

11th Conference on Retroviruses and
Opportunistic Infections:

An Update on Antiretroviral Therapy

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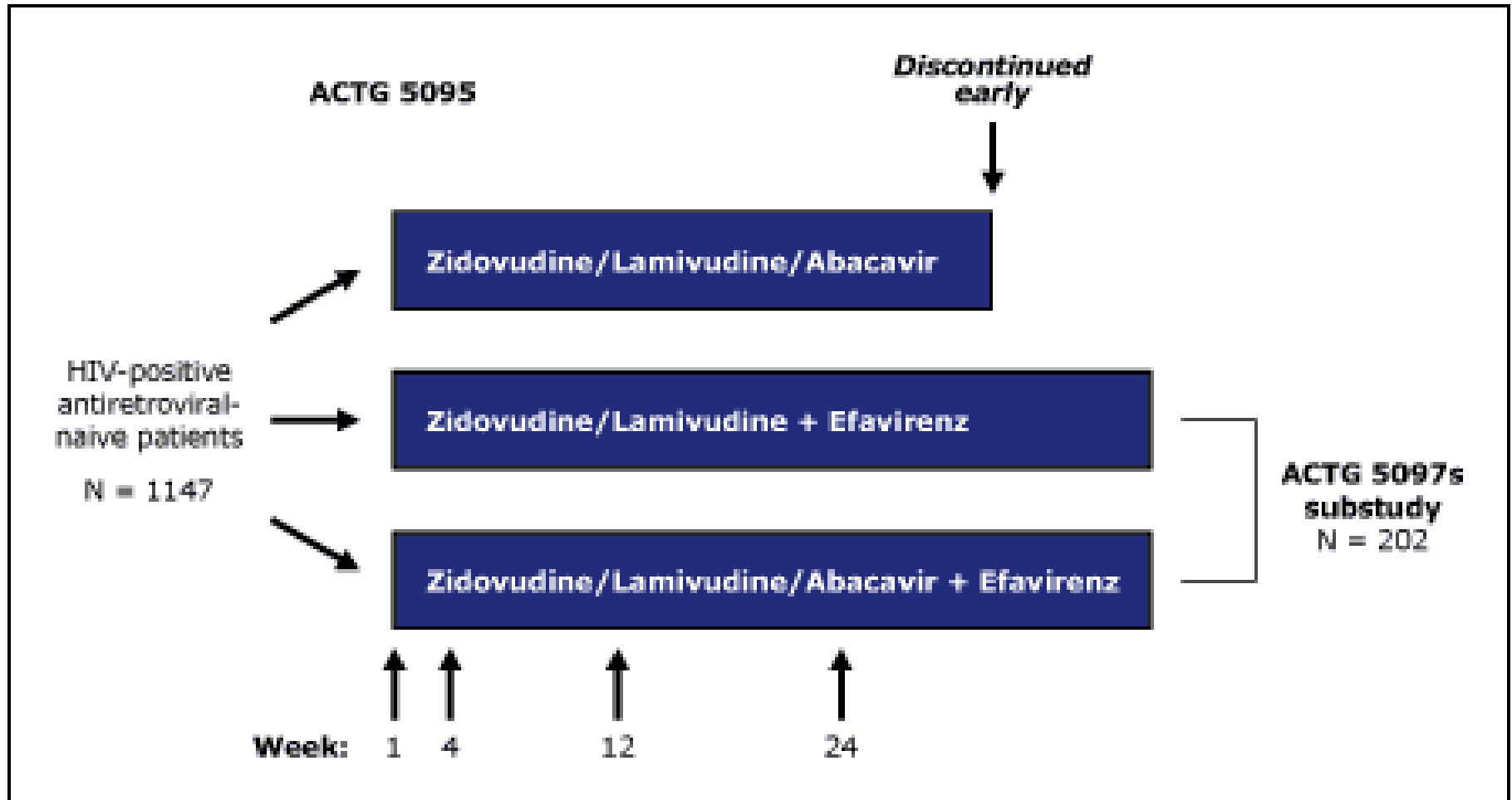
NNRTI Metabolism

Cytochrome P450 Metabolism of HIV Therapy

Ritonavir	3A4, 2D6
Indinavir	3A4
Saquinavir	3A4
Nelfinavir	3A4, 2D6, 2C9, 2C19
Efavirenz	3A4, 2B6
Nevirapine	3A4, 2B6

Drug transporters (PGP) and cytochrome isoenzymes levels and activity vary between individuals, suggesting that this may impact on response to HAART

Efavirenz Metabolism: Host Factors



N=190 with at least one sample

Racial differences in EFV metabolism

- Strong association between clearance and race
 - 32% decrease in blacks/others ($P < 0.001$)
- Some evidence of an increased rate of EFV discontinuation with decreasing clearance ($P=0.052$, test for trend)
 - < 9.67 HR=2.53, 95%CI=0.97, 6.6
 - 9.67 - 13.9 HR=1.85, 95% CI=0.69, 5.0
- No apparent associations between EFV PK and rates of first CNS toxicity ($P=0.46$) or VL <200 c/ml ($P=0.99$)

Discontinuation of NNRTI-based regimens

- PK study: 10 patients stopping 2 NRTIs + EFV underwent extensive PK sampling (days 0, 4, 7, 14 and 21)
 - 5/10 had $T_{1/2}$ 40–50 h
 - 5/10 had $T_{1/2} > 100$ h
 - 4/5 black African women
 - 3/5 had therapeutic levels (> 1000 ng/mL) 2 weeks after stopping EFV
- Primary infection study: 25 patients with VL < 50 c/mL stopped therapy after treatment for early infection (ZDV/3TC continued 5–7 days after stopping EFV)
 - No new NNRTI resistance mutations

Genetic polymorphisms and EFV metabolism

- ACTG 5095: NRTIs + efavirenz (N=157)
 - Single nucleotide polymorphisms in CYP2B6, 3A4, 3A5 and MDR1
 - Population PK performed at weeks 1, 4, 12 and 24

Genetic polymorphisms and EFV metabolism

- Polymorphisms in CYP2B6 G516T
 - EFV AUC associated with genotype: TT > GT > GG (P = 0.001)

G/G	44 h* μ g/mL (n = 78)
G/T	60 h* μ g/mL (n = 60)
T/T	130 h* μ g/mL (n = 14)
 - Similar trends with clearance and Cmin
- Homozygous T/T genotype common in blacks (20%) than whites (3%)
- Association with outcome
 - TT genotype associated with higher CNS Toxicity (P=0.04)
 - No association between genotype and virologic or immunologic outcomes

Genetic polymorphisms and EFV metabolism

- Polymorphisms at CYP3A4 1B (A392G) also associated with EFV levels ($p < 0.001$)
- No association between drug concentrations and MDR1 (P-glycoprotein transporter pump)
 - Contrasts with Fellay/Telenti Lancet 2002

NNRTI Metabolism: Conclusions

- Efavirenz clearance strongly associated with race
 - EFV AUC, C_{max}, and C_{24h} show similar trends
 - Trend toward increased EFV concentration and increased discontinuation
 - Likely applies to nevirapine as well
- Potential options for discontinuation of NNRTI-based regimens
 - Continue NRTIs 7 days after stopping NNRTI (BHIVA recommendation)
 - Switch to PI for 1–2 weeks before stopping regimen
- Rate of NNRTI resistance emergence likely depends on degree of residual viral replication at time drug is discontinued
 - MCPT studies/NIAID STI studies

Triple NRTI Regimens

Implications for how to use these drugs in naïve and experienced patients

Tonus Study: ABC, TNF, 3TC

- Single arm pilot study (n=38) of once daily ABC, 3TC, TNF
 - Baseline viral load 4.87 log, CD4 cell count 226
- Results
 - 12/36 met virologic failure endpoint by week 24 (study closed by DSMB)
 - 11/12 had K65R and M184V
 - 9/10 “successes” had 184V; 7/10 had 65R

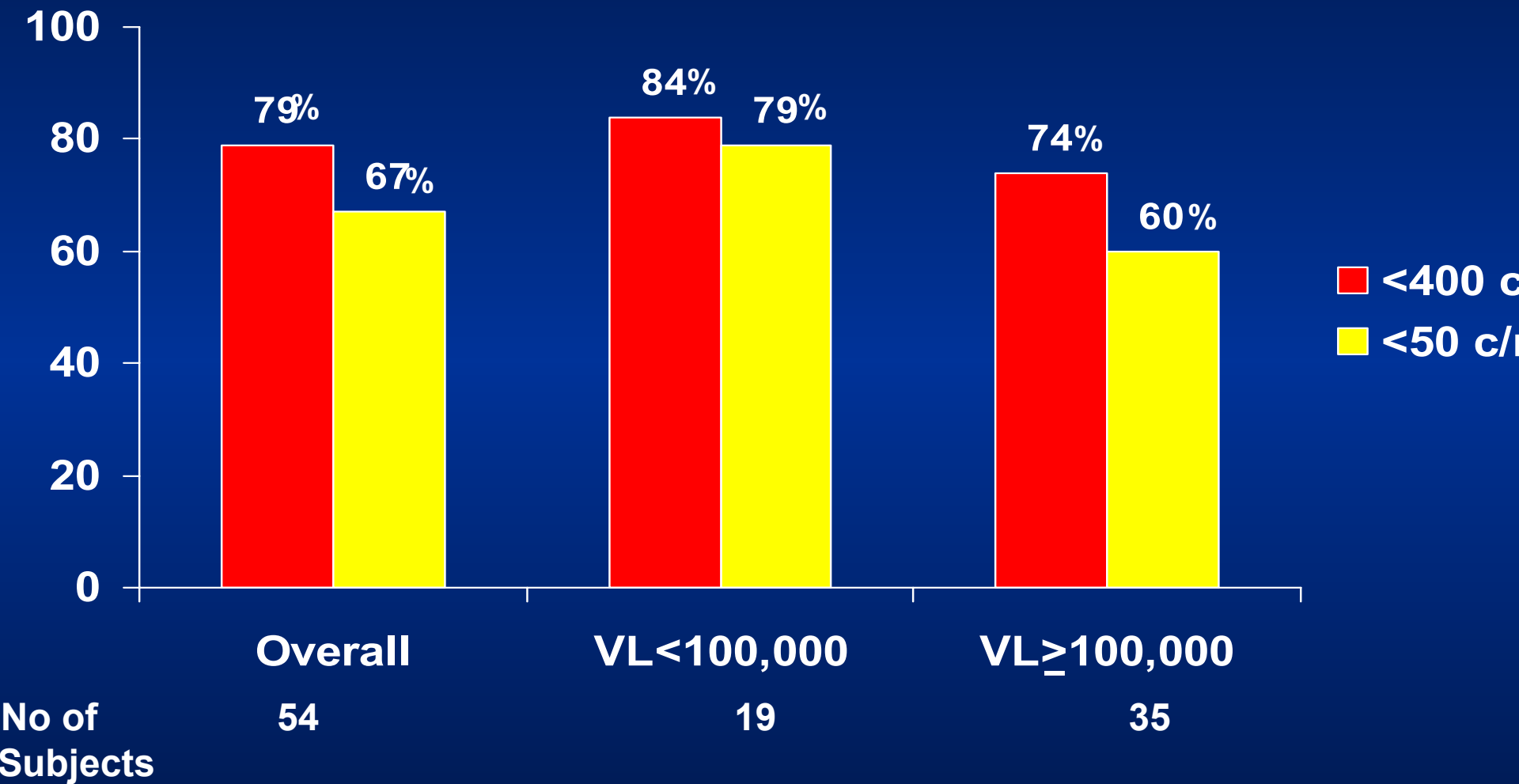
ddl + 3TC + TDF (once daily)

- Single-site pilot study of ddl EC (250), 3TC (300) and TNF (300)
 - Treatment naïve, VL > 10K, no pre-treatment NRTI resistance
- Baseline (n=22)
 - Median viral load 4.91 log, CD4+ (range) 133 (4-475)
- Results (median treatment duration 20 weeks):
 - Median decrease in viral load at week 12 was –0.61 log copies/mL
 - 21/22 had suboptimal response
- Resistance
 - 20/24 pts with M184V/I, 10 patients with with K65R

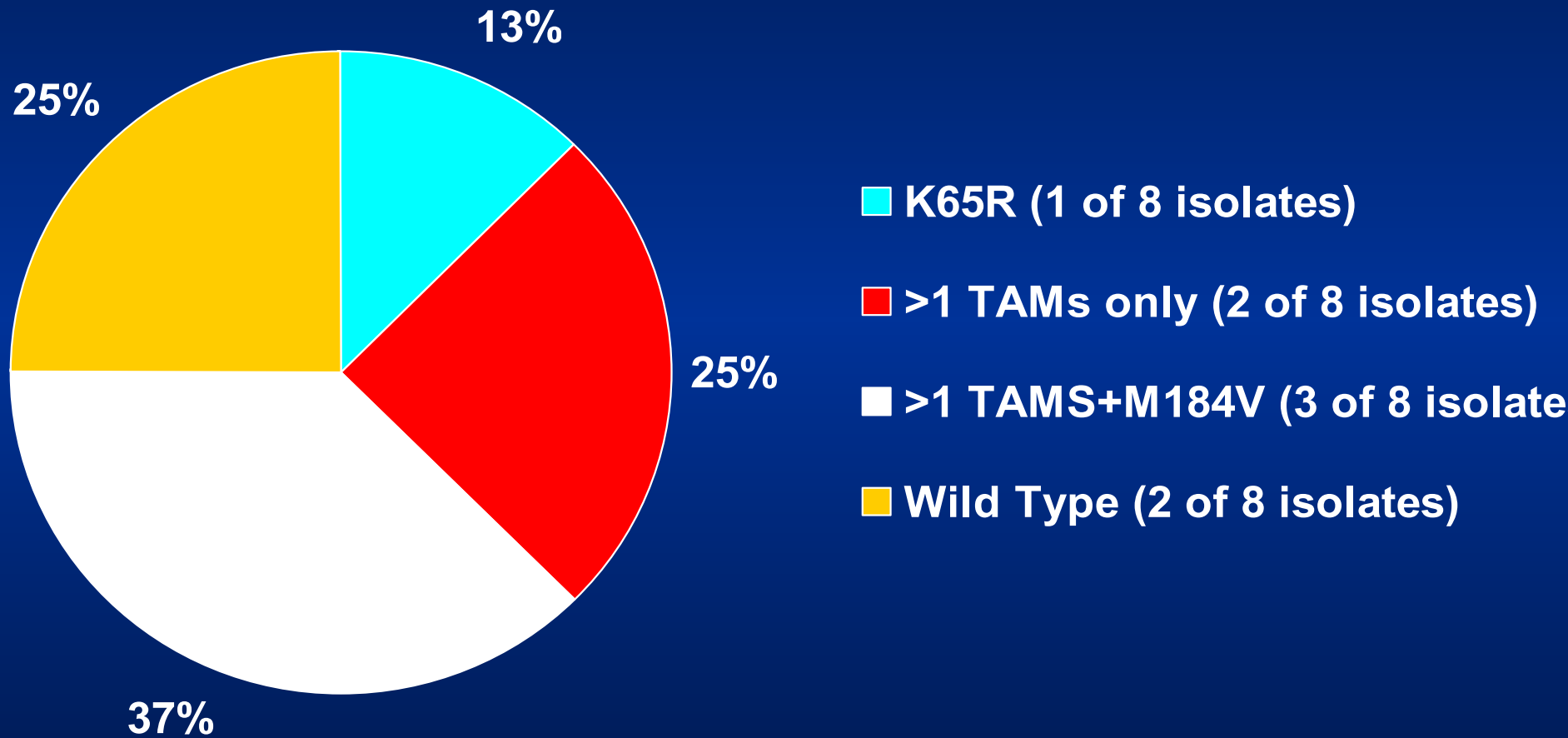
Why do these regimens fail?

- Mechanisms accounting for rapid failure of these regimens remain unclear
 - Not likely due to “potency”
 - Likely mechanisms include drug interactions (including intracellular) and low-genetic barrier
- Pharmacokinetic sub-study of Tonus (ABC, TNF, 3TC)
 - 32/37 (86%) had adequate plasma Cmin for all drugs at week 4
 - All had detectable intracellular triphosphate levels for > 1 agent

COL40263: Once-Daily ZDV/3TC/ABC and TNF (Week 24)

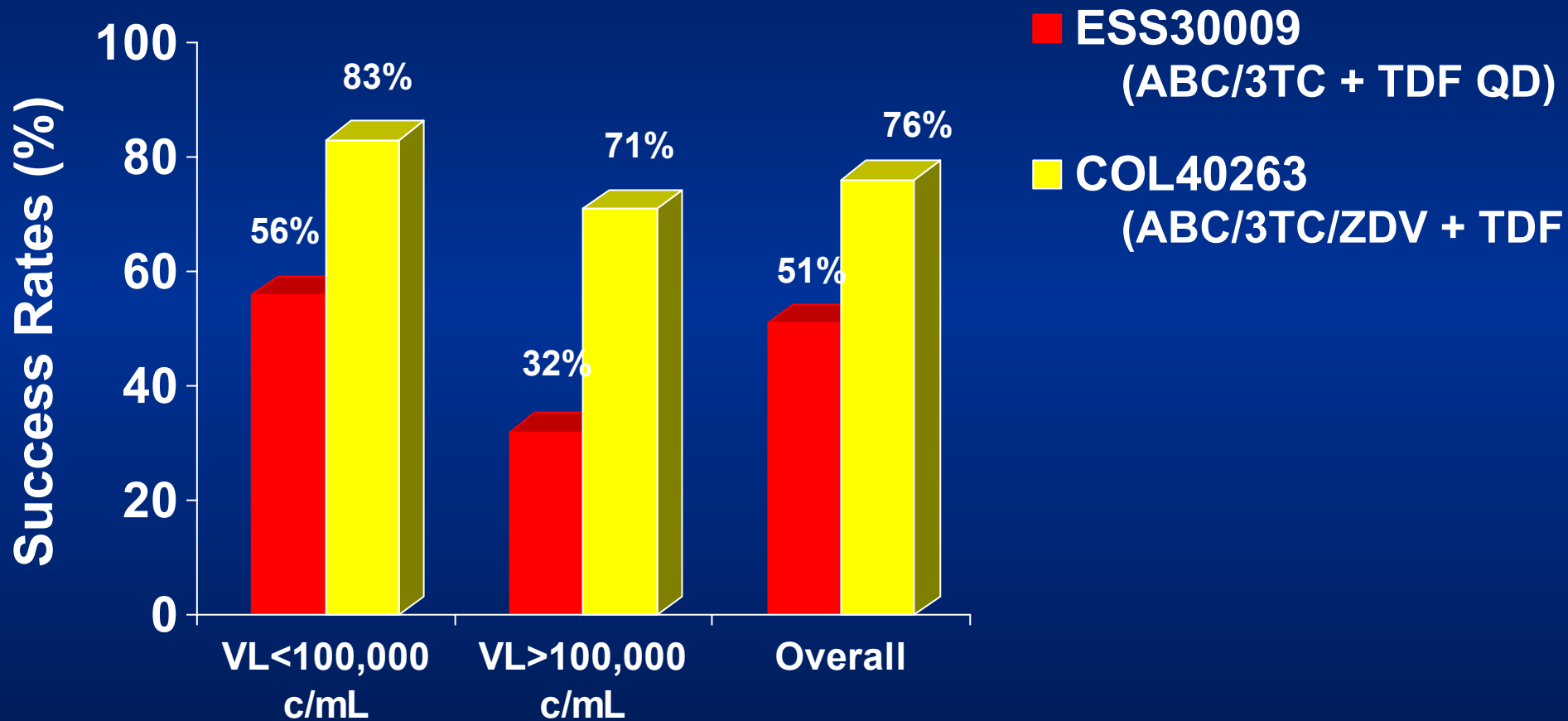


COL40263: RT Genotypic Patterns at Last Visit* (n=8)



Early Virologic Response

ZDV/3TC/ABC/TNF vs. 3TC/ABC/TNF



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COL40263

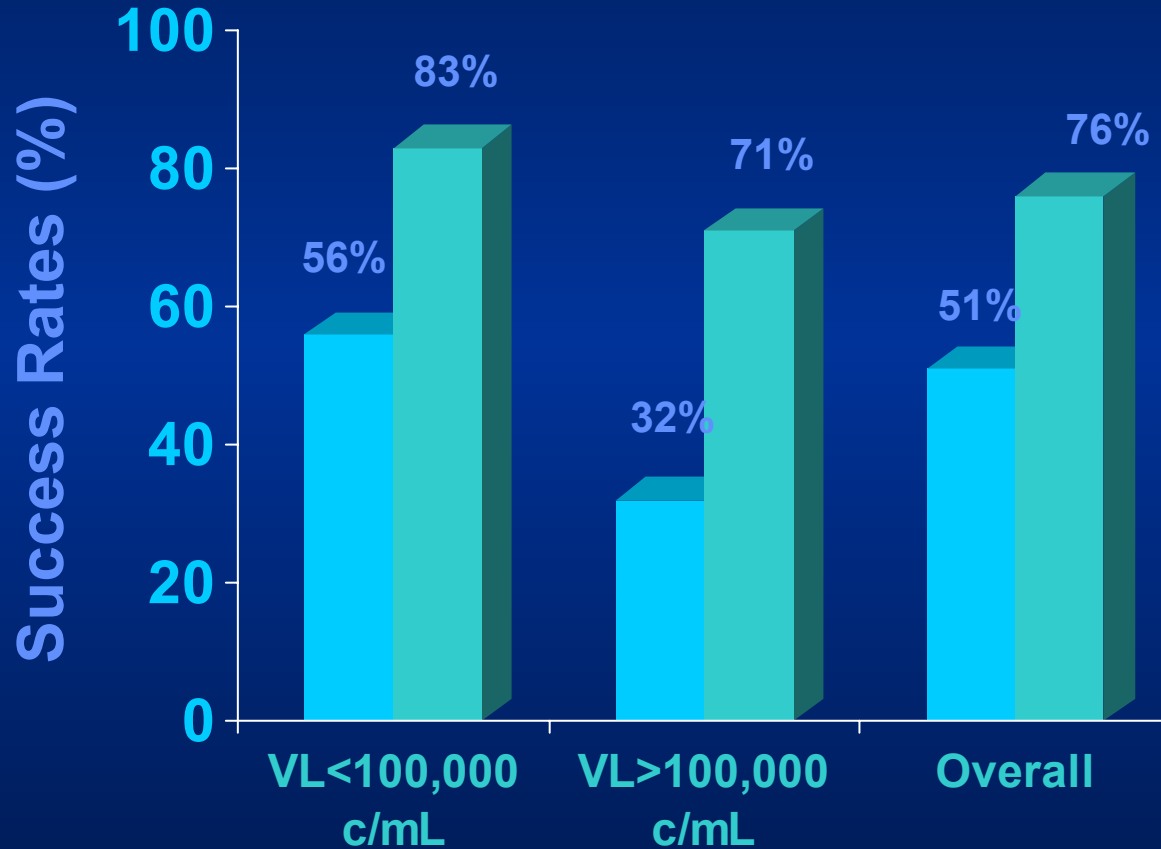
N = 80
N = 36

N = 22
N = 52

N = 102
N = 88

Early Virologic Response

ZDV/3TC/ABC/TNF vs. 3TC/ABC/TNF



The lack of K65R and the improved virologic response by addition of once daily ZDV suggests a strong role for this drug in resistance modulation

K65R: Resistance vs. Fitness

- K65R decreases incorporation of all NRTIs

- K65R decreases the excision of all NRTIs, particularly AZT

- K65R confers resistance to TDF, ddl, ABC, 3TC and perhaps d4T but hypersusceptibility to AZT:

NRTI	Incorporation	Stability	Net Effect
AZT	↓	↑↑	Hypersusceptibility
d4T	↓	--	Sensitive based on clinical cut-offs
TNF	↓↓	↑ / --	↓
ddl	↓↓	--	↓
ABC	↓↓	↑	Sensitive

Clinical Trials

High dose LPV/r in Heavily Pre-treated Patients

- Multiple PI- and NNRTI-experienced pts (n=33)
 - 667/167 mg (5 x 133/33 RTV/LPV tabs) BID or
 - 400/300 mg (3 x 133/33 RTV/LPV tabs + RTV 2x100 mg) BID
 - 2 to 3 NRTIs selected by investigator
- 12 hour PK sampling done at week 3
- Baseline
 - Median fold IC50 was 4.1 (range 0.6 to 273)
 - Median number of mutations: 5 (range 0 to 8)
 - Previous protease inhibitors: 4
- LPV trough 1.60-1.70 x 400/100 bid

High dose LPV/r in Heavily Pre-treated Patients

- Outcome (week 48)
 - 21/36 (58%) had HIV-1 RNA < 400 copies/mL
 - 16/33 (48%) had HIV-1 RNA < 50 copies/mL
 - Mean (SD) change was -1.39 (1.09) log₁₀ copies/mL
- Trend to better tolerability for 667/167 mg vs 400/300 mg
 - Lower incidence of drug-related diarrhea: 11% vs 24%
 - Lower rates of vomiting: 0% vs 12%
 - Lower level of grade 3/4 triglycerides (> 750 mg/dL): 26% vs 65%

High dose LPV/r in Heavily Pre-treated Patients

- Predictors of a viral load < 400 at week 48

Predictor	Unadjusted	Adjusted
Baseline VL	0.01	NS
Fold change IC50	0.02	NS
Number of LPV mutations	0.04	NS
Active NRTIs	0.02	0.04
LPV IQ	0.002	0.007

- Higher doses of LPV/RTV may provide sufficient LPV to overcome certain degrees of LPV resistance

COLATE Trial: Continued 3TC vs discontinuation

- Patients (n=131) with incomplete viral suppression on a 3TC-containing regimen randomized to:
 - Continued (150 mg) BID or
 - Discontinued 3TC
- Three drug regimen selected prior to randomization
- Baseline
 - VL: 4.0 log
 - CD4: 310
 - CD4 nadir: 125

COLATE Trial: Week 48

	3TC	No 3TC
% on treatment	83%	91%
AAUCMB	-1.4	-1.5
% <50 c/mL	52%	44%
% <400 c/mL	66%	65%

$p=N$

Vista ANRS 109: Reduced drug pressure to maintain MDR

- HIV drug resistance is often associated with significant reductions in viral replicative and pathogenic capacities.
 - Maintaining a failing full-dose HAART regimen results in significant drug toxicity and in continued accumulation of resistance mutations
- Objective: Use a calibrated reduction in drug pressure exerted both on protease and RT to stabilize viral evolution while maintaining the reduced pathogenic potential of resistant virus.

Vista ANRS 109: Reduced drug pressure to maintain MDR

- Prospective pilot study of 3TC and low dose RTV/IDV (100/200 bid)
 - MDR HIV (< 2 remaining active drugs)
 - Viral load > 10,000
 - CD4 > 100
- Baseline (N =28)
 - Median CD4 = 340
 - Median viral load = 4.48 log

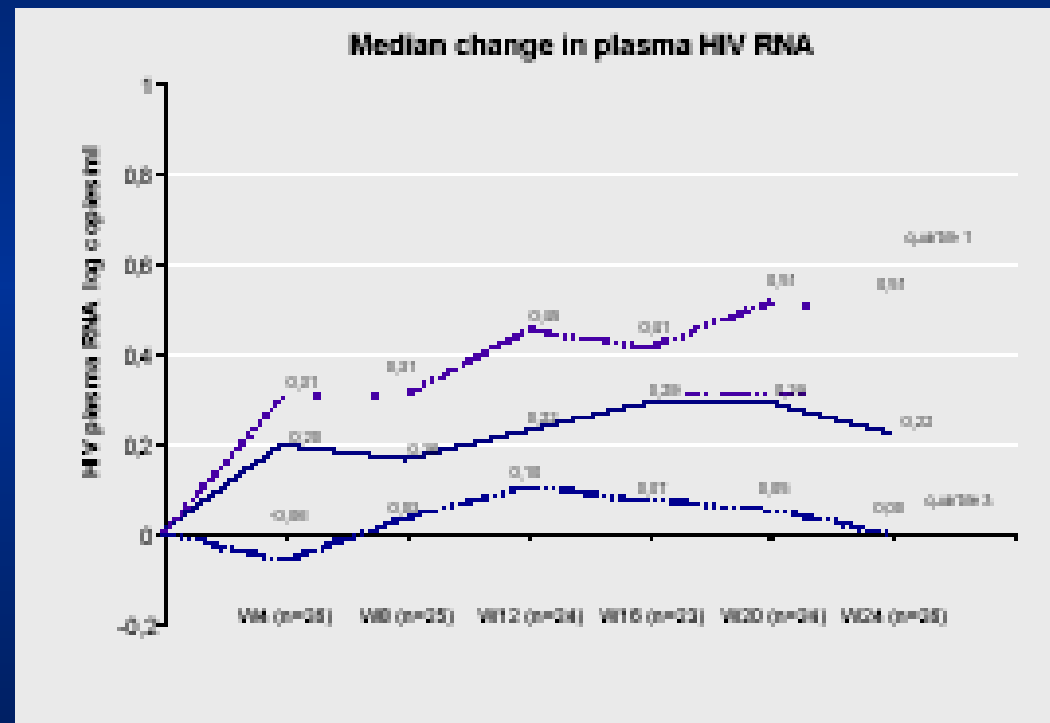
Vista ANRS 109: Reduced drug pressure to maintain MDR

10/26 patients (38%) reached a primary endpoint : 6 due to > 25% loss of CD4 and 3 due to > 0.7 log increase in viral load

Median increase in VL at week 24 was 0.22 log₁₀ (IQR : 0 ; 0.51, p=0.003)

Median slope in CD4 cell count decrease during the study did not significantly change

No significant changes in the numbers of resistance mutations were seen in PR or in RT



FORTE: Induction/maintenance

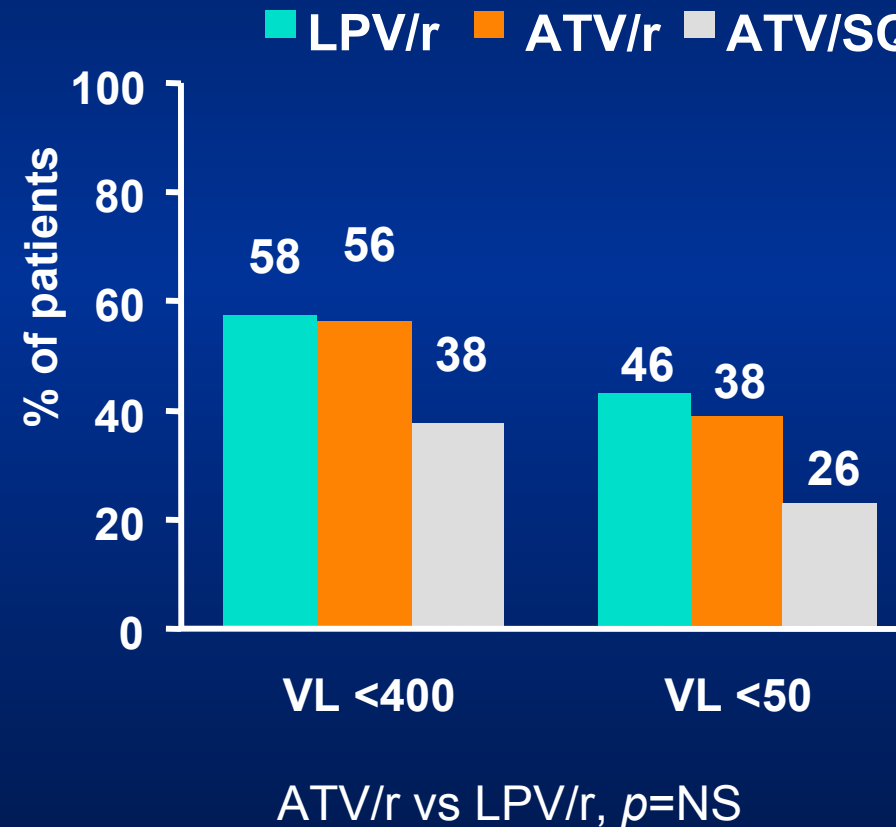
- 122 treatment naïve patients randomized to
 - Induction/maintenance: PI, NNRTI, and 2 NRTIs for 24-32 weeks until plasma HIV RNA < 50 followed by NNRT/2NRTIs
 - Standard: NNRTI plus 2 NRTIs
- Baseline
 - Median CD4 160 cells/mm (IQR 92-260); viral load 98,830 copies/mL
- Primary endpoint: Time to virologic failure

FORTE: Induction/maintenance

- Intent-to-treat time to virologic failure analysis
 - More patients on the standard therapy arm had virological failure at or after 24 weeks (48% vs 31%, $p = 0.06$ log rank test)
 - Similar results at at or after 32 weeks (43% vs 18%, $p = 0.002$).
- Week 48 analysis
 - Mean viral load decrease at 48 weeks was 0.86 (SE 0.35) \log_{10} copies/mL greater in the induction/maintenance arm ($p = 0.01$).
 - 81% of patients in the induction/maintenance arm and 65% in the standard therapy arm had viral load <50 ($p = 0.07$)
 - 100% in the induction/maintenance arm and 86% in the standard therapy arm had a viral load <400 ($p = 0.01$).
- There was not a significant difference in T-cell increase or in adverse events between the groups.

BMS 045: LPV/r vs ATV/r vs ATV/SQV (Week 48; ITT)

- Failure of ≥ 2 regimens, ≥ 1 ARV drug from each class
- Randomized (with TDF + 1 NRTI):
 - LPV/r 400/100 mg BID ($n=123$)
 - ATV/r 300/100 mg QD ($n=120$)
 - ATV/SQV 400/1200 mg QD ($n=115$)
- Baseline:
 - VL $\sim 4.4 \log_{10}$ c/mL
 - CD4 ~ 300 cells/mm³
- D/C before wk 48 for TX failure/lack of efficacy: 5% LPV/r, 14% ATV/r
- TC: LPV/r +6, ATV/r -8 ($p < .005$)



ACTG 372A: Abacavir intensification

- Randomized, double-blind, placebo-controlled trial: addition of ABC vs. placebo
 - Patients with HIV RNA <500 c/mL on IDV + 3TC + (ZDV or d4T) in ACTG 320 (or on same regimen outside study), N=220
- Composite endpoint:
 - 2 consecutive viral loads >500 c/mL (later >200 c/mL)
 - Treatment discontinuation (other than ZDV→d4T switch)

ACTG 372A: Abacavir intensification

No difference between ABC and placebo arms in:

- Ultrasensitive viral load (<6 c/mL)
- Proviral DNA
- Frequency of blips
- Emergence of 65R, 184V, 74V
- CD4 counts
- Mortality or tolerability

	ABC	Placebo
N	116	113
Composite Endpoint (ITT)	53%	55%
Virologic Failure (ITT)	29%	37%
Virologic Failure (on Rx)	21%	27%