History/Evolution of Clinical Trials in Rx-Experienced Patients

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Rx-Experienced Pts: First Studies

Study	Population	Rx	Results
BMS AI454-010 Spruance Ann Int Med 1994	ZDV-exp. (N=312)	Continue ZDV vs. ddI	Changing to ddI led to fewer clinical events
CPCRA 002 Abrams NEJM 1994	ZDV-exp. (N=467)	Change to ddI vs. ddC	No difference in clinical progression
DELTA Delta Coord. Comm Lancet 1996	ZDV-exp (N=1087)	ZDV + (ddI or ddC)	No difference in clinical progression

Rx-Experienced Pts: Early 1990s

Study	Population	Rx	Results
BMS 019 Spruance Ann Int Med 1997	ZDV-exp. (N=822)	Continue ZDV vs. change to d4T	Changing to d4T led to fewer clinical events
ACTG 241 D'Aquila Ann Int Med 1996	NRTI-exp. (N=398)	ZDV/ddI +/- NVP	VL (Δ=0.25 logs) and CD4 (Δ=18%) responses better in 3-drug group

Rx-Experienced Pts: Mid-1990s

Study	Population	Rx	Results
Abbott 247 Cameron Lancet 1998	NRTI-exp. (N=1090)	"optimal NRTIs" +/- RTV	~50% reduction in clinical events (median f/u 7 mos.)
Merck 035 Gulick NEJM 1997	ZDV-exp. (N=97)	ZDV/3TC, IDV, ZDV/3TC/ IDV	VL<500 at wk 24: 0% vs. 43% vs. 90%
ACTG 364 Albrecht NEJM 2001	NRTI-exp. (N=195)	2 NRTI + NFV, EFV, or both	VL<500 at wk 40-48: 35% vs. 60% vs. 74%

Rx-Experienced Pts: PI-Experienced

Study	Population	Rx	Results
ACTG 333 Para JID 2000	SQV-experienced (N=72)	IDV	VL<200 wk 8: 37%
Pilot Tebas AIDS 1999	NFV-experienced (N=26)	RTV/ SQV	VL<500 wk 48: 54%

Rx-Experienced Pts: Late 1990s

Study	N	Rx	Results
ACTG 359 Gulick JID 2000	IDV-experienced (N=277)	RTV/SQV or RTV/NFV + DLV, ADV, or both	30% VL<500 wk 16
ACTG 372b Hammer Antiviral Rx 2003	IDV-experienced (N=84)	EFV/ADV ±ABC±NFV	35% VL<500 wk 16
CNAA 2007 Eron AIDS 1998 (abst)	PI-experienced (N=99)	ABC/EFV/APV	26% VL<400 wk 16
ACTG 398 Hammer JAMA 2002	PI-experienced (N=481)	APV/ABC/ EFV/ADV ± 2nd PI	31% VL<200 wk 24

Salvage Studies: Lessons Learned

- Improved response with:
  - lower baseline HIV RNA level
  - adding new class of drugs (e.g. NNRTI)
  - using 2 PI (vs. 1 PI)
  - using a ritonavir-boosted PI
- Sequencing of PI can be important (SQV, NFV, APV)
- 3 “new” drugs (i.e. drugs not yet taken) is not sufficient (due to cross resistance)

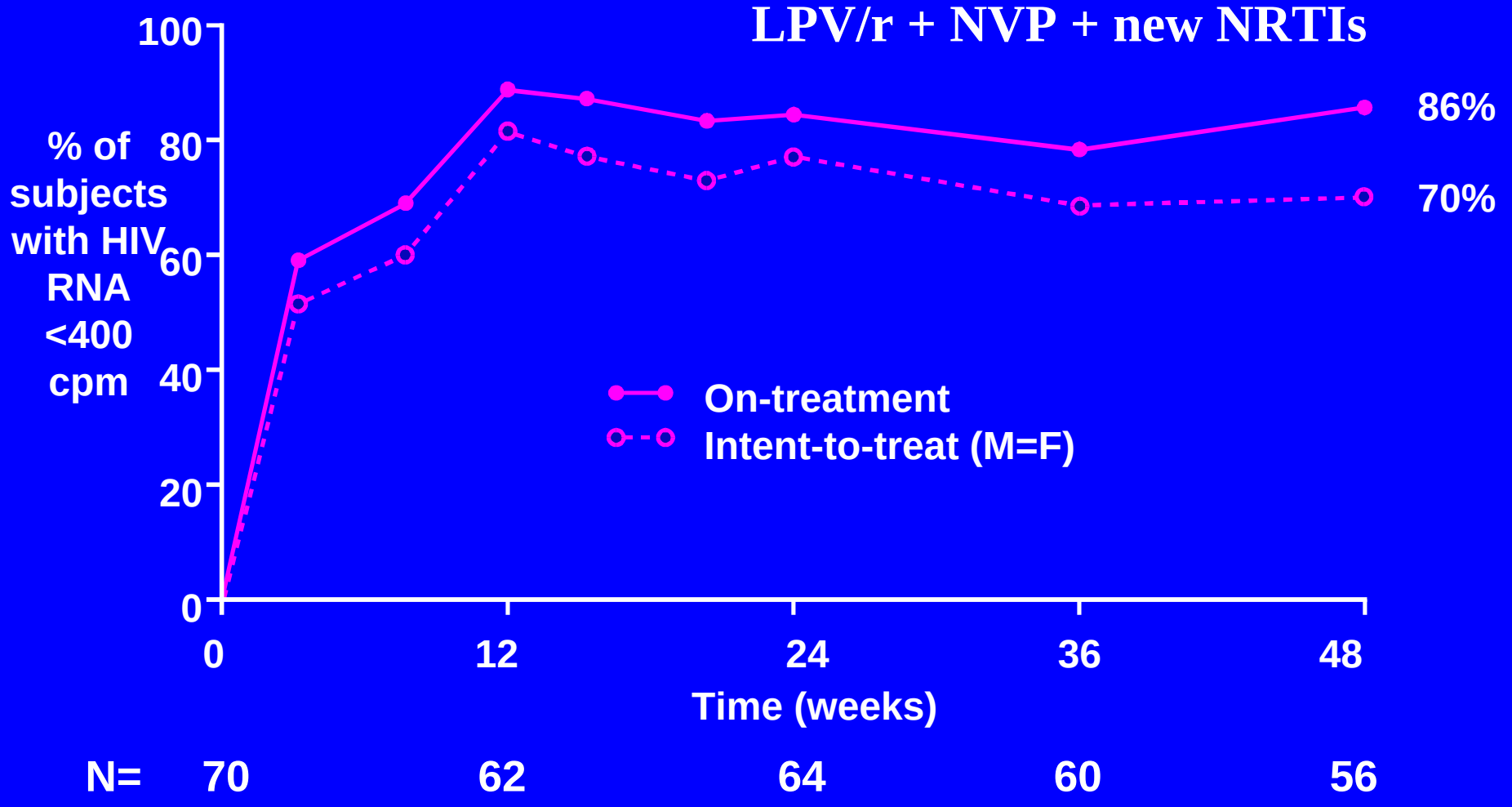
Abbott M97-765: PI-experienced

- Study population: HIV+, single PI failure, NNRTI-naïve, HIV RNA 1-100K (N=70)
- Baseline: VL 4.1 logs, CD4 372
- Study treatment: Change PI to LPV/RTV, then after 2 weeks, add NVP + "new" NRTIs

Benson, et al. JID 2002;185:599.

M97-765: PI-Experienced Study

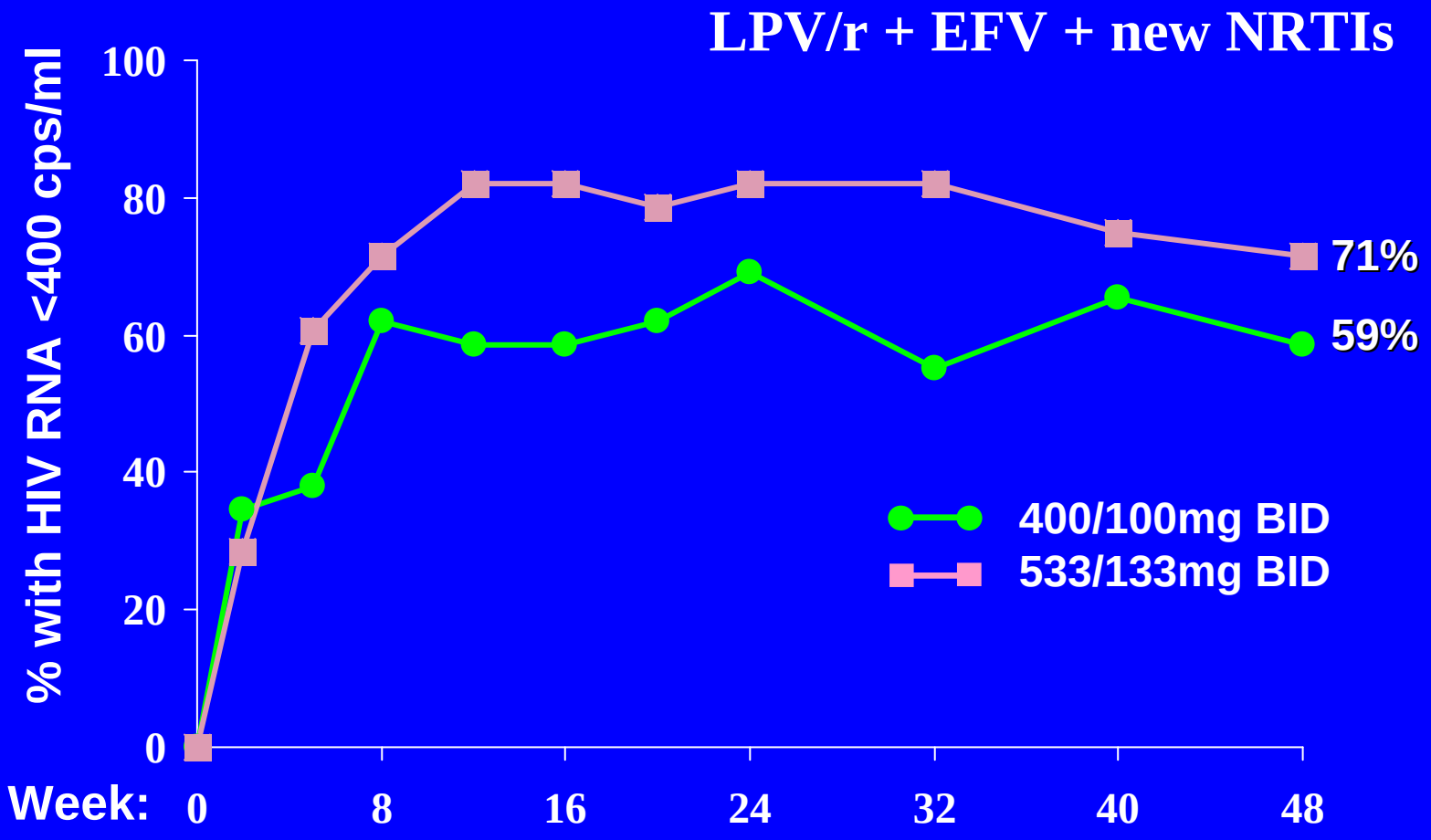
Study Population: HIV+, single PI failure, NNRTI-naïve, VL 1-100K



Benson, et al. JID 2002;185:599.

M98-957: PI-Experienced Study

Study Population: HIV+, ≥2 PI failure, NNRTI-naïve, VL >1K



400/100mg n = 29
533/133mg n = 28

Rockstroh, Glasgow Meeting 2000

Resistance Studies

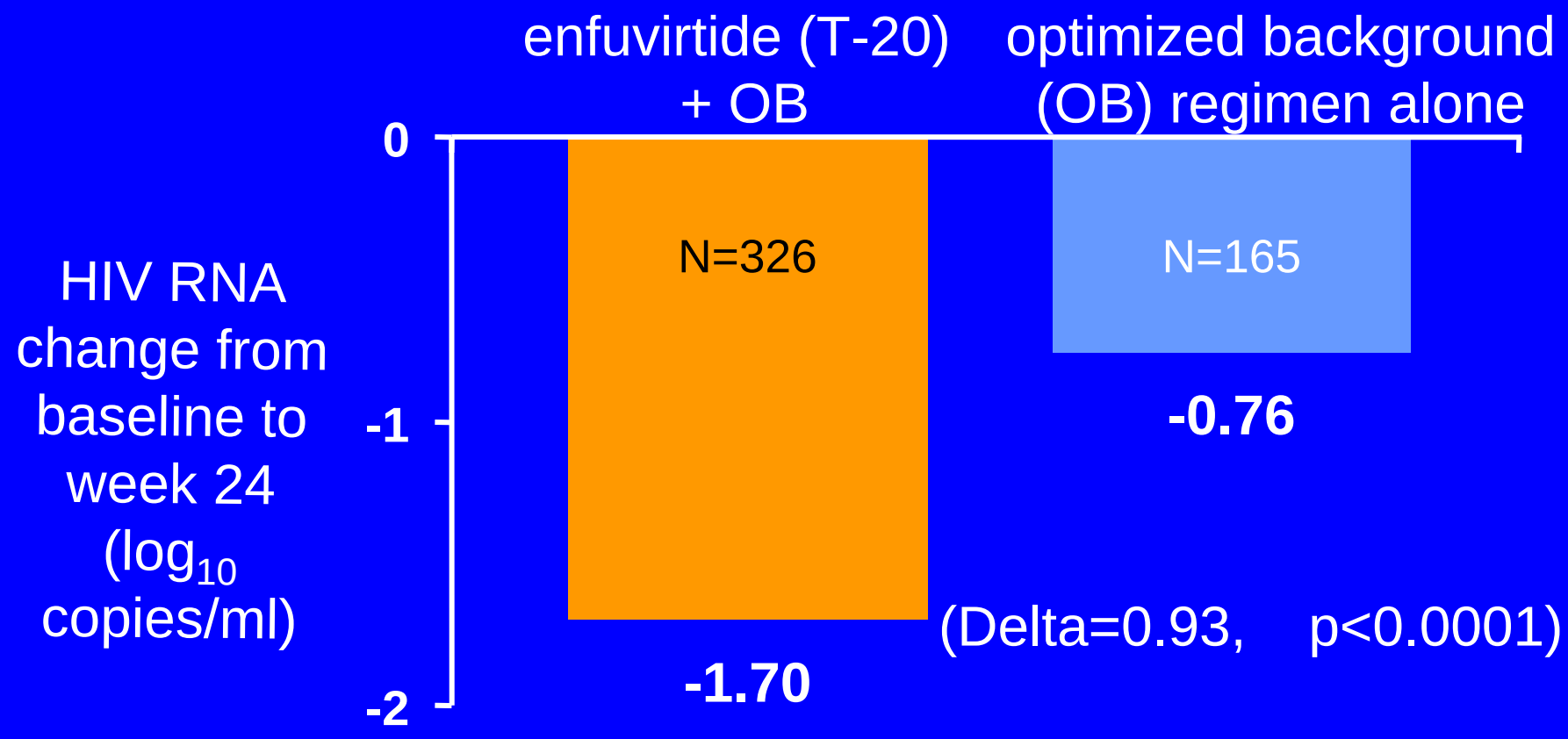
Study	N	Dura-tion	Design	Change in VL (logs)
VIRADAPT Durant Lancet 1999	108	24 wks	geno vs. SOC	-1.2 vs. - 0.7*
GART Baxter AIDS 1999	153	8 wks	geno vs. SOC	-1.2 vs. - 0.6*
VIRA 3001 Cohen AIDS 2002	271	16 wks	pheno vs. SOC	-1.2 vs. - 0.9*

SOC = standard of care

* $p < 0.05$

TORO 1: 3-Class Experienced Study

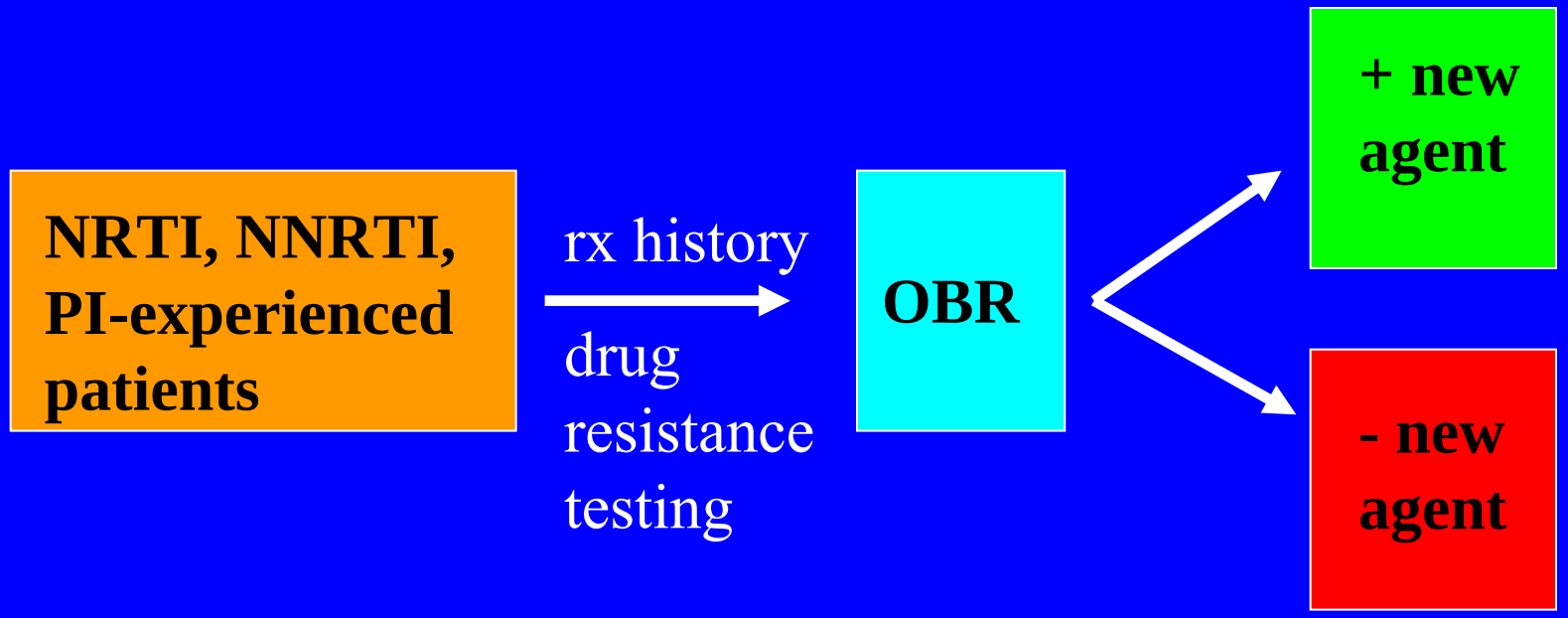
N=491, VL 158K, CD4 80, 3-class experienced (avg 12 drugs)



Least Squared Means Log Change from Baseline - ITT Population (LOCF)

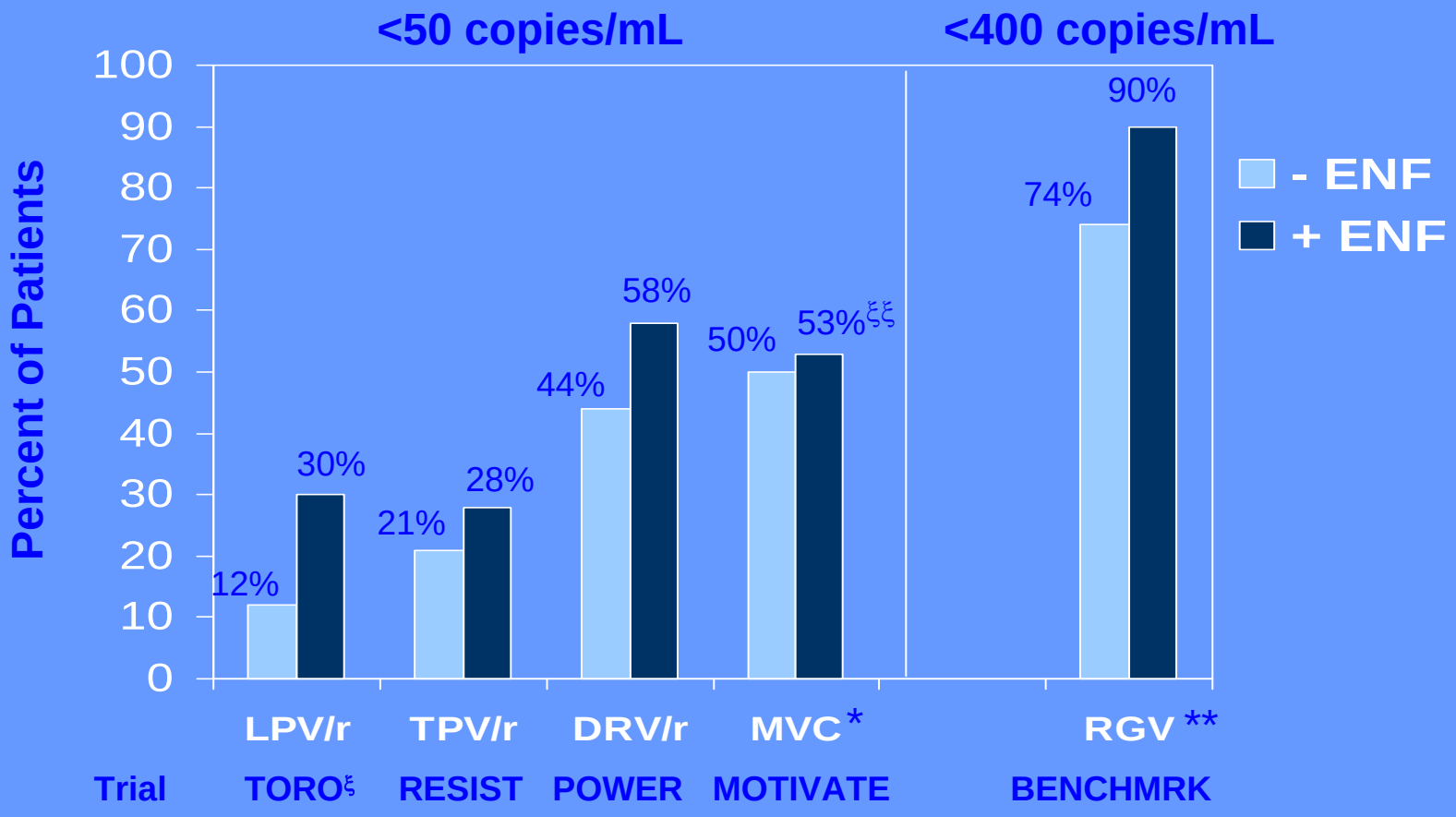
Lalezari, NEJM 2003;348:2175

Rx-Experienced Study: Early-Mid 2000s



Inclusion of 2 Fully Active Agents in OBT

48 weeks results (unless noted)



*24-week data; **16-week data

ξnew LPV/r use; ξξnew ENF use

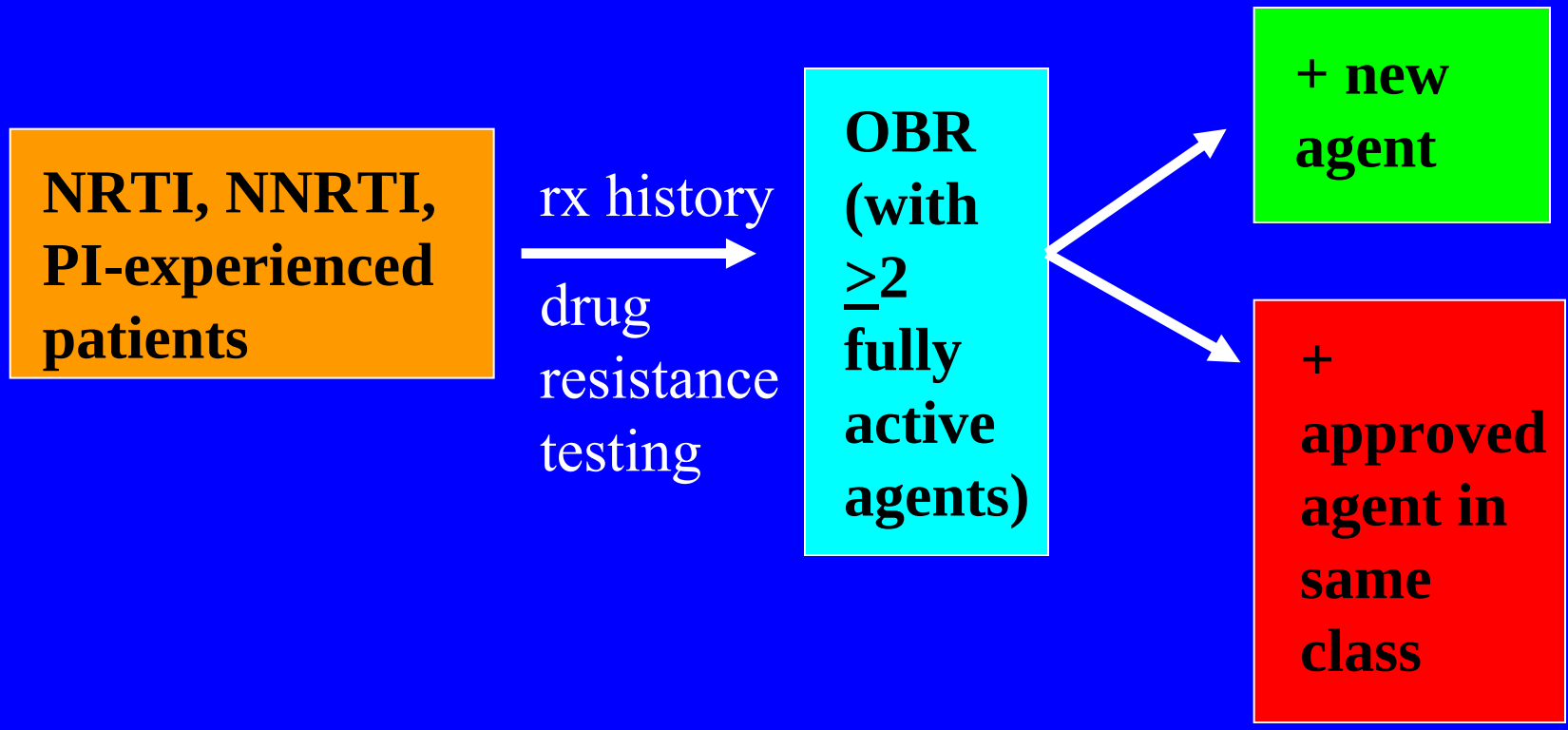
Lalezari IDSA 2007 #964

What to change to?: DHHS Guidelines

- Review goals of therapy
  - Maximal virologic suppression (HIV RNA <50 c/ml)
  - For some pts with extensive prior rx and no rx options: preserve immune fx and avoid clinical progression
- Review ART history
- Assess adherence, tolerability, and PK
- Perform resistance testing while on drugs
- Identify susceptible drugs/drug classes
- Consider newer agents (expanded access/clinical trials)
- Goal: Design a regimen with 2 (or preferably 3) fully active agents

DHHS Guidelines, 12/1/07

Rx-Experienced Study: 2007-8



ACTG 5241: OPTIONS

- Study population: Rx-experienced with VL >1000 cps/ml; no prior integrase inhibitor
- Study evaluation: Hx, GT and PT, tropism testing
- Study rx:

  Choice among: TPV/r, DRV/r, ENF, MVC, RAL, and ETR (+/- NRTIs)