

Treatment for Adult HIV Infection

2004 Recommendations of the International AIDS Society-USA Panel

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THE INTERNATIONAL AIDS SOCIETY-USA panel last updated its guidelines for antiretroviral therapy in 2002.¹ Over the past 2 years, substantial new information has emerged influencing antiretroviral management. This includes the availability of several new drugs that increase therapeutic options (ie, atazanavir, emtricitabine, enfuvirtide, and fosamprenavir), the reporting of ma-

Context Substantial changes in the field of human immunodeficiency virus (HIV) treatment have occurred in the last 2 years, prompting revision of the guidelines for antiretroviral management of adults with established HIV infection.

Objective To update recommendations for physicians who provide HIV care regarding when to start antiretroviral therapy, what drugs to start with, when to change drug regimens, and what drug regimens to switch to after therapy fails.

Data Sources Evidence was identified and reviewed by a 16-member noncompensated panel of physicians with expertise in HIV-related basic science and clinical research, antiretroviral therapy, and HIV patient care. The panel was designed to have broad US and international representation for areas with adequate access to antiretroviral management.

Study Selection Evidence considered included published basic science, clinical research, and epidemiological data (identified by experts in the field or extracted through MEDLINE searches using terms relevant to antiretroviral therapy) and abstracts from HIV-oriented scientific conferences between July 2002 and May 2004.

Data Extraction Data were reviewed to identify any information that might change previous guidelines. Based on panel discussion, guidelines were drafted by a writing committee and discussed by the panel until consensus was reached.

Data Synthesis Four antiretroviral drugs recently have been made available and have broadened the options for initial and subsequent regimens. New data allow more definitive recommendations for specific drugs or regimens to include or avoid, particularly with regard to initial therapy. Recommendations are rated according to 7 evidence categories, ranging from I (data from prospective randomized clinical trials) to VII (expert opinion of the panel).

Conclusion Further insights into the roles of drug toxic effects, drug resistance, and pharmacological interactions have resulted in additional guidance for strategic approaches to antiretroviral management.

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for randomized, multicenter trials that help define optimal initial regimens; an evolving understanding of the mechanisms and clinical significance of drug resistance, toxic effects, and interactions; and clinical trial results that address questions concerning strategic approaches to antiretroviral therapy (eg, structured treatment interruption).

These updated guidelines reflect the international perspectives of the panelists and are designed to serve as a tool for clinicians in countries where resources are sufficient to provide rela-

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For editorial comment see p 266.

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Treatment for Adult HIV Infection: 2004 Recommendations of the International AIDS Society-USA Panel

Yeni G, Hammer SM, Hirsch MS, et al.
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Methods: Data Review

- Published reports between July 2002-May 2004 identified by panel and through MEDLINE
- Published data and abstracts from scientific conferences: CROI, IAS, ICAAC, IDSA, others

Scope of Guidelines

- Recommendations are for antiretroviral drugs approved for adult use as of mid-2004
- These guidelines are designed for use by clinicians in countries where resources are sufficient to provide relatively unrestricted choices of drugs and monitoring tools
- New guidelines for resource-limited settings have been issued by World Health Organization

(Of note, updates available at www.iasusa.org, or www.who.org, or jama.ama-assn.org/)

Methods: Strength of Evidence Rating Scale

- I. Prospective clinical trials (ie, properly randomized controlled trials) or data from ancillary trials (pharmacological and drug interaction studies)
 - A. Published
 - B. Abstracts presented at scientific conferences
- II. Cohort studies
- III. Observation studies (including meta-analyses)
- IV. Inferences from studies with similar drugs (or in similar settings)
- V. Extrapolations from pathogenesis studies
- VI. Uncontrolled studies (eg, pilot studies, exploratory studies, etc)
- VII. Expert opinion (consensus of the panel in the absence of above evidence)

When to Start: Recommendations for Initiating Therapy

Disease Stage	Recommendation	Evidence Rating
Symptomatic HIV Disease	Antiretroviral treatment	IA
Asymptomatic HIV Disease ≤200 CD4 cells/μL	Antiretroviral treatment	II
>200 CD4 cells/μL but ≤350 CD4 cells/μL	Antiretroviral treatment should be considered	II
>350 CD4 cells/μL but ≤500 CD4 cells/μL	Continued monitoring, counseling for HIV transmission prevention	II
>500 CD4 cells/μL	Continued monitoring; counseling for HIV transmission prevention	II

When to Start: Key Points for Asymptomatic Disease

- Evidence (evidence rating II) is to start treatment **before** CD4+ 200/ μ L. Do not wait until CD4+ is below 200/ μ L
- Individualize therapy decision
 - Recommendation for treatment is stronger for CD4+ >200-350/ μ L when viral load is high (>50,000-100,000 copies/mL) or if rapid CD4+ decline (>100/ μ L per year)
 - At CD4+ >350-500/ μ L, consider therapy if high viral load or rapid CD4+ decline

Initial Regimens

Generally Recommended

- NNRTI + 2 NRTIs
- Boosted PI + 2 NRTIs

Generally NOT Recommended

- 4-drug regimens
- 3-NRTI regimens, except when NNRTI and PI use is precluded
- 2-drug regimens or monotherapy (eg, 1 PI)

Recommended Components for Initial Antiretroviral Regimens

Slide #8

Recommended Components

NRTI component

Efavirenz

(Nevirapine in selected patients)

Protease Inhibitor component

Lopinavir/ritonavir

Atazanavir/ritonavir

OR

Saquinavir/ritonavir

Indinavir/ritonavir

NRTI component

Zidovudine or tenofovir and lamivudine or emtricitabine

Didanosine and emtricitabine, or efavirenz if a qd regimen is sought

SEE TEXT

Alternative Components for Initial Antiretroviral Regimens ^{Slide #9}

Alternative Components

Protease inhibitor component

Fosamprenavir/ritonavir
Atazanavir
Nelfinavir

NRTI component

Abacavir and lamivudine
Didanosine and lamivudine
Didanosine and tenofovir
Stavudine and lamivudine
Zalcitabine and abacavir

**SEE
TEXT**

Special Circumstance Only and Other Components for Initial Antiretroviral Regimens (cont'd)

Special Circumstances Only	Do Not Combine
<p>3-NRTI regimen</p> <ul style="list-style-type: none"> • Zidovudine, lamivudine, and abacavir 	<ul style="list-style-type: none"> • Stavudine and zidovudine • Stavudine and didanosine • Stavudine and zalcitabine
<p>Do Not Use</p>	
<p>3-NRTI regimen</p> <ul style="list-style-type: none"> • Tenofovir, abacavir, and lamivudine • Tenofovir, didanosine, and lamivudine • Stavudine, didanosine, and abacavir 	

Initial Therapy: NNRTIs

- Weight of available evidence favors efavirenz

But

- Nevirapine is a reasonable option
 - Due to toxicity, less satisfactory in some patients—eg, those with HCV or elevated liver enzymes or women with CD4+ >250/ μ L (evidence IB)

Initial Therapy: PIs

- Lopinavir/r or atazanavir/r: more evidence is available for lopinavir/r, but it is not clear that it is the preferred boosted PI regimen versus ATZ/r (less likely to cause lipid abnormalities than lopinavir/r), saquinavir/r, or indinavir/r
- Indinavir/r or saquinavir/r are options

Initial Therapy: PIs

Less attractive options due to lower relative potency:

- Nelfinavir
- Unboosted atazanavir
- Fosamprenavir/r

Initial Therapy: Double-NRTI Backbone

- Recommended
 - Zidovudine + lamivudine (or emtricitabine)
 - Tenofovir + lamivudine (or emtricitabine)
 - Emtricitabine + didanosine; alternatively abacavir/lamivudine can be used with efavirenz when qd regimen is desired

Note: Lamivudine and emtricitabine are considered interchangeable, but confirmatory data are lacking

Initial Therapy: Double-NRTI Backbone (cont'd)

- Not recommended
 - Stavudine/zidovudine is contraindicated
 - Stavudine/didanosine and combinations including zalcitabine not recommended due to increased toxicity

Initial Therapy: ZDV/3TC/ EFV vs 3-Drug and 4-Drug Regimens—ACTG 384 (Robbins et al, Schafer et al, *NEJM*, 2003) Slide #16

- Multicenter, randomized, partially double-blind trial in 980 patients
- ZDV/3TC/EFV was superior to ZDV/3TC/NFV, d4T/ddI/NFV, and d4T/ddI/EFV and similar to 4-drug regimen of NFV/EFV + either ZDV/3TC or d4T/ddI
- No difference in duration of successful treatment between 4-drug regimen and 2 consecutive 3-drug regimens

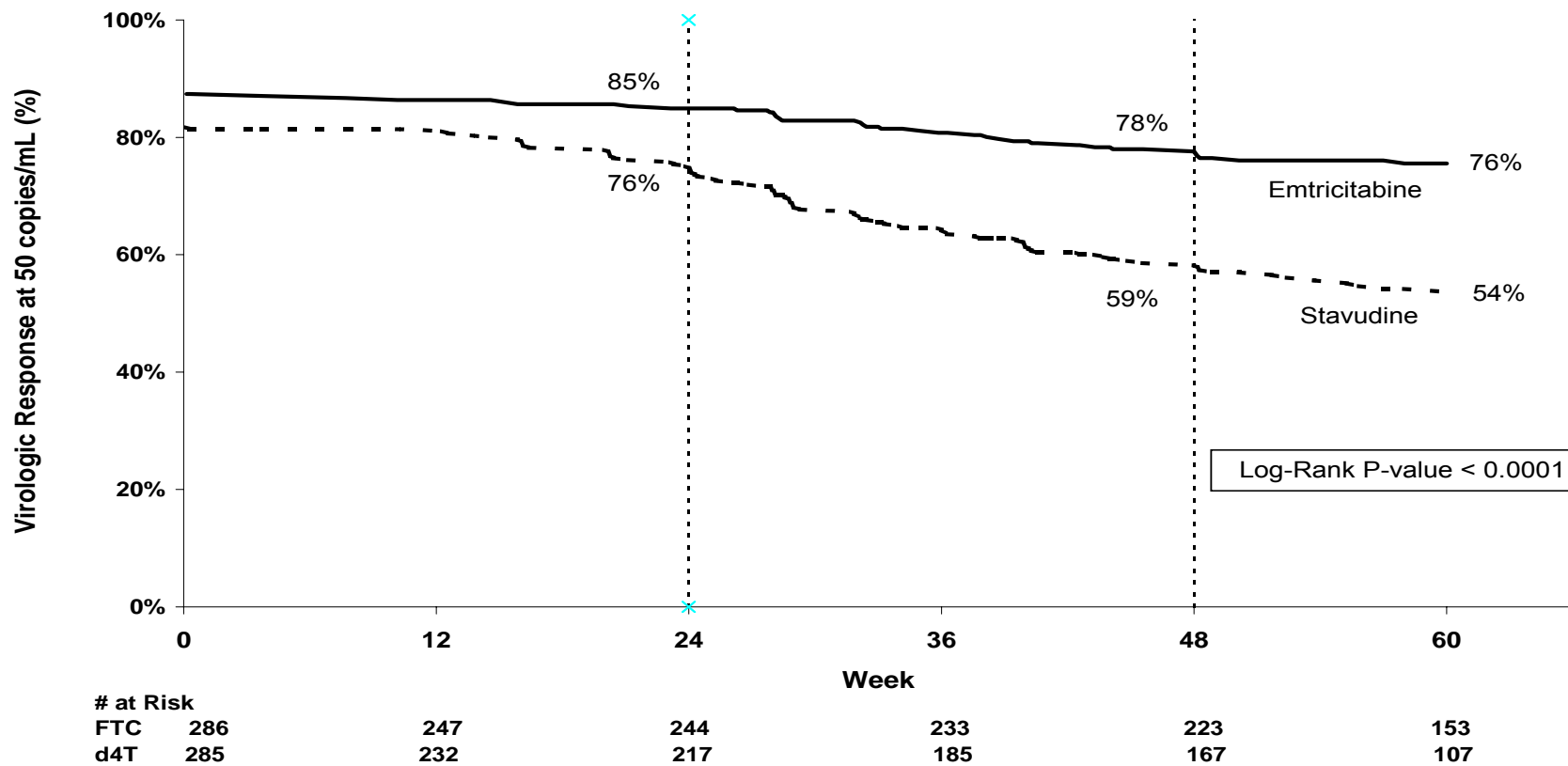
Initial Therapy: ZDV/3TC/ EFV vs 3-Drug and 4-Drug Regimens—ACTG 384 (cont'd)

- 4-drug regimen had longer time to initial regimen failure than all 3-drug regimens except ZDV/3TC/EFV
- Peripheral neuropathy, pancreatitis, liver enzyme abnormality risks higher with stavudine/didanosine regimens

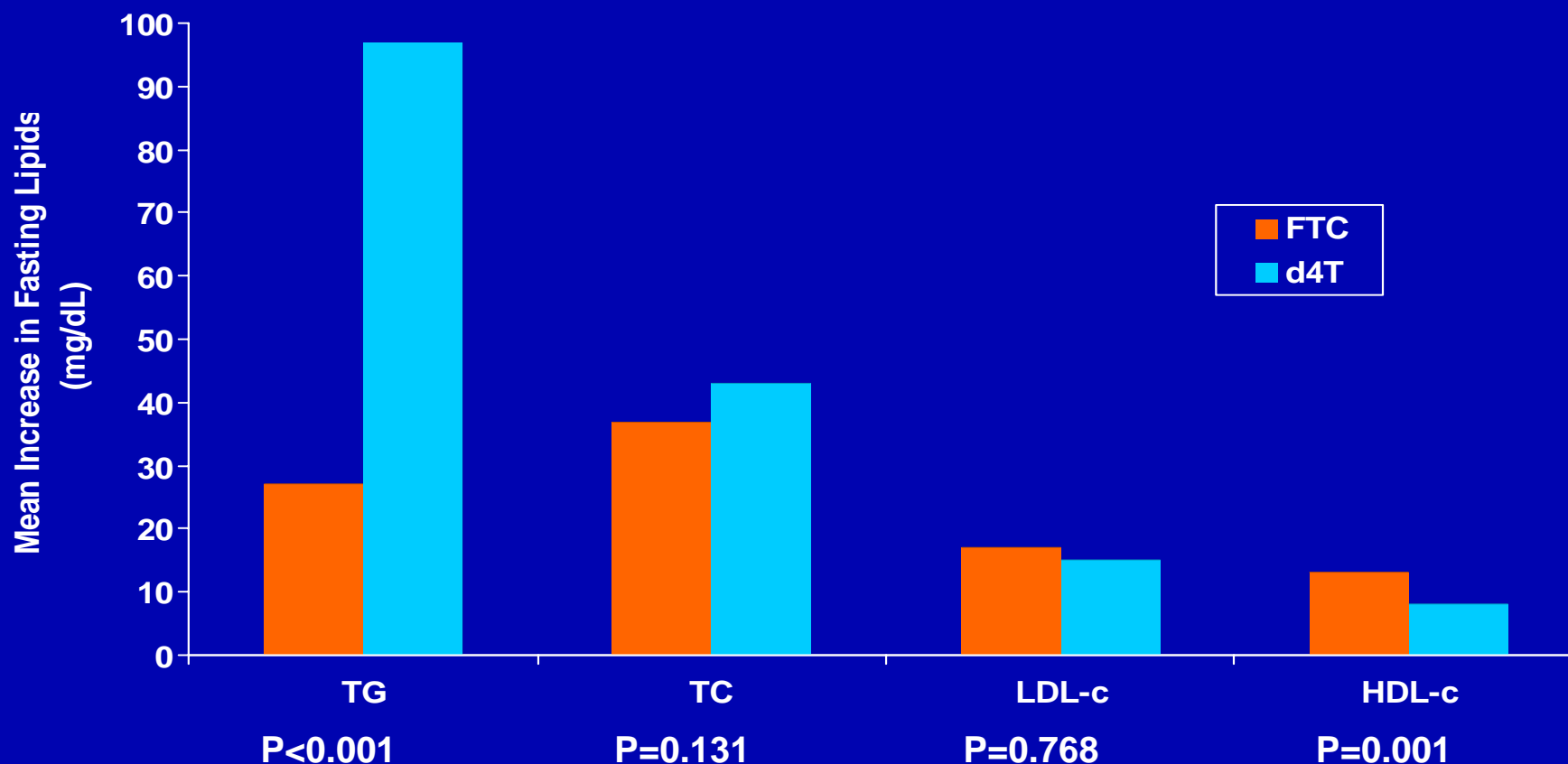
Initial Therapy: FTC vs d4T + ddI/EFV— FTC-301 (Saag et al, *JAMA*, 2004)

- Randomized, double-blind, placebo-controlled trial in 571 patients
- Emtricitabine regimen superior to stavudine regimen; study discontinued at week 24
- Emtricitabine associated with smaller increase in triglycerides and greater increase in HDL cholesterol

FTC-301 Efficacy Endpoints at Week 48



FTC-301 Changes in Fasting Lipid Profile at 72 weeks



New Evidence Against Routine Initial 3-NRTI^{STP} #21 Therapy—ACTG 5095 (Gulick et al, *NEJM* 2003)

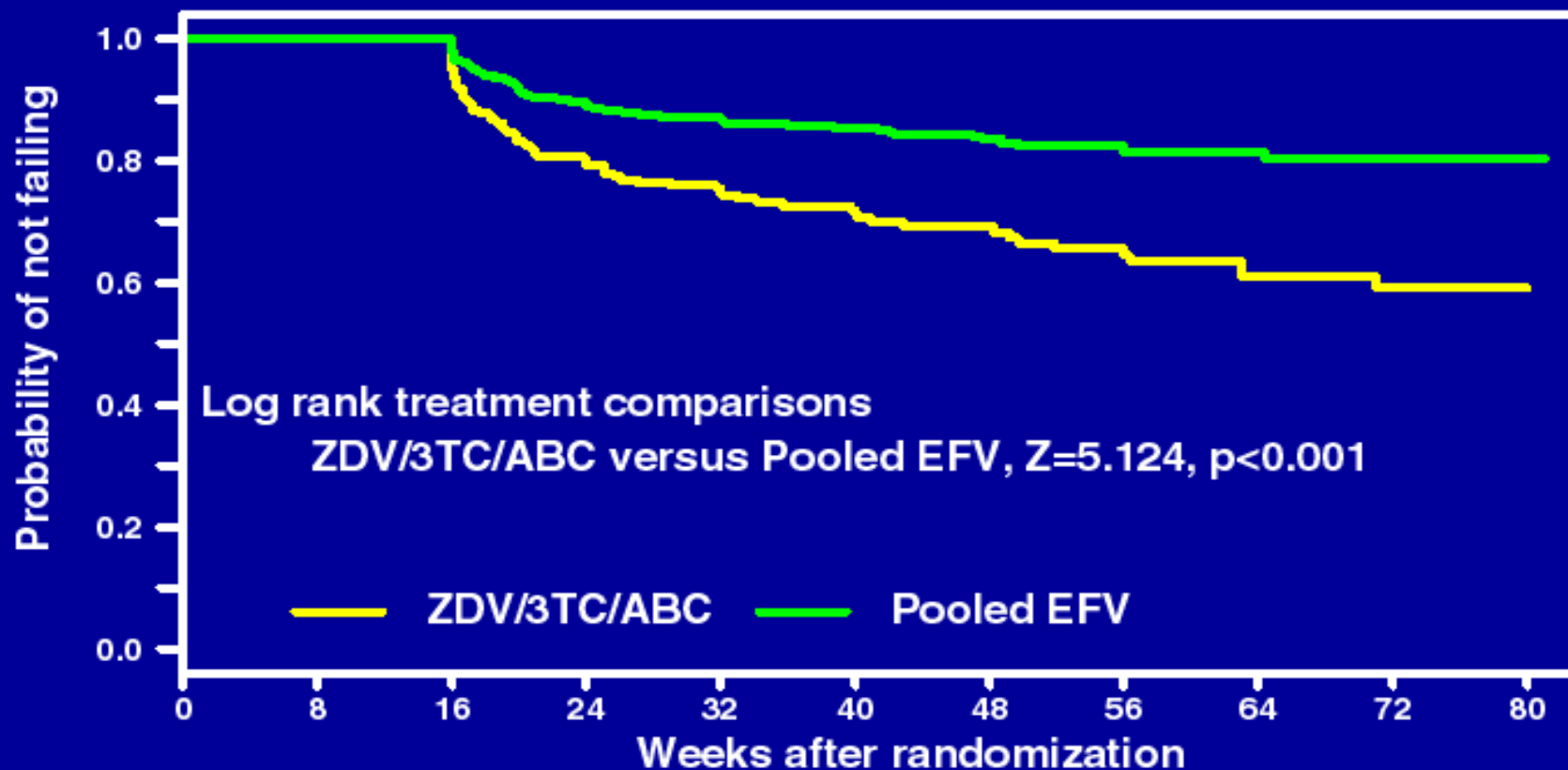
- Ongoing randomized, double-blind, placebo-controlled trial in 1147 patients
- ZDV/3TC/ABC vs ZDV/3TC/EFV vs ZDV/3TC/ABC/EFV
- Scheduled DSMB review found differences between 3-NRTI group and EFV groups that crossed prespecified stopping boundaries; the 3-NRTI group was discontinued

New Evidence Against Routine Initial 3-NRTI Therapy—ACTG 5095 (cont'd)

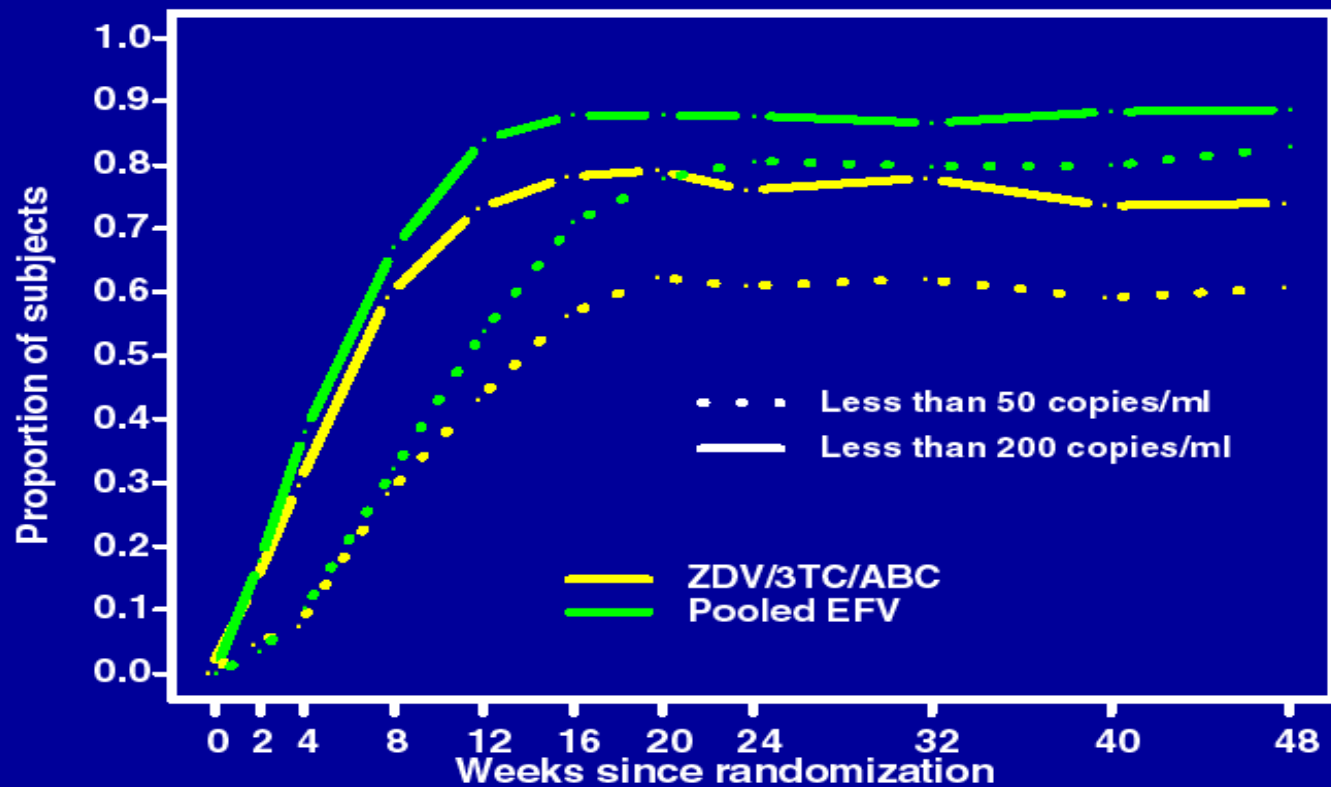
- After median of 32 weeks, treatment failed in 21% of 3-NRTI group and 11% of pooled efavirenz groups (regardless of pretreatment plasma HIV RNA level $>$ or $<$ 100,000 copies/mL)
- How the 79% response rate with 3 NRTIs compares with rates for PI-containing regimens to be explored

ACTG 5095: Time to first virologic failure

ALL study subjects



ACTG 5095: Proportion of subjects with HIV-1 RNA <200 and <50 c/mL



89% (85, 93%)
 83% (78, 88%)
 74% (65, 83%)
 61% (50, 72%)

pt estimate
(95% CI) at
wk 48

Number of subjects in the denominator

ZDV/3TC/ABC	382	349	314	293	270	250	238	195	159	127
Pooled EFV	765	699	638	583	543	508	481	396	319	256

Adapted from Gulick et al, *NEJM*, 2003.

Initial Therapy: 3-NRTI Used in Special Circumstances

- 3-NRTI regimens no longer recommended due to insufficient potency vs efavirenz-containing regimens
- If NNRTI or PI use is precluded, zidovudine/abacavir/lamivudine may be considered
- Close monitoring of plasma HIV RNA is mandatory to detect early failure

Initial Therapy: 3-NRTIs

- 3-NRTI regimens that should **not** be used
 - TNF/ABC/3TC (evidence IB)
 - TNF/ddI/3TC (evidence IB)
 - d4T/ddI/ABC (evidence IB)

Interactions Between Antiretroviral Drug Pairs Requiring Dosing Alteration or Avoidance

- Attention to potential interactions among all components in antiretroviral regimens is necessary
- Caution is necessary in use of combinations not adequately tested in clinical trials or pharmacokinetic evaluations

Interactions Between ARV Drug Pairs Requiring Dosing Alteration or Avoidance (cont'd)

- Example: Combined use of tenofovir/didanosine, an alternative 2-NRTI backbone in initial therapy, requires reduction in enteric-coated didanosine dose to 250 mg, due to increase in didanosine levels with tenofovir use

Interactions Between ARV Drug Pairs Requiring Dosing Alteration or Avoidance

Drug 1	Drug 2	Results	Panel Suggestion
Zidovudine	Stavudine	Intracellular antagonism	Do not combine
Stavudine	Didanosine	Toxicity (peripheral neuropathy, lactic acidosis)	Avoid, especially during pregnancy
Lamivudine	Emtricitabine	Similar drugs	Do not combine
Tenofovir	Enteric-coated Didanosine	↑ ddi level	↓ ddi to 250 mg
Tenofovir	Atazanavir	↑ TDF level, ↓ ATV	Add RTV boosting
Delavirdine	Amprenavir	↑ APV level	Avoid, or ↓ APV dose
Delavirdine	Indinavir	↑ IDV level	Avoid, or ↓ IDV dose
Delavirdine	Saquinavir	↑ SQV level	↓ SQV dose

Interactions Between ARV Drug Pairs Requiring Dosing Alteration or Avoidance (cont'd)

Slide #30

Drug 1	Drug 2	Results	Panel Suggestion
Efavirenz	Indinavir	↓ IDV level	↑ IDV dose
Efavirenz	Lopinavir/ritonavir	↓ LPV level	↑ LPV and RTV dose to twice daily
Efavirenz	Nevirapine	↓ EFV level	Not recommended
Efavirenz	Ritonavir	↑ EFV and RTV levels	↓ RTV dose
Efavirenz	Amprenavir	↓ APV level	Add RTV boosting
Efavirenz	Atazanavir	↓ ATV level	Add RTV boosting
Efavirenz	Saquinavir	↓ SQV level	Add RTV boosting

Interactions Between ARV Drug Pairs Requiring Dosing Alteration or Avoidance (cont'd)

Drug 1	Drug 2	Results	Panel Suggestion
Nevirapine	Lopinavir/r	↓ LPV level	↑ LPV and RTV dose to twice daily
Nevirapine	Indinavir	↓ IDV level	↑ IDV dose or add RTV boosting
Nevirapine	Saquinavir	↓ SQV level	Add RTV boosting
Nelfinavir	Saquinavir	↑ NFV level	↓ SQV dose
Atazanavir	Indinavir	Hyperbilirubinemia	Do not combine
Fosamprenavir or Amprenavir	Lopinavir/r	↓ APV and LPV levels	Avoid unless doses can be adjusted according to plasma concentrations of APV and LPV
Fosamprenavir	Amprenavir	Similar drugs	Do not combine

Changing Therapy: Considerations for Toxicity

- For toxicity known to be due to single agent, single agent substitution may be indicated
- For toxicity that can't be ascribed to single drug that is severe enough to warrant discontinuation, all agents should be stopped; introduce new regimen after resolution of toxicity
 - Staggered discontinuation of drugs with different half-lives should be considered to avert resistance; but clinical relevance unknown

Changing Therapy: Considerations for Toxicity (cont'd)

- For PI-associated lipid abnormalities, manage abnormalities if benefit of maintaining PI outweighs risk of changing
 - If drug-susceptible virus at baseline, switch to NNRTI can be considered
- For fat maldistribution syndromes, early switching of responsible drug(s) is recommended if drug options exist

Changing Therapy: Considerations for Treatment Failure—First Regimen Failure

- Adherence, adherence, adherence
- First regimen failure
 - Resistance testing for plasma viral load >500 to 1000 HIV RNA copies/mL
 - Alter regimen if resistance is documented
 - Target for new therapy is <50 copies/mL (below detection)

Changing Therapy: Considerations for Treatment Failure—Subsequent Failure

- If durable suppression of plasma viral load to <50 HIV RNA copies/mL is not considered achievable, goal is to maintain immunologic integrity and prevent clinical disease progression
- Evaluate drug options that remain based on resistance testing and treatment history, plasma viral load, CD4+ count

Changing Therapy: Considerations for Treatment Failure—Subsequent Failure (cont'd)

- Strong consideration should be given to change if a new regimen containing at least 2 or 3 active drugs can be constructed, so that further drug resistance compromising entire drug classes can be avoided
- If such a regimen cannot be constructed, change can be deferred unless imminent risk of opportunistic disease is considered high

Changing Therapy: Considerations for Treatment Failure—Subsequent Failure

- In context of NRTI/NNRTI resistance or intolerance, use of double boosted PIs has been proposed. Paucity of data on pharmacokinetic interactions, tolerance, and long-term adverse effects for most combinations warrants extreme caution.
 - Do not combine drugs without knowing interactions—eg, coadministration of lopinavir/r and fosamprenavir lowers levels of both
 - Insufficient data to currently recommend therapeutic drug monitoring

Changing Therapy: Considerations for Treatment Failure—Subsequent Failure (cont'd)

- For discordant response (suppressed viral load, blunted CD4+ response), check medications for hematologic toxicity; changing/intensifying regimen has not been shown to affect CD4+ response
- Strategic/structured treatment interruptions not currently recommended

Changing Therapy: New Drugs—Enfuvirtide

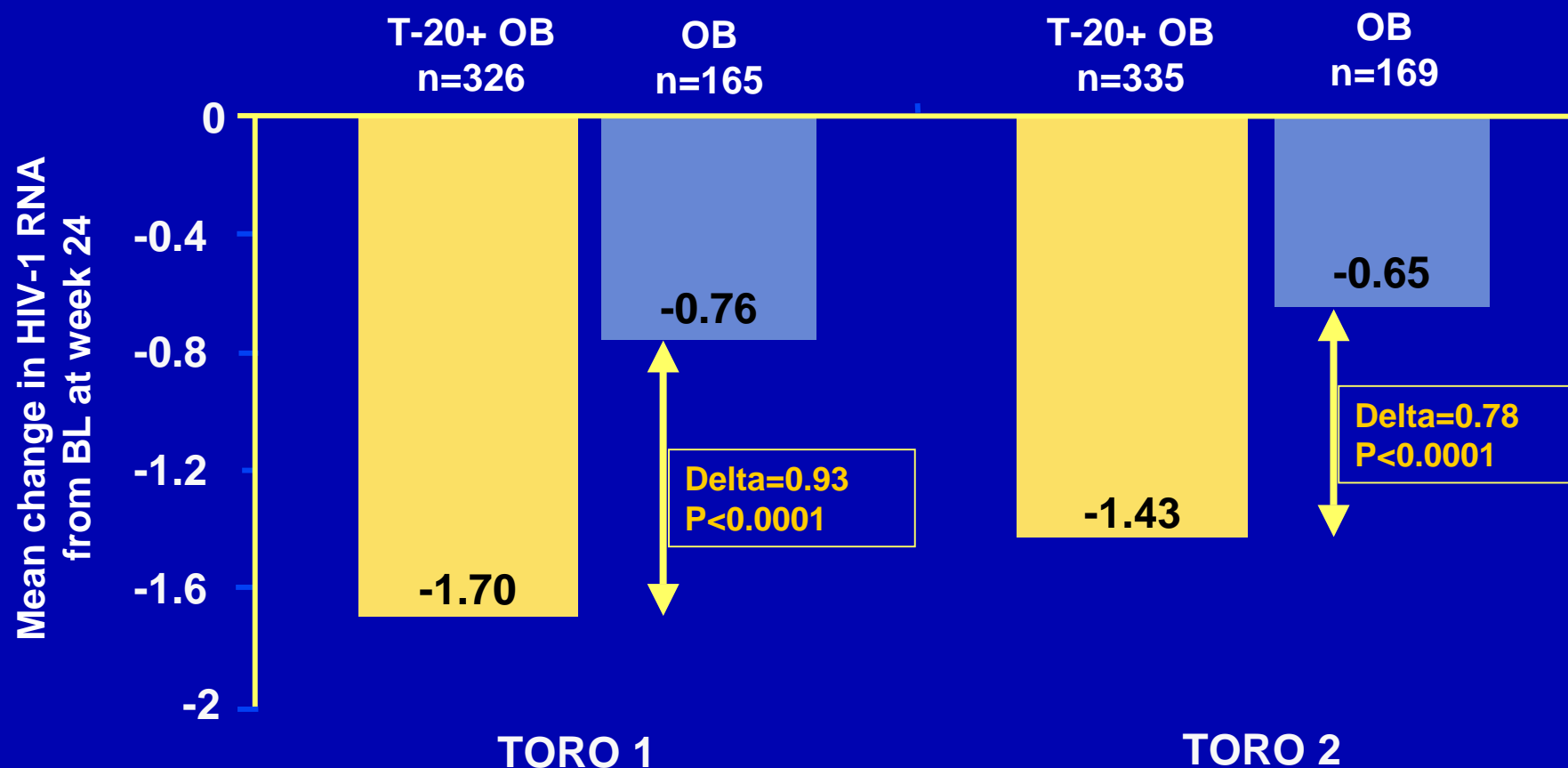
- HIV fusion inhibitor administered SC
- Assessed in two large-scale phase III trials (*TORO 1 and 2) in patients with advanced disease (median CD4+ 90/ μ L), with multiple previous and current treatment failure (median of 12 prior drugs), and with median plasma HIV RNA of 130,000 copies/mL
- Patients randomized to optimized background (OB) therapy +/- enfuvirtide

* Lalezari et al, *NEJM*, 2003; Lazzarin et al, *NEJM*, 2003.

Changing Therapy: New Drugs—Enfuvirtide

- At 48 weeks, enfuvirtide associated with significantly greater reduction in viral load—1.48 \log_{10} vs 0.63 \log_{10}
- Well tolerated except for frequent injection site reactions; hypersensitivity reactions <1%; more frequent bacterial pneumonia (6.6% vs 0.6%)
- Analysis of combined database showed viral load <400 copies/mL at 24 weeks in 37.4% with enfuvirtide vs 16.2% without enfuvirtide ($P<0.001$)

TORO 1 and 2: Virologic Responses

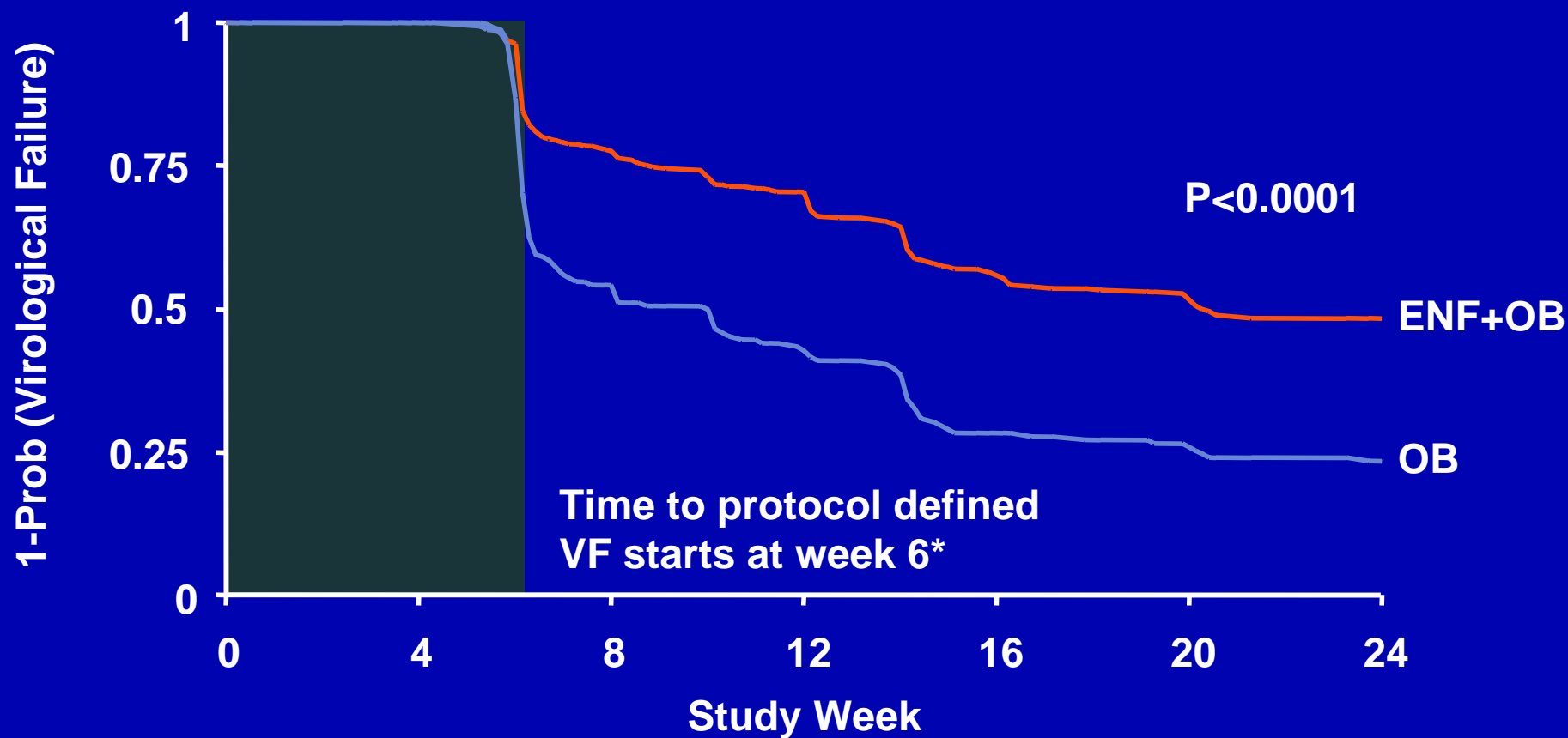


* Lalezari et al, *NEJM*, 2003; Lazzarin et al, *NEJM*, 2003.

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TORO 2: Secondary Analysis

Time to Virological Failure



* For definition of virologic failure, see poster LbOr19a

Lazzarin et al, *NEJM*, 2003.

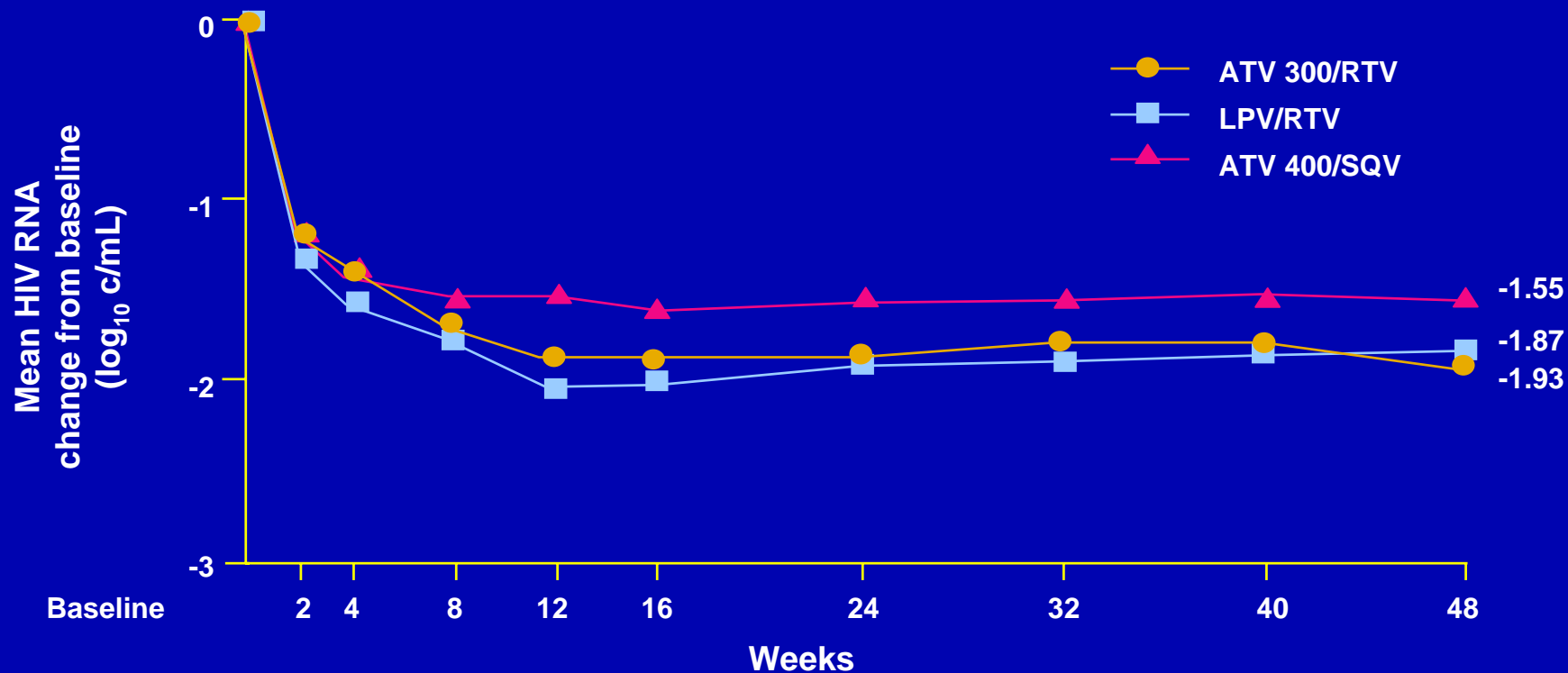
Changing Therapy: New Drugs—Atazanavir

- Atazanavir 300 mg/d plus low-dose ritonavir (100 mg/d) produced viral load reduction at 24 weeks comparable to that with lopinavir/r in patients with failure on multiple antiretroviral regimens (BMS 045 study)
- Other data indicate that unboosted atazanavir is inferior to lopinavir/r in reducing viral load (Gulick et al, *NEJM*, 2004)

Changing Therapy: New Drugs— Atazanavir (cont'd)

- The atazanavir/r combination was associated with less elevation of plasma lipids than lopinavir/r or atazanavir/saquinavir in BMS 045
- Note in particular that use of tenofovir decreases oral bioavailability of atazanavir; atazanavir should always be boosted with ritonavir in regimens containing tenofovir

Mean Change in HIV RNA Through Week 48



Time Averaged Difference Estimate:

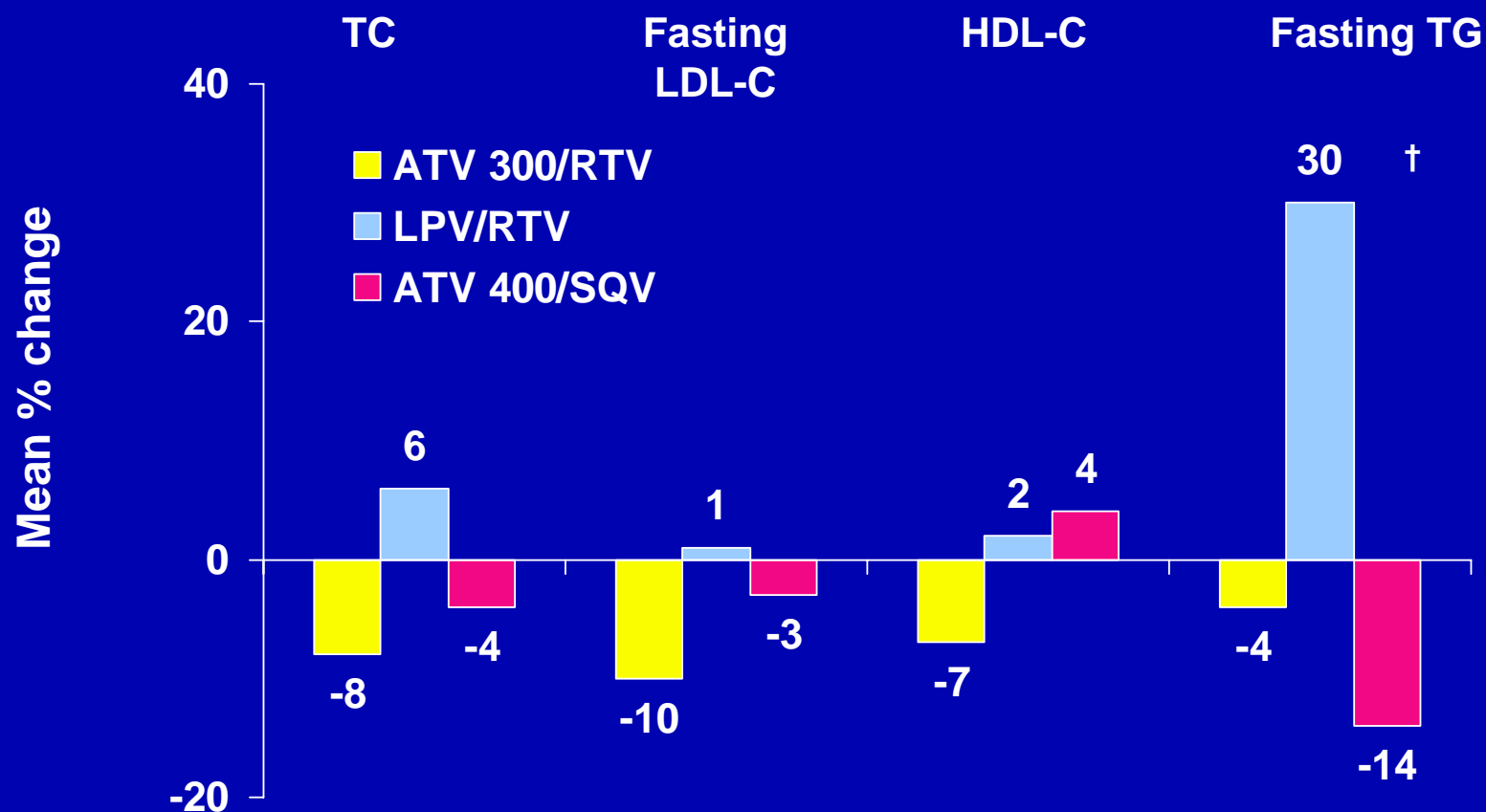
ATV 300/RTV – LPV/RTV: 0.13 log₁₀ c/mL (97.5% CI: -0.12, 0.39)

ATV 400/SQV – LPV/RTV: 0.33 log₁₀ c/mL (97.5% CI: 0.07, 0.60)

The mean change in HIV RNA from baseline at week 2 was similar between regimens (-1.18 log₁₀ copies/mL for the ATV 300/RTV group, -1.31 log₁₀ copies/mL for the LPV/RTV group, and -1.14 log₁₀ copies/mL for the ATV 400/SQV group)

BMS 045

Mean % Change in Lipids from Baseline to Week 48*



*Patients on lipid-lowering therapy excluded

†Both ATV regimens vs LPV/RTV: $P \leq 0.005$

DeJesus, 11th CROI, San Francisco, 2004, # 547

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Changing Therapy: New Drugs— Fosamprenavir

- Prodrug of amprenavir with greater bioavailability
- In the CONTEXT study in PI-experienced patients with treatment failure, fosamprenavir with low-dose ritonavir twice daily had activity and tolerability similar to lopinavir/r at 24 weeks

Changing Therapy: Role of New Drugs in Treatment-Experienced Patients

Enfuvirtide

- Timing of use involves considering its inconvenience (generally acceptable in patients with limited options) and high cost
- Best considered at time of 2nd, 3rd, or 4th failure, depending on number of active drugs that remain as options
- Incremental, functional monotherapy should be avoided whenever possible
- No evidence that enfuvirtide can be discontinued without viral rebound in patients achieving plasma viral load below detection limits

Changing Therapy: Role of New Drugs in Treatment-Experienced Patients (cont'd)

Atazanavir

- Atazanavir should be boosted with ritonavir when used in treatment-experienced patients
- Role of atazanavir in multiple treatment failure is unknown
- Use should be guided by resistance testing results

Changing Therapy: Role of New Drugs in Treatment-Experienced Patients (cont'd)

Fosamprenavir

- Fosamprenavir should be boosted with ritonavir and given twice daily, especially in setting of multidrug-resistant virus
- Use should be guided by resistance testing results

Conclusions

- Antiretroviral therapy remains a rapidly evolving and challenging area of HIV medicine
- The field will continue to evolve with additional insights into pathogenesis and new drug development
- New agents in existing classes (eg, D-d4FC, SPD-754, TMC-125, tipranavir, TMC-114) and in new classes (eg, CCR5 inhibitors, integrase inhibitors, maturation inhibitors) that have reached clinical testing provide hope that new treatment options will be available in the next few years

Conclusions (cont'd)

- Clinicians and patients are confronted with the contrast of increasingly complex individualization of treatment in the developed world and massive antiretroviral implementation programs ongoing or planned in the developing world
- The principles of pathogenesis and treatment learned in both settings can ultimately contribute to improved care for all