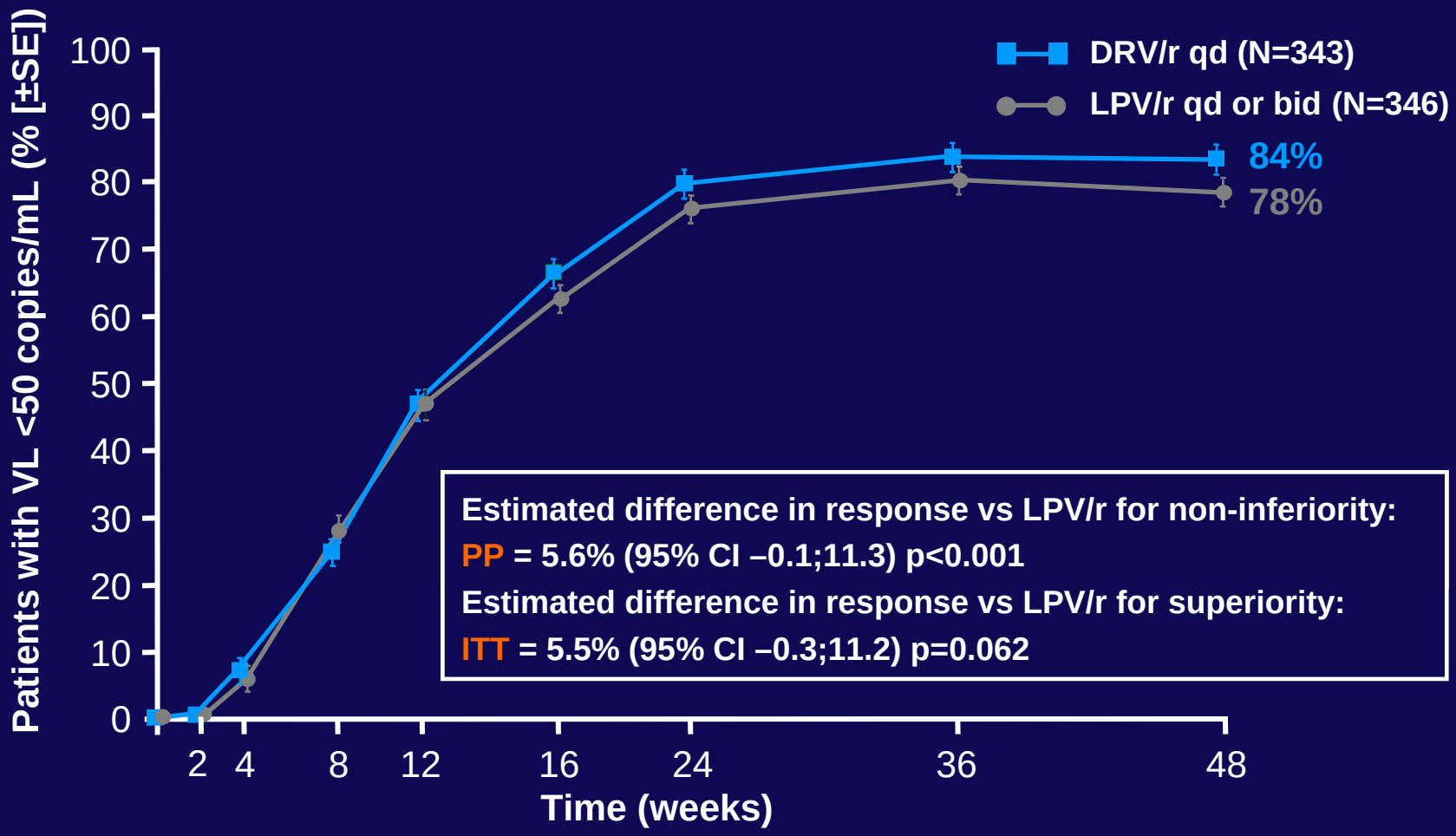
Virologic Response HIV-1 RNA <400 copies/mL



no (obs)						
FPV/r = 434	399	387	375	358	340	328
LPV/r = 444	408	396	389	371	359	341

Eron et al. Lancet 2006; 368: 476–82

ARTEMIS: Viral load <50 copies/mL to Week 48 (ITT-TLOVR)

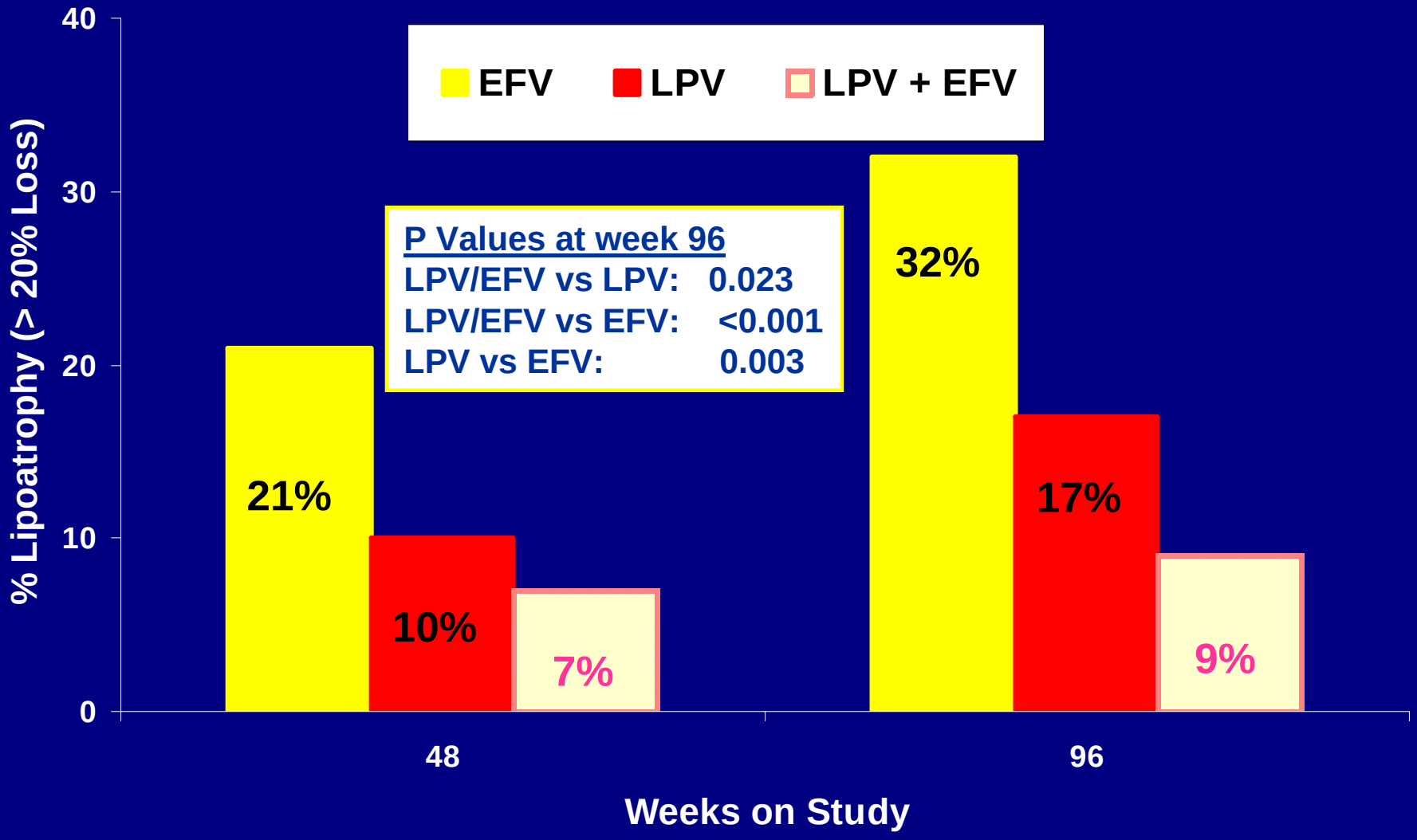


De Jesus et al. ICAAC 2007: H-718B

Can We do Better

- Adherence (better than daily?)
- Subtle chronic toxicity
- Know toxicity
  - Acute: CNS, GI, rash, hypersensitivity, hepatic
  - Chronic: lipids, lipoatrophy, fat gain, diabetes, bone, renal, cardiovascular
- Formulation- more FDC
- Cost

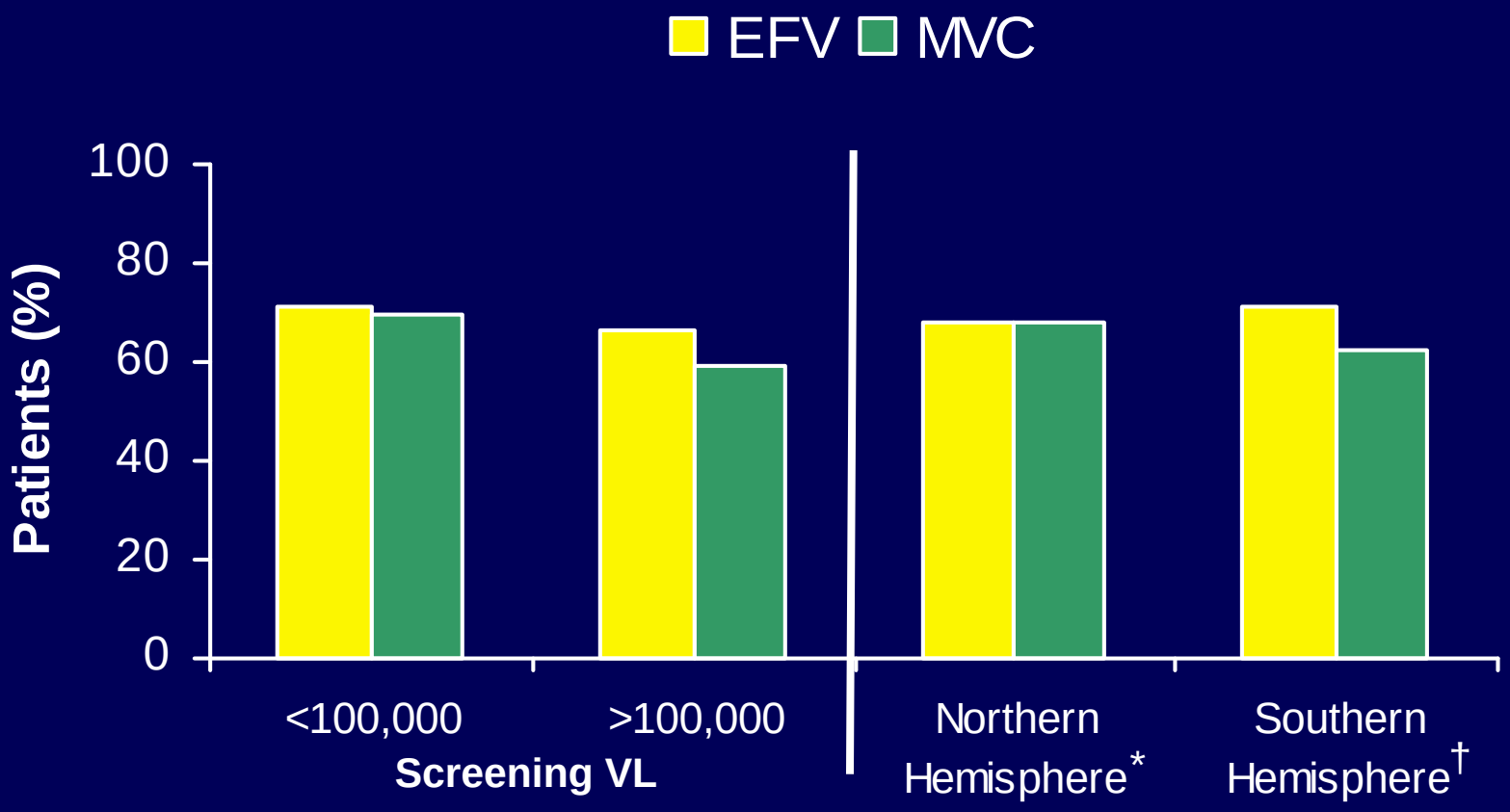
Lipoatrophy (> 20% loss Extremity Fat)



EFV	188	171
LPV/r	191	166
LPV/r + EFV	197	173

MERIT: 48-week VL results

<50 copies/mL by the two pre-specified stratifications

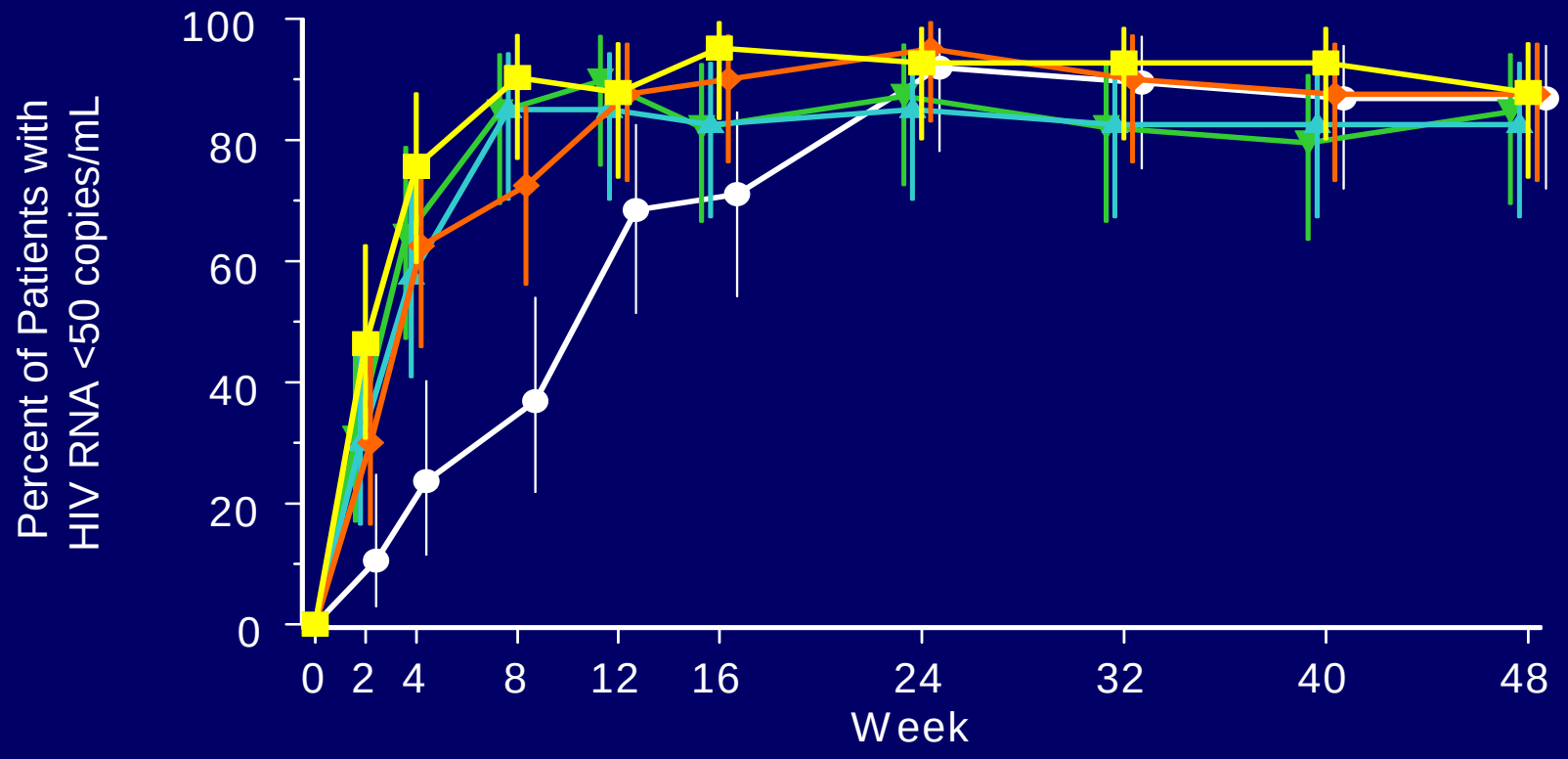


*North America and Europe
†Argentina, South Africa and Australia

Clumeck N, *et al. 4th IAS,* Sydney 2007, #WESS104

HIV RNA <50 Copies/mL (95% CI)

[Non-Completer=Failure]



Markowitz et al. 2007 IAS; TUAB104

Effect on Serum Lipids

- Total cholesterol, LDL-cholesterol, triglycerides not increased by raltegravir

Mean change from baseline (mg/dL) at week 48

	Raltegravir*		Efavirenz		
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	RAL vs EFV
Cholesterol	165.9	-2.3	168.7	+20.7	P<0.001
LDL-C	103.8	-7.5	108.9	+3.0	P=0.016
Triglycerides	131.8	-1.0	127.3	+49.5	P=0.068
Total:HDL ratio	4.59	-0.59	4.72	-0.47	P=0.52

* All raltegravir dose groups combined.

Markowitz et al. 2007 IAS; TUAB104

Change the Paradigm of 2NRTI + X

- NRTI sparing regimens
  - LPV/ EFV
  - RAL/ LPV
  - RAL/ ATV
  - RAL/ DRV
  - MVC/ PI (or NNRTI)

Will we see New Drugs for HIV?

- 2007-FDA's approved only 16 "new molecular entities" and vaccines and two biologics
- Peak of 53 drugs in 1996
- Only twice lower in the past 30 years
  - 17 in 2002
  - 14 in 1983
- Possible reasons
  - Cheap generics
  - Increased scrutiny; i.e., Vioxx
  - No new blockbusters

NATAP 1/9/08: G. JORDAN; NJ Star-Ledger Staff

Do We Need New Medicines for HIV?

"Drug therapies are replacing a lot of medicines as we used to know it."

Why we do need

- Efficacy rates ~ 80%
- Treatment efficacy remains an important unmet medical need

The better the initial treatment, longer duration and less resistance when treatment failure happens

Why we do need

- Given the overall recent improvements in the safety, efficacy, and tolerability of initial antiretroviral therapy (ART), the pendulum has been swinging back in favour of earlier treatment initiation in asymptomatic patients
- As a consequence, the search for even better drugs to start therapy will be needed

Why we do need

- Increasing occurrence of primary HIV drug resistance in treatment-naive patients is affecting front-line treatment strategies

Why we do need

- ART are needed that have less toxicities/pk interactions related to TB treatment
- TB is a major public health issue in the developing countries, where most new HIV infections are occurring

Why we do need

- Patients with psychiatric co-morbidities-efavirenz based regimens may not be adequate-depression, suicide...
- Patients with substance use problems
- Patients on methadone

Why we do need

- Women account for a substantial fraction of new infections in developing countries.
- Women need options to start ARV that don’t necessarily interfere with their fertility desires
- Efavirenz based regimens are problematic for women with reproductive potential; thus, the most recommended regimen is not available due to the risk of teratogenicity

Why we do need-the patient perspective

- Less toxicity
- Less long term toxicities
- Resistance profile after failure
- Quality of life
- Adherence
- Drug interactions
- Fertility desires

Programmatic Issues

- Costs related to new drugs/regimens for the developing world-patent protection x available “old” generics
- Stavudine is still a major component of HAART in the developing world
- the gap tends to increase

Programmatic Issues

- New drugs are always more expensive, and from the public health perspective additional benefit needs to be demonstrated

- New drugs for treatment naive patients are tested using a non-inferiority study design

Programmatic Issues

- How these issues can impact the decision about incorporating a new ARV in a public health setting