Optimal management of the antiretroviral-naive HIV-infected patient:

Possible strategies for a correct sequencing of cART

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Available ARVs: 2012

NRTI/NtRTI	NNRTI	Protease	Fusion
Tenofovir[4]	**Efavirenz[6]**	Darunavir	Enfuvirtide
3TC[2]	Nevirapine	Atazanavir	
FTC[5]	Etravirine	**Lopinavir/r**	**Integrase**
Abacavir[3]	Rilpivirine	Saquinavir	Raltegravir
ZDV[1]		Fosamprenavir	
ddI		Nelfinavir	**CCR5**
		Indinavir	Maraviroc
		Tipranavir	

Combivir[1,2], Trizivir[1,2,3], Kivexa[2,3], Truvada[4,5], Atripla[4,5,6]

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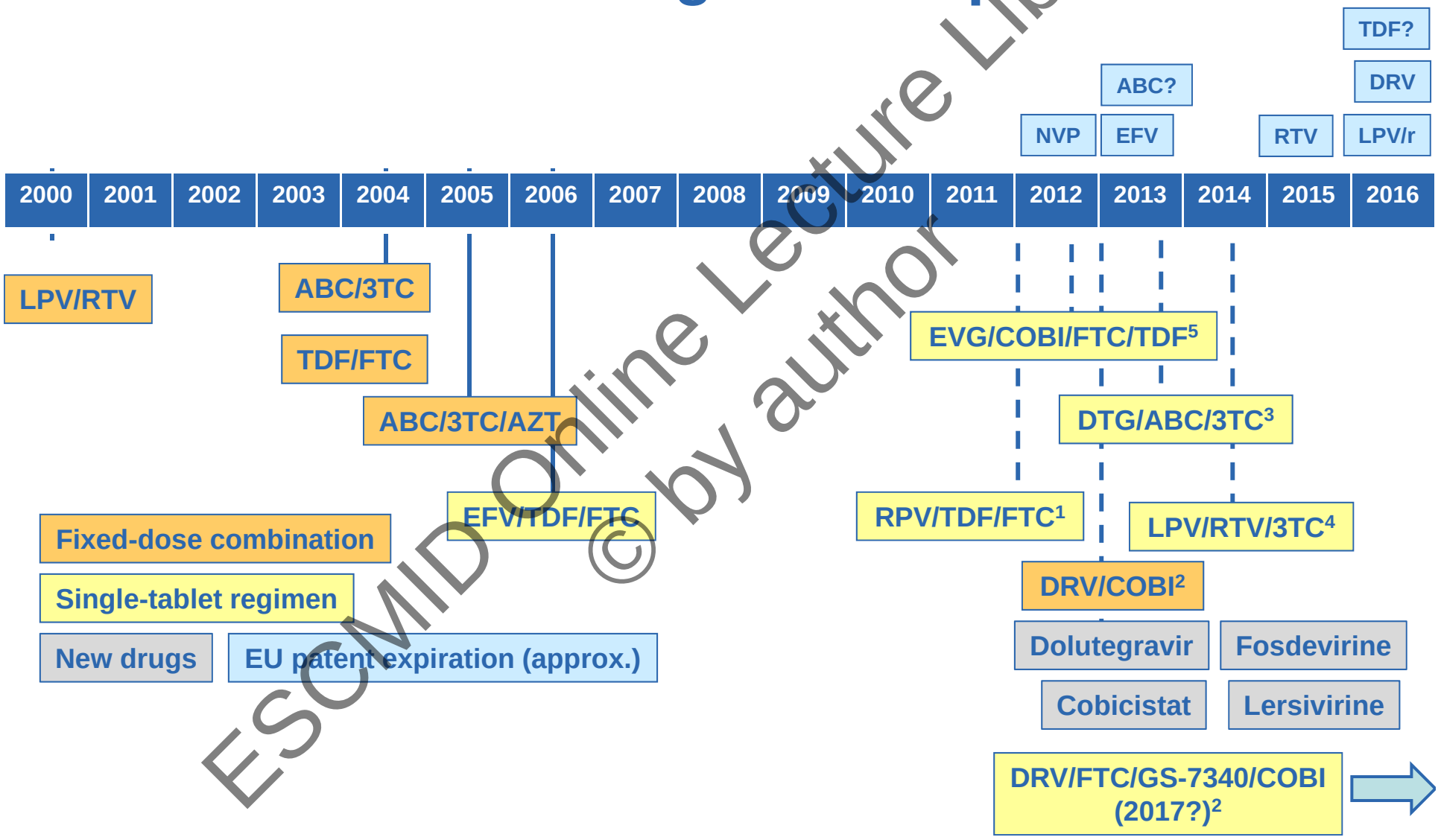
An evolving landscape



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www.clinicaltrials.gov and

Considerations for Selecting first-line therapy "Sequencing not a factor?"

Patient factors	Antiretroviral drug factors
Readiness	**EFFICACY**
	Baseline drug susceptibility/resistance
Baseline CD4+ cell count/HIV-1 RNA	Tolerability
Age	Long-term toxicity, metabolic
Sex	Drug interactions
Occupation (night shifts)	Dosing frequency
Comorbidity	Pill burden
Plans for pregnancy	Pharmacokinetics
Access to care	Cost
Co-medications (methadone, PPI)	
Adherence	Genetic: HLA B5701

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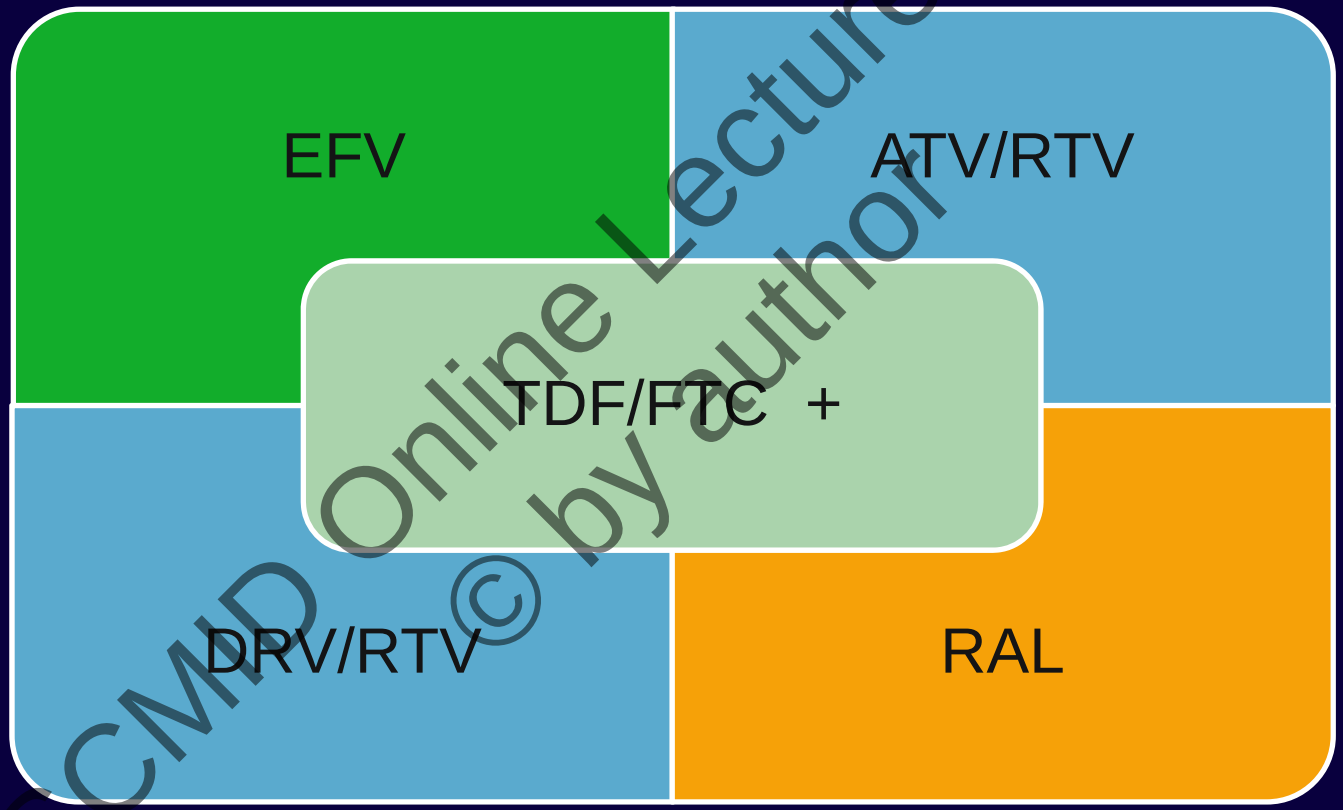
The Guidelines

Initial Regimen: Recommended/Preferred Agents



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Efavirenz primary end points Not beaten

Study	Comparator	Comparator Result
▪ECHO, THRIVE	▪Rilpivirine (TMC-278)	▪Non inferiority
▪STARTMRK	▪Raltegravir	▪Non inferiority
▪MERIT	▪Maraviroc	▪Not-Non inferiority. Non-inferiority
▪ACTG 5202	▪Atazanavir/ritonavir	▪Equivalence not shown
▪ACTG 5142	▪Lopinavir/ritonavir	▪Inferioritiy
▪2NN	▪Nevirapine	▪Not-Non inferiority
▪CLASS	▪Amprenavir/ritonavir	▪Inferiority
▪FOCUS	▪Saquinavir/ritonavir	▪Inferiority
▪ACTG 5095	▪Abacavir	▪Inferiority

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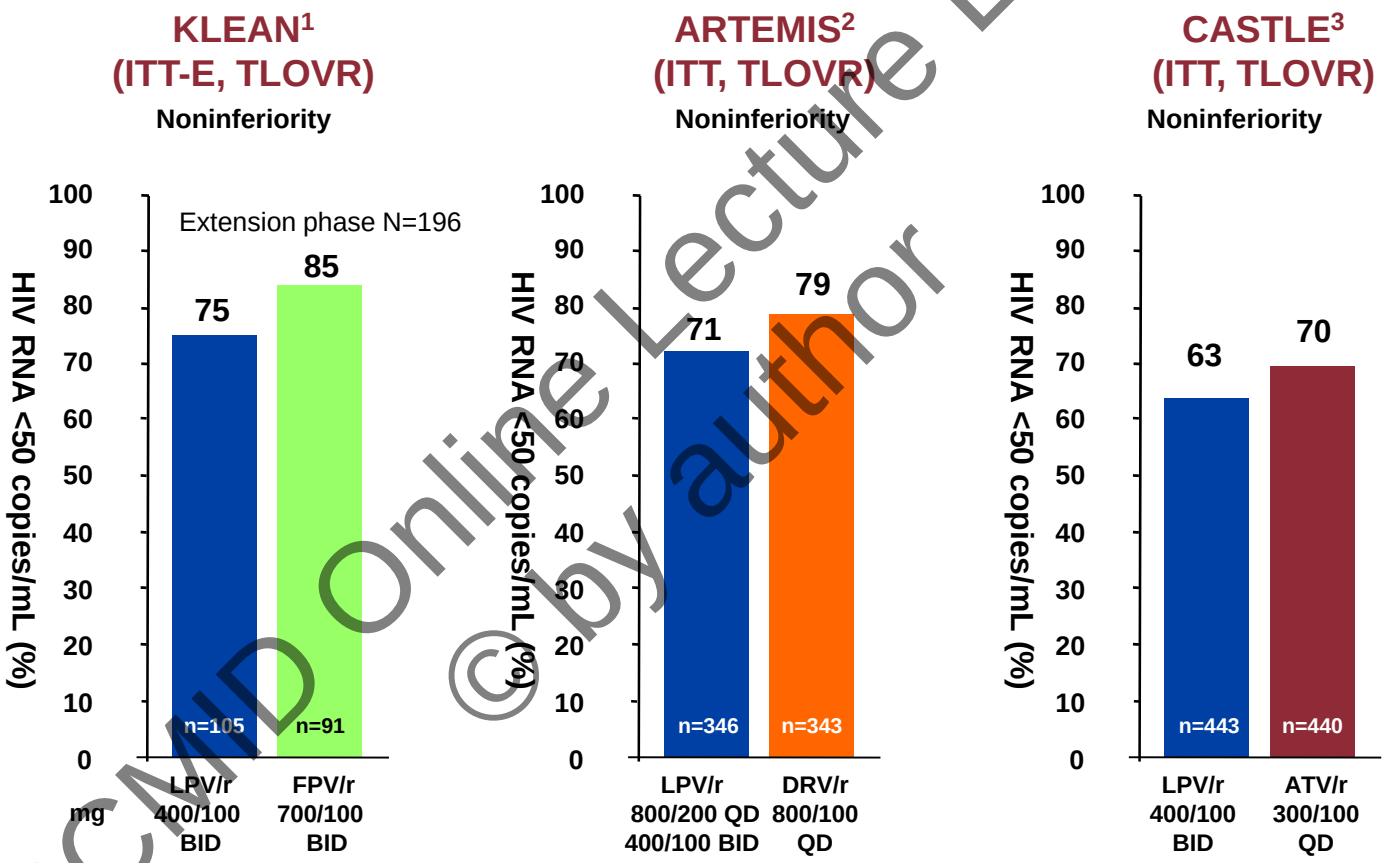
PI/r Which has best efficacy in ARV-naïve patients?

Virological suppression at 96 weeks



Data in figures are from different studies and cannot be compared directly
ITT, intent-to-treat; ITT-E, intent-to-treat exposed; M=NR, missing = non-response; NC=F, non-completer = failure; TLOVR, time to loss of virological response

Adapted from: 1. Pulido F, et al. 47th ICAAC Chicago, 17–20 Sept, 2007; Abstract H-361; 2. Mills A, et al. 48th ICAAC. Washington DC, Oct 25–28, 2008. Abstract H-1250c; 3. Molina JM, et al. 48th ICAAC. Washington, DC, Oct 25–28, 2008. Abstract H-1250d

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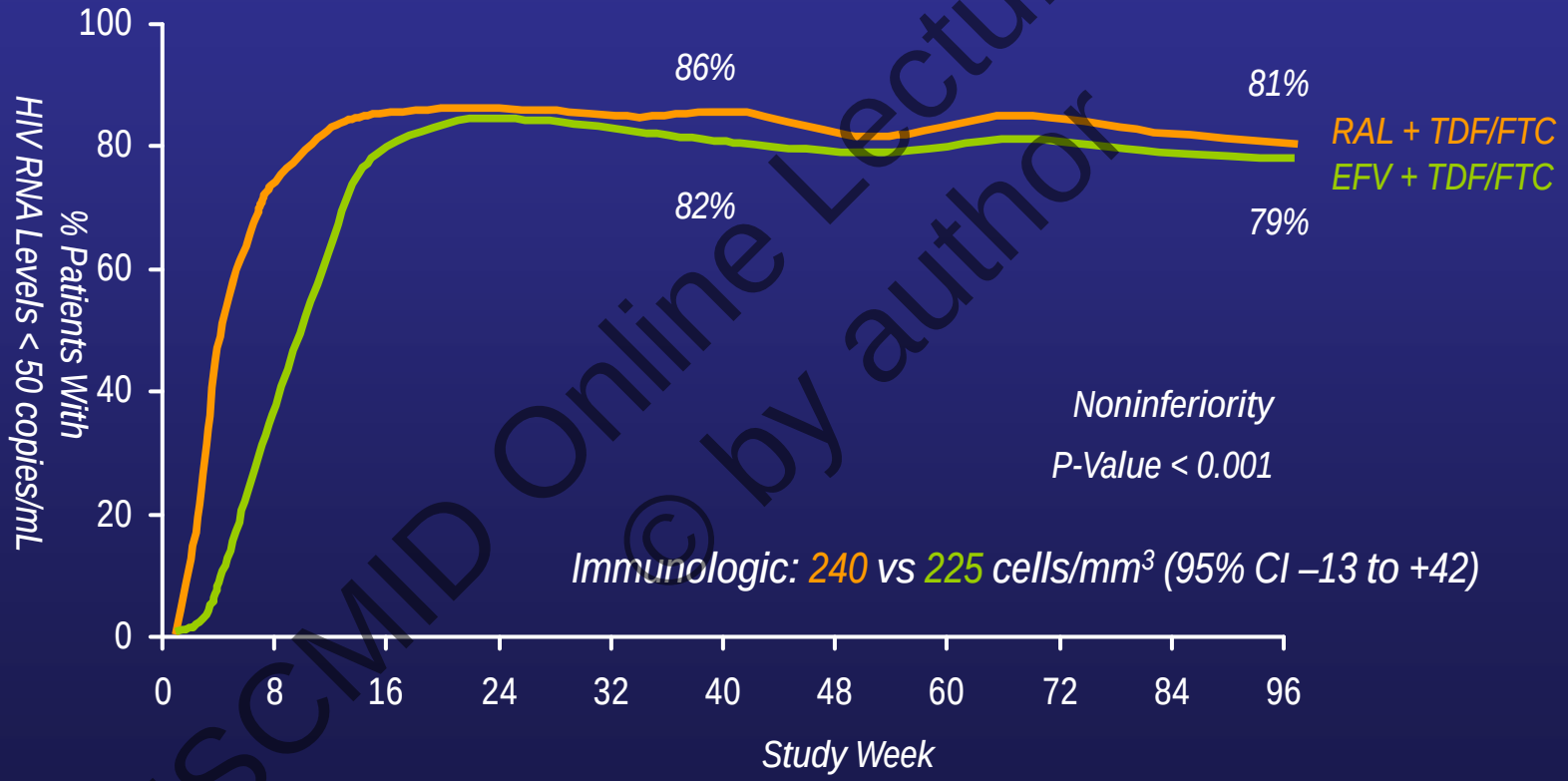
STARTMRK: Raltegravir vs Efavirenz 96 week

Patients with HIV RNA < 50 copies/mL through 96 weeks (Noncompleter = Failure)



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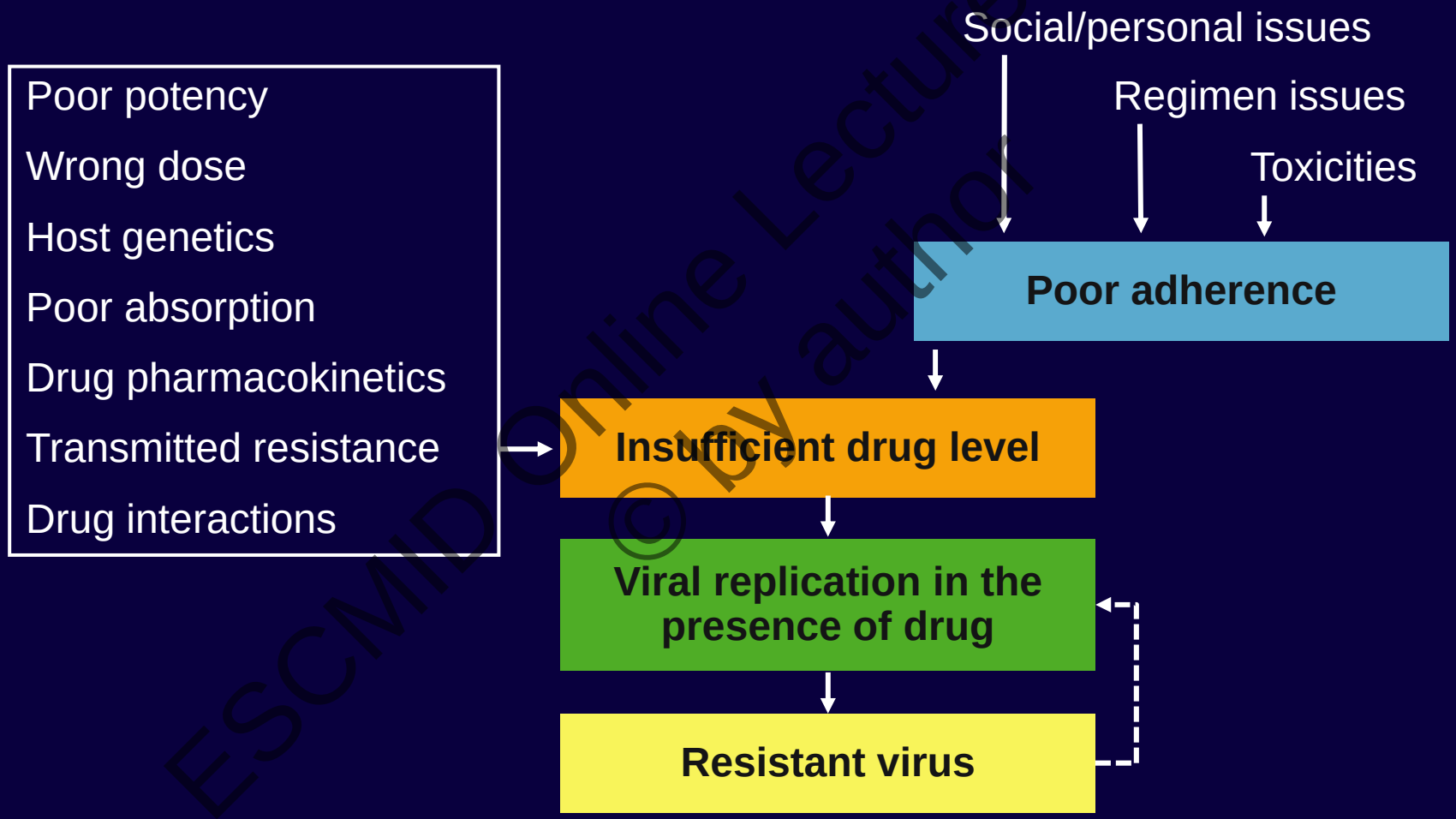
Lennox J, et al. Presented at: 49th Annual ICAAC; September 12-15, 2009; San Francisco, CA. Abstract H-924b.

Causes of ARV Treatment Failure
Few patients fail with resistant mutations



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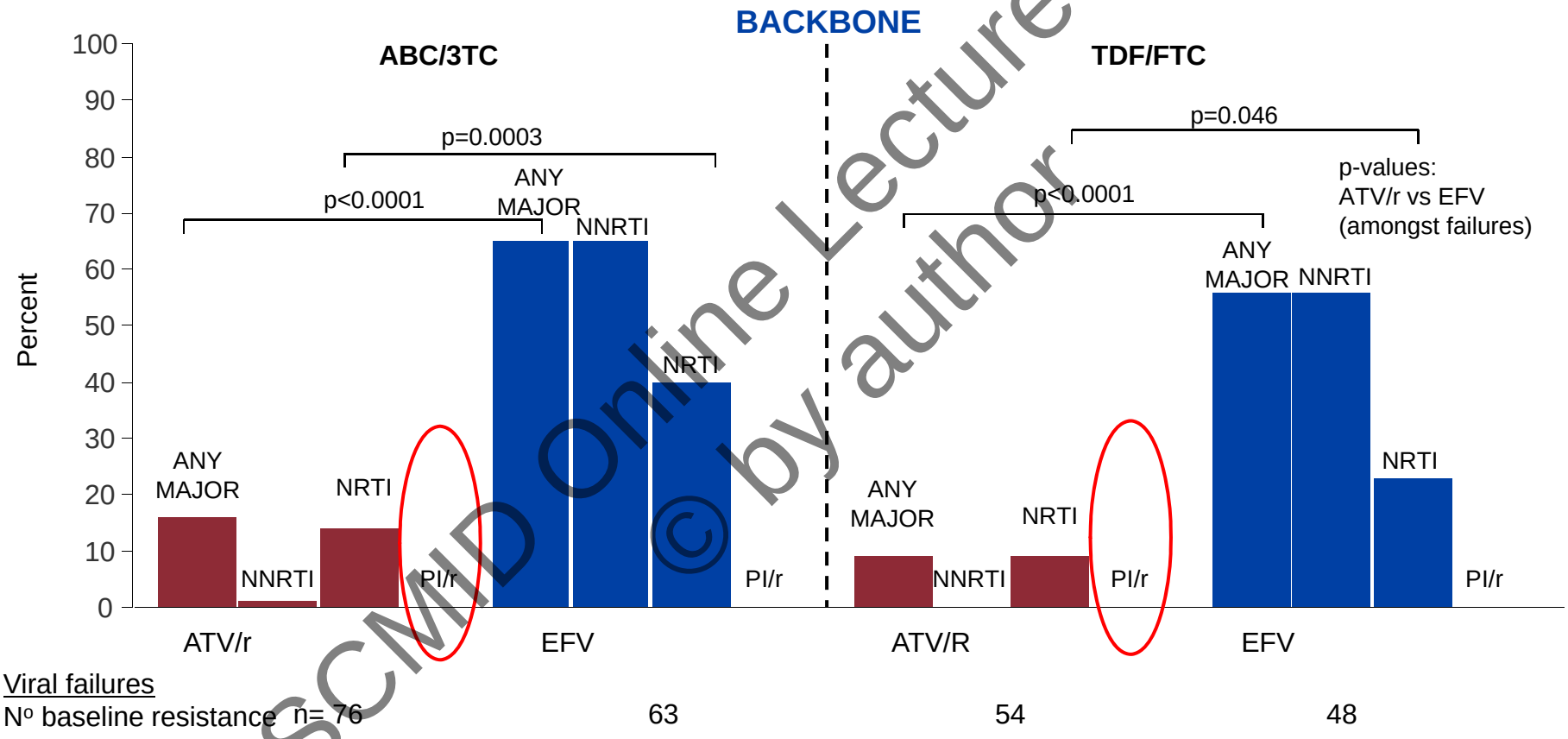
ACTG 5202:

ATV/r or EFV in Combination with ABC/3TC or TDF/FTC in Antiretroviral Naïve Patients

Total (n=1857)



Viral failures

Nº baseline resistance n= 76 63 54 48

*Major mutations defined by IAS-USA (2008) list plus T69D, L74I, G190C/E/Q/T/V for RT and L24I, F53L, I54V/A/T/S and G73C/S/T/A for PR

Daar E et al. 17th CROI 2010, San Francisco, California, USA. Oral presentation 59LB

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Resistance Consequences of Initial PI-Based Regimen Failure

Likely (> 30%) Less likely (10% to 30%) Rare (< 10%) or none

DHHS "Preferred" and/or IAS-USA "Recommended" Regimens	HIV-1 RNA < 50 copies/mL at Wk 48, %	Detectable Resistance at VF*		
		NRTI		PI
		M184V/I	Other	
ATV/RTV, TDF/FTC	78 (n = 440)[1]			
	89 (n = 465)[2]†			
DRV/RTV, TDF/FTC	84 (n = 340)[3]			

*For patients with available baseline and postfailure genotypes. †96 weeks

1. Molina JM, et al. Lancet. 2008;372:646-655 2. Daar E, et al. CROI 2010 59 LB. 3. Ortiz R, et al. AIDS. 2008;22:1389-1397.

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Resistance After Virologic Failure in the STARTMRK Trial at 96 Wks

Resistance in Patients With Virologic Failure	RAL + TDF/FTC (n = 281)	EFV + TDF/FTC (n = 282)
Virologic failure confirmed, n	39	45
Genotype obtained, n	16	11
RAL RAMs, n	4 (Q148H + G140S; Q148R + G140S; Y143H + L74L/M + E92Q + T97A; Y143R)	0
EFV RAMs, n	0	6
Resistance to FTC, n	2	2

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Lennox J, et al. ICAAC 2009. Abstract H924b.

Should we sequence based on resistance ?

- Very few patients fail with resistant mutations
- All first line recommended combinations might fail with the 184V/I mutation +/- K65R losing the utility of FTC ,3TC +/- tenofovir
- Fail with efavirenz might stay with NNRTI class eg etravirine
- Fail with boosted PI then can continue

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Resistance to FTC/3TC what can you use?

NRTI/NtRTI	NNRTI	Protease	
Tenofovir	Efavirenz	Darunavir	
ZDV	Nevirapine	Atazanavir	
ddI	Etravirine		Integrase
	Rilpivirine		Raltegravir
			CCR5
			Maraviroc

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Resistance to Tenofovir and FTC/3TC what can you use?

NRTI/NtRTI	NNRTI	Protease	
ZDV	Efavirenz	Darunavir	
	Nevirapine	Atazanavir	
	Etravirine		Integrase
	Rilpivirine		Raltegravir
			CCR5
			Maraviroc

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Resistance to Tenofovir and FTC/3TC +Resistance to efavirenz -what can you use?

NNRTI	Protease	
	Darunavir	
	Atazanavir	
Etravirine		Integrase
Rilpivirine?		Raltegravir
		CCR5
		Maraviroc

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Resistance to Tenofovir and FTC/3TC +Resistance to PI/r -what can you use?

NNRTI	Protease	
Efavirenz	Darunavir	
	Atazanavir	
Etravirine		Integrase
Rilpivirine?		Raltegravir
		CCR5
		Maraviroc

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Resistance to Tenofovir and FTC/3TC +Resistance to Integrase -what can you use?

NNRTI	Protease	
Efavirenz	Darunavir	
	Atazanavir	
Etravirine		
Rilpivirine?		
		CCR5
		Maraviroc

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After first failure what should we do?

- Very few patients fail with resistant mutations-perhaps deep sequencing will find more
- But if they do and have mutations to the nucleoside backbone …
- No one really wants to use ZDV or DDI
- So if no tenofovir resistance re use tenofovir with a boosted PI
- Use a combination of other drugs

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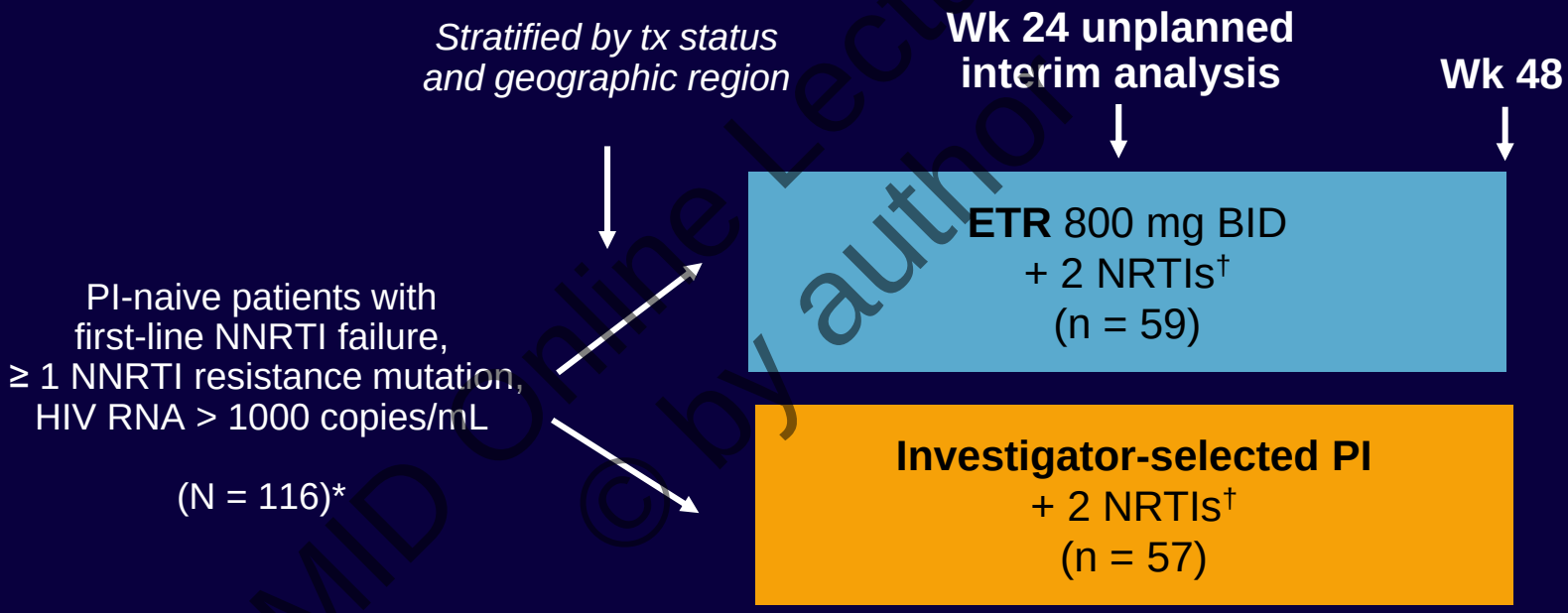
Don’t sequence to continue nucleosides and a drug with low genetic barrier to resistance

TMC125-C227: ETR vs PI in Patients With First-line NNRTI Failure, Resistance

- Exploratory phase II, randomized, controlled, open-label trial



*Majority of study population from resource-limited nations. Major centers: South Africa (41%), Brazil (23%), Thailand (16%), Mexico (2%); other patients from Spain, Russia, UK, Mexico.

†NRTIs selected using resistance testing. Most common: ZDV/ddI (17%), ZDV/TDF (16%), ZDV/3TC (12%).

Ruxrungtham K, et al. HIV Med. 2008;9:883-896.

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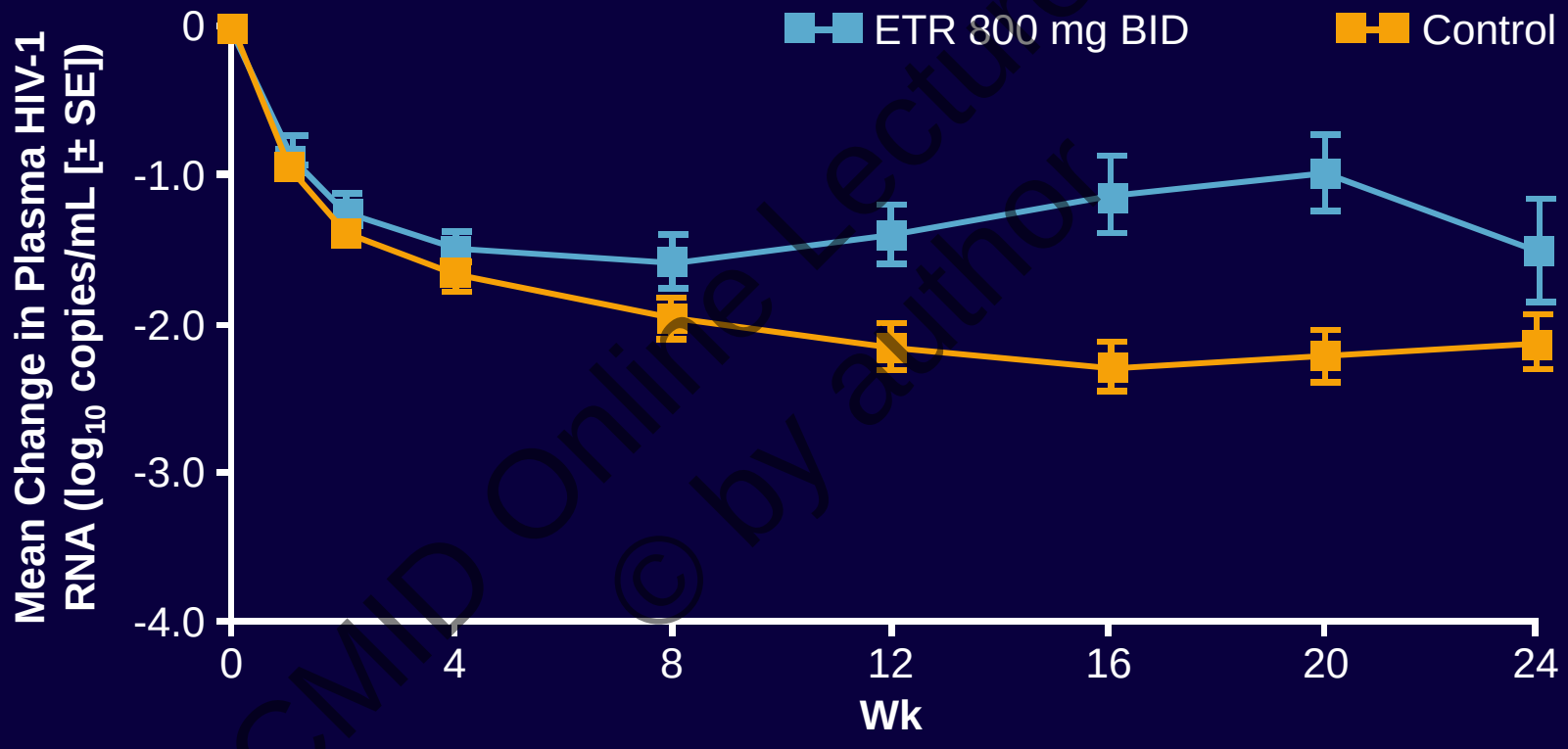
TMC125-C227: Virologic Response to ETR vs PI/r in NNRTI-Experienced Patients



ETR, n	59	55	47	40	28	17	8
Control, n	57	55	56	53	52	41	52

Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naive, nonnucleoside reverse transcriptase inhibitor-experienced patients: study TMC125-C227. Ruxrungtham K, et al. HIV Med. Vol ;9:883-896 .Copyright © 2009. Reproduced with permission of John Wiley & Sons, Inc..

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Second-Line Regimens: How Many Drugs? Which Drugs?

- At least 2, and preferably 3, active drugs should be in new regimen based on resistance testing
- To date, virtually all data/clinical experience reflect NRTI-containing second-line regimens
- Availability of 5 approved classes of antiretrovirals potentially allows use of 2 entirely new classes in second regimen
  - However, very few data on such regimens

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Second Line for nuke resistance

Nuke sparing/limiting regimens

- PI/r with raltegravir
- PI/r with maraviroc
- PI/r with single nucleoside

But all being tried in Naives!!

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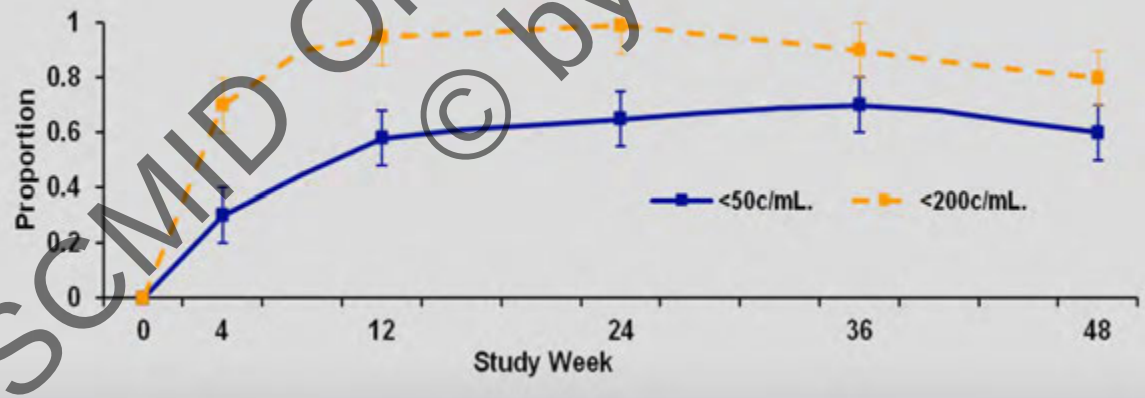
Darunavir/r + Raltegravir: NRTI Sparing Regimen for ARV-naïve Patients-ACTG A5262

Single arm study of DRV/r (800/100 mg) QD + RAL (400 mg BID) (N=112)		
Age (years)	Median (Q1,Q3)	36 (27, 45)
Sex	Male	98 (88%)
Race	White	49 (44%)
CD4 cell count (cells/mm^3)	<200 200<350 ≥350	40 (36%) 32 (29%) 40 (36%)
HIV-1 RNA (copies/mL)	≤100,000 ≥100,000	63 (56%) 49 (44%)

Proportion Of Subjects With HIV-1 RNA <200 and <50 copies/mL
(ITT analysis, missing/off study= ignored



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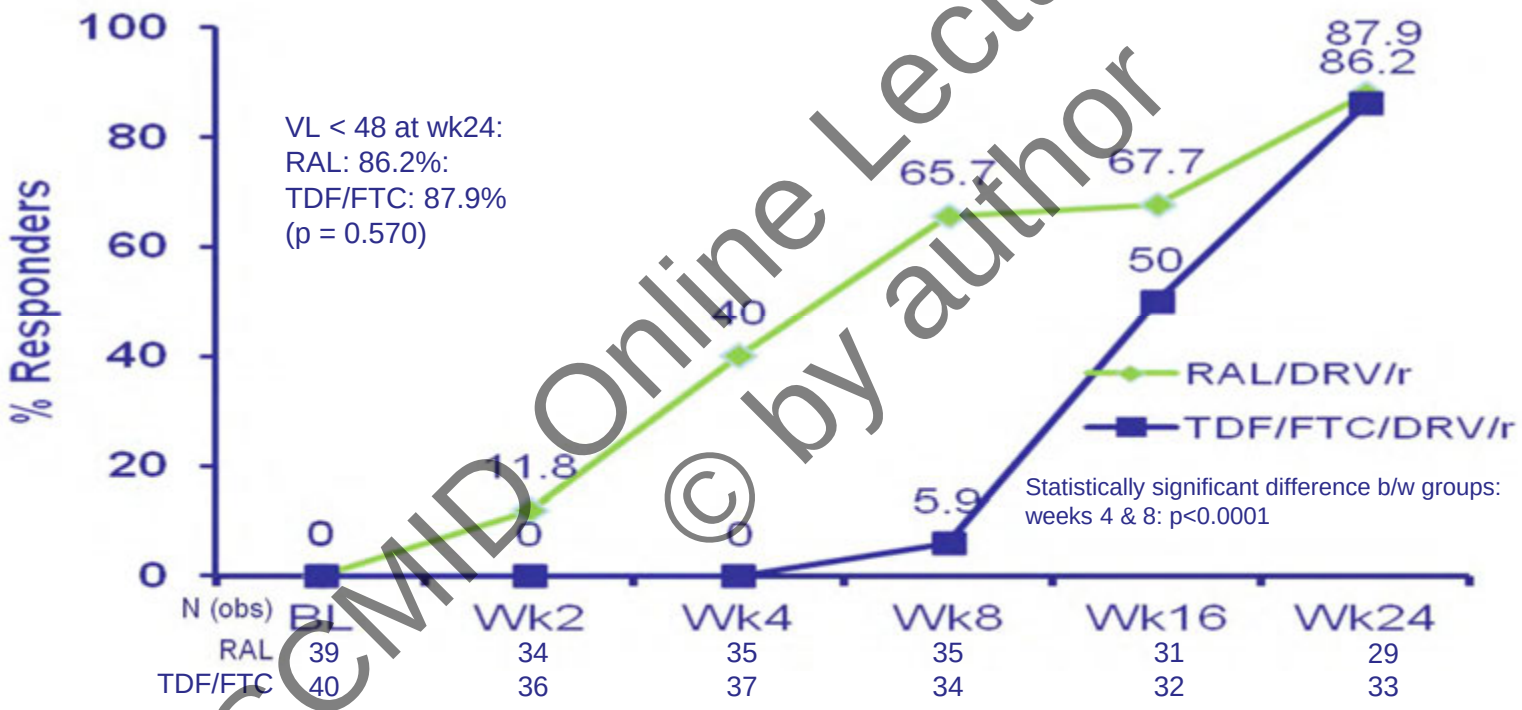
Taiwo B, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 551.

RADAR: Darunavir/RTV + Raltegravir vs Darunavir/RTV+TDF/FTC

Proportion of patients with HIV RNA < 48 c/mL through week 24 (NC=M)*



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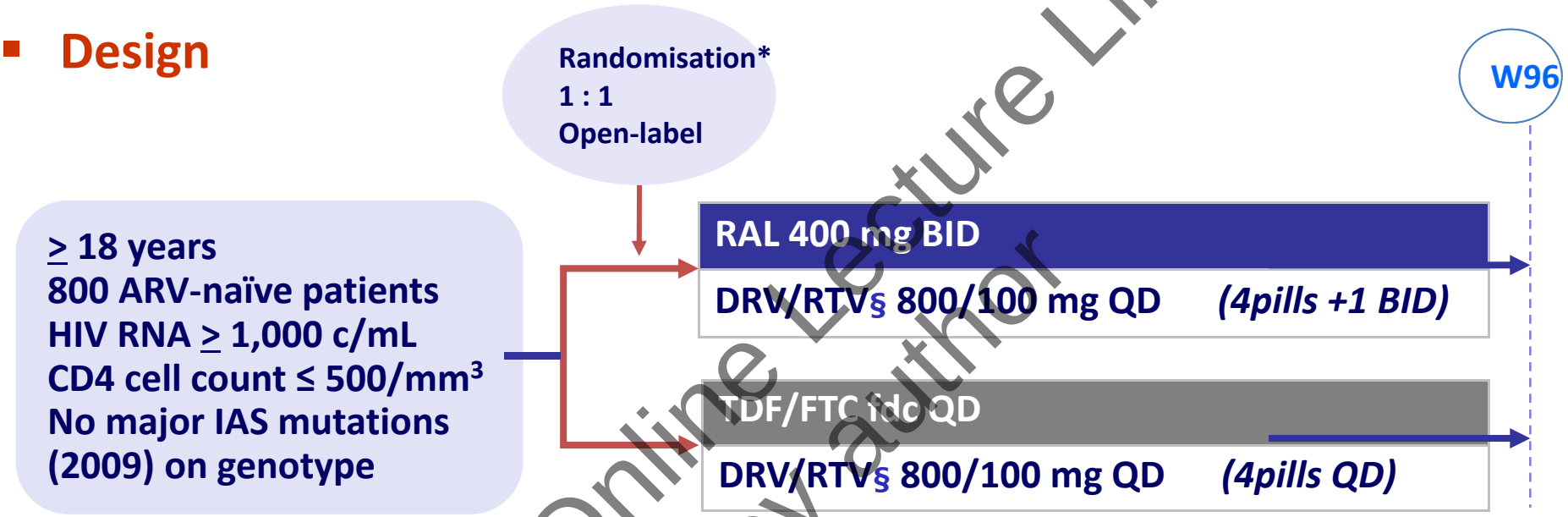
Bedimo R et al. IAS 2011. Abstract MOPE214.

NEAT 001/ANRS 143: Study design

- **Design**



Planned study duration : 96 weeks after enrolment of the last patient

*** Randomization will be stratified by:**

- Country
- Participation at viro-immunological sub-studyv

§ At starting point RTV old formulation will be used, an amendment for the use of heat-stable tablets of RTV will be presented during the trial

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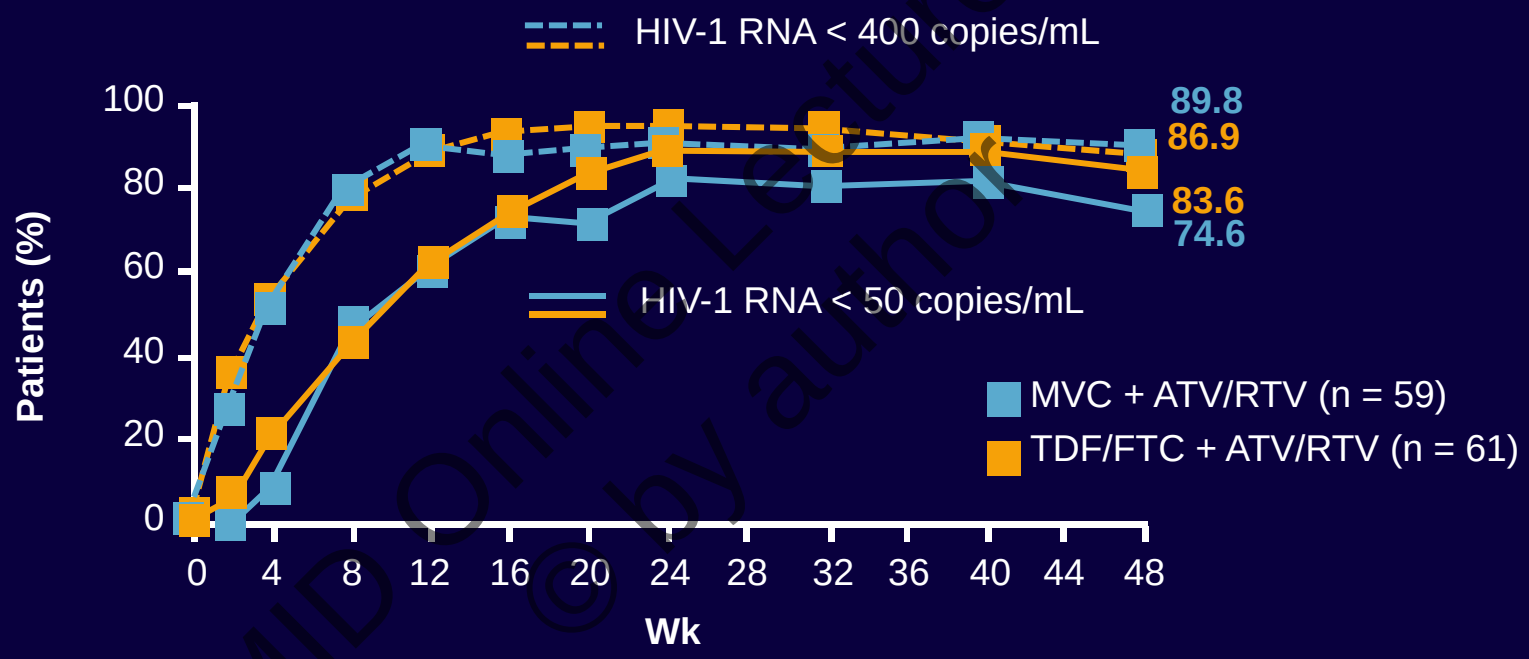
MVC vs TDF/FTC With ATV/RTV in ART-Naive Patients: Wk 48 Results



- **Frequency of all-grade adverse events similar between arms**
  - **Grade 3/4 adverse events, including hyperbilirubinemia, numerically higher in MVC arm**

Portsmouth S, et al. IAS 2011. Abstract TUAB0103.

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When to start antiretroviral therapy Should this influence sequencing of ARVs ?

CD4+ Cell Count	EACS	DHHS	IAS
▪< 350 cells/mm³	▪ Start	▪ Start	▪ Start
▪350-500 cells/mm³	▪ Start if…	▪ Start	▪ Start
▪>500 cells/mm³	▪ Generally deferred	▪ Start/Optional	▪ Considered

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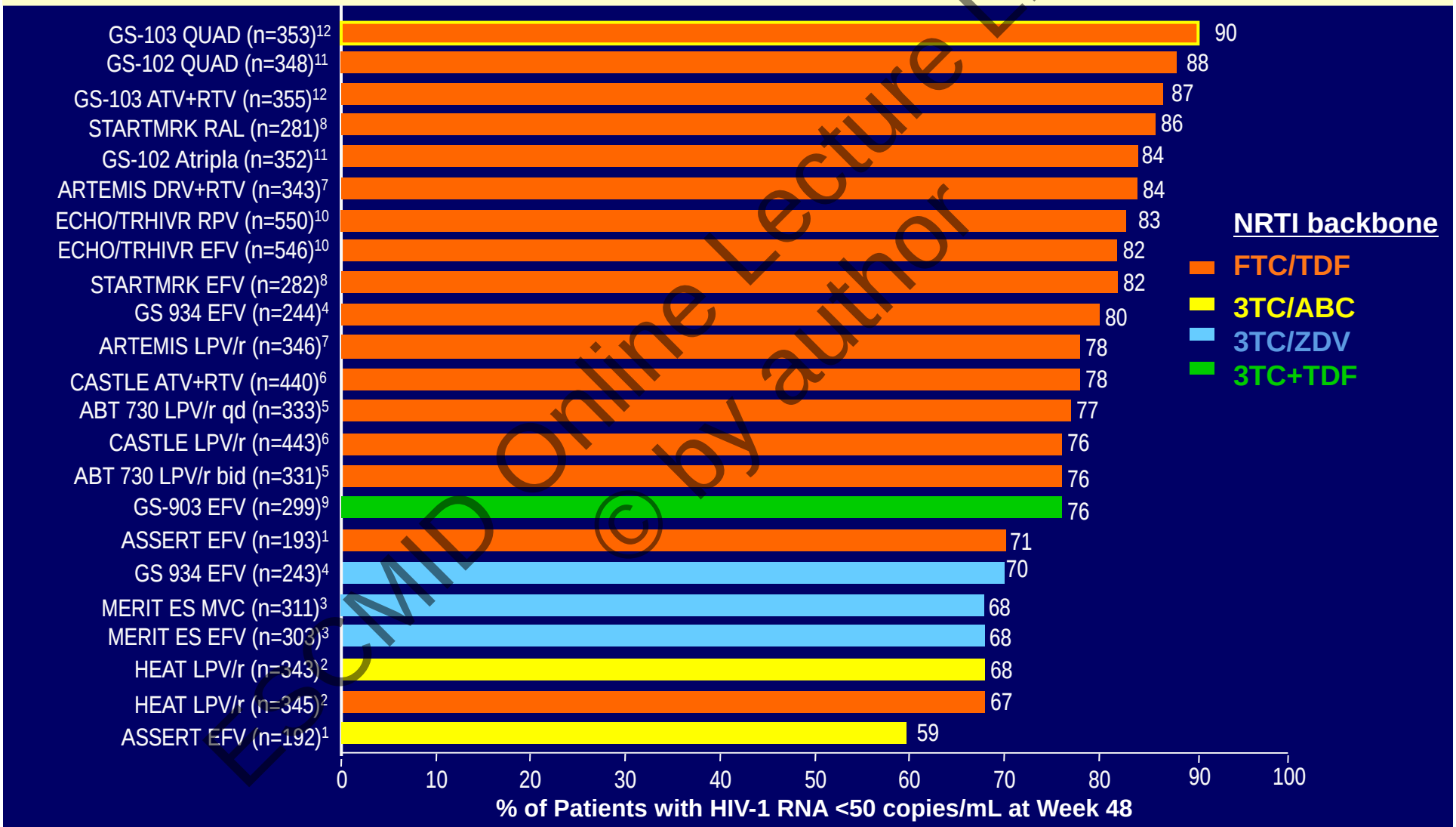
Background: Cross-Study Comparison of Treatment-Naive Clinical Trials

HIV RNA <50 copies/mL at Week 48



This slide depicts data from multiple studies published from 2004-2012. Not all regimens have been compared head-to-head in a clinical trial

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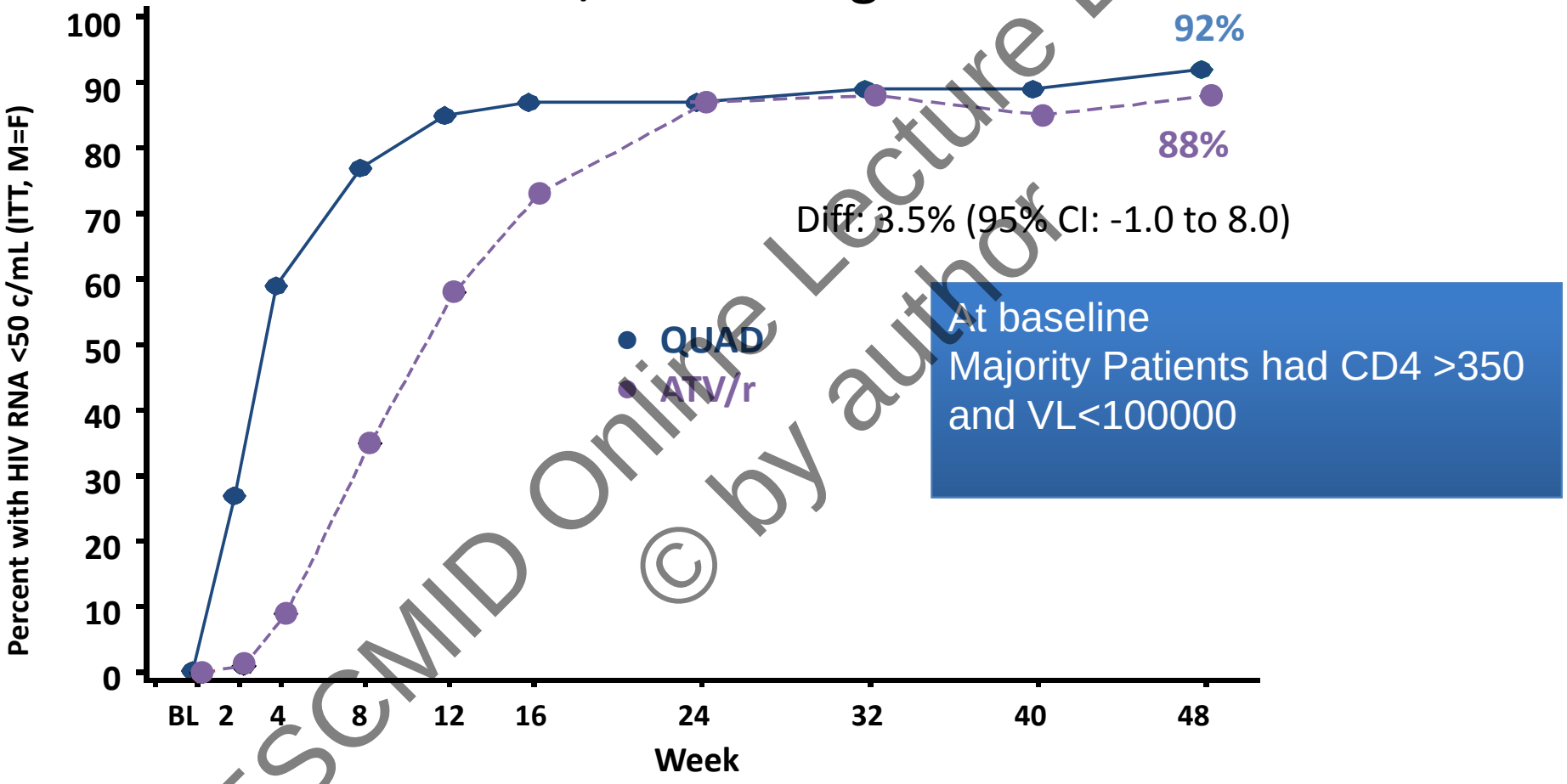
Elvitegravir/Cobicistat/FTC/TDF (Quad) vs. ATV/r + FTC/TDF (Study 236-103)

< 50 c/mL Through Week 48



Diff: 3.5% (95% CI: -1.0 to 8.0)

At baseline
Majority Patients had CD4 >350 and VL<100000

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Abacavir ,Rilpivirine, lopinavir
High Viral Load and Low CD4 count

It appears that there are more VFs in the high VL strata and if CD4 is low

Where do we place Abacavir ,rilpivirine and lopinavir in our treatment strategies?

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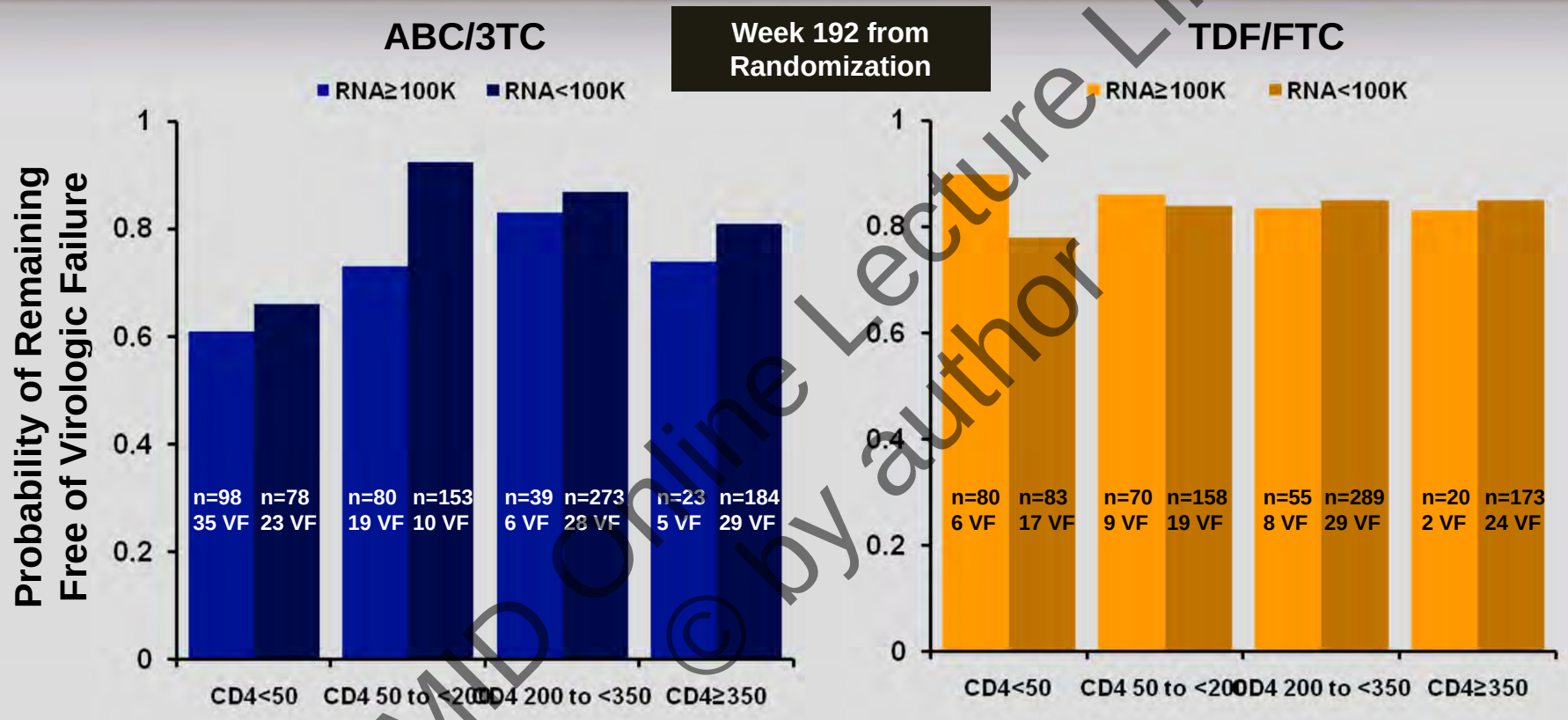
A5202: Time to Virologic Failure by Baseline Viral Load and CD4 Count



- Increased risk of VF with baseline lower CD4 or higher VL in those assigned ABC/3TC
- Results confirm previously reported analysis based on *screening* viral load

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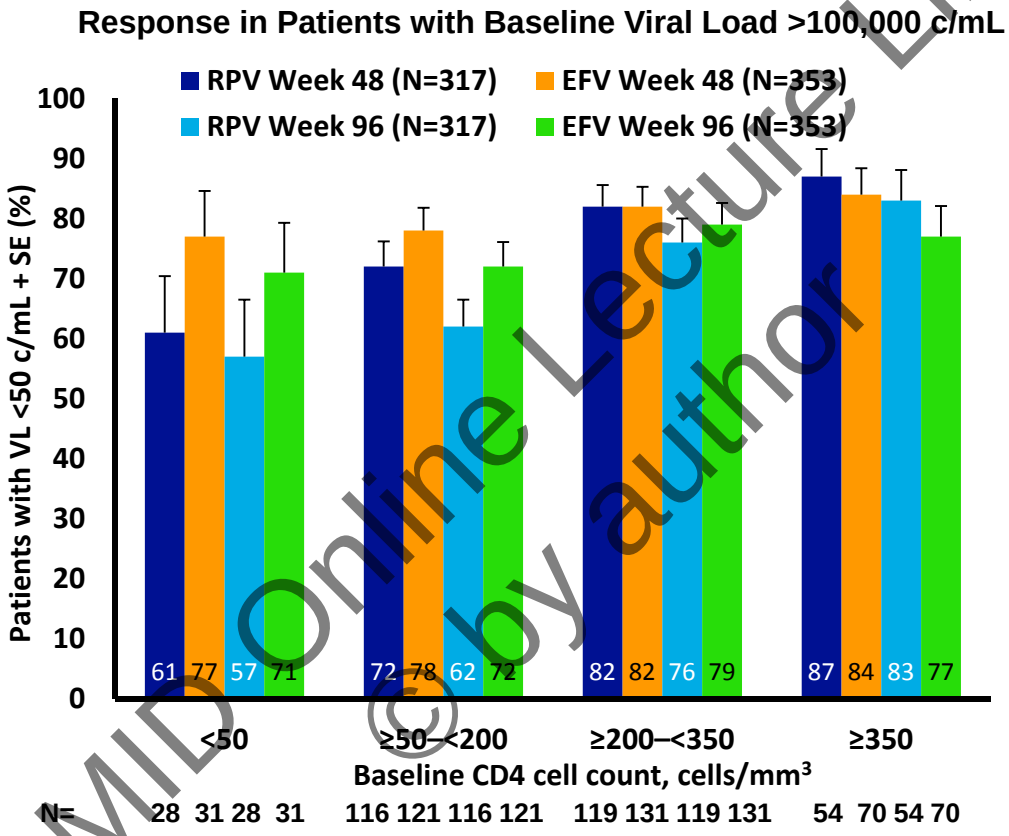
Grant P, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 535.

Rilpivirine-caution in low CD4 and high VL

Pooled ECHO and THRIVE:

Response with Baseline Viral Load >100,000 c/mL by Baseline CD4



- For baseline viral load >100,000 c/mL:
  - Virologic failure rates higher for RPV than EFV

Cohen C, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 626.

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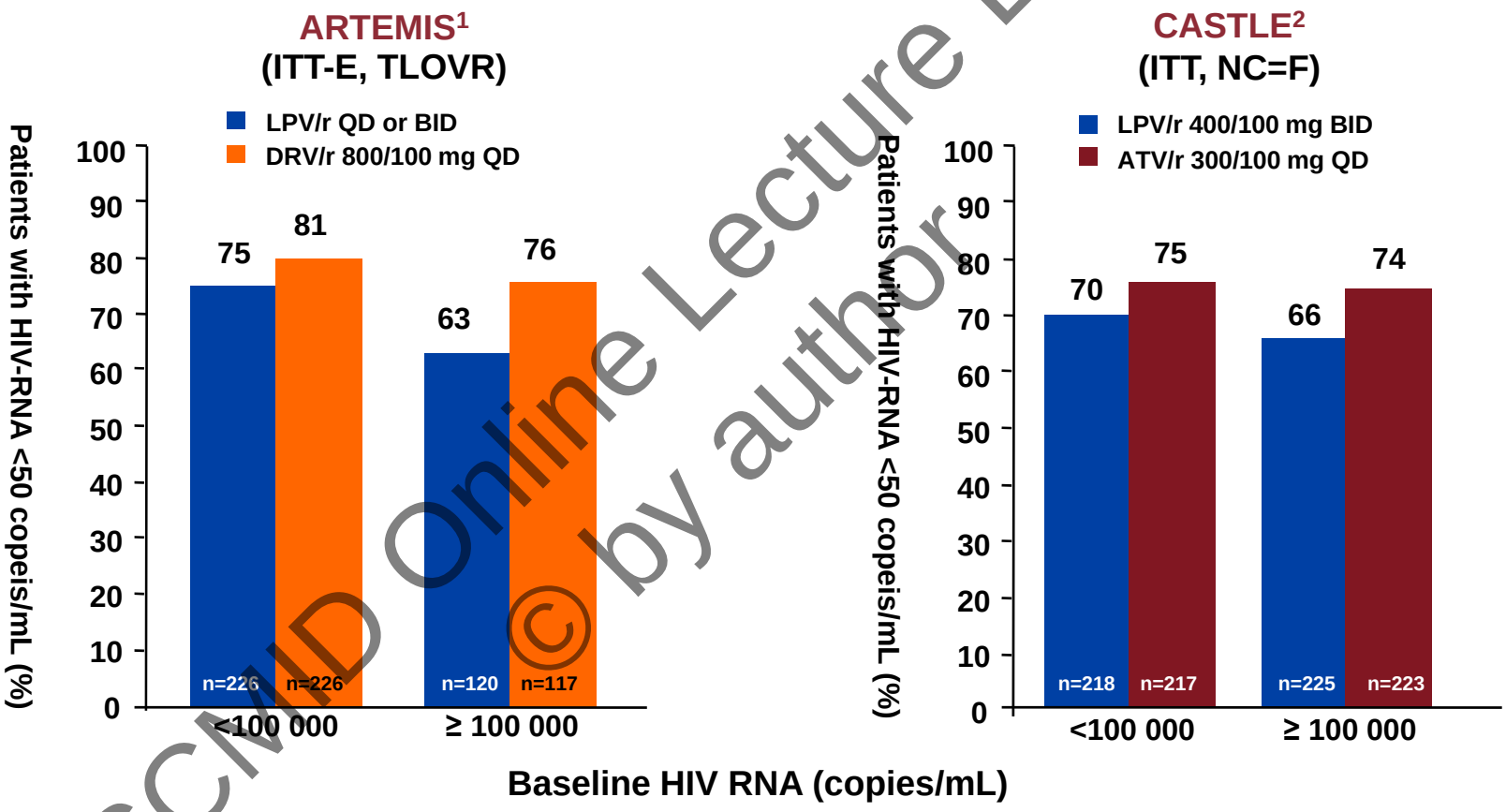
Which boosted PI is best at High Viral loads?

Boosted PIs in ARV-naïve patients: (96 weeks)



LPV/r QD is not approved in the EU.
Data in figures are from different studies and cannot be compared directly
ITT, intent to treat; ITT-E, intent to treat, exposed; TLOVR, time to loss of virological response; VL, viral load; NC=F, non-completer = failure

Adapted from: 1. Mills A, et al. 48th ICAAC. Washington DC, Oct 25–28, 2008, Abstract H-1250c;
2. Molina JM, et al. 48th ICAAC. Washington, DC, Oct 25–28, 2008, Abstract H-1250d

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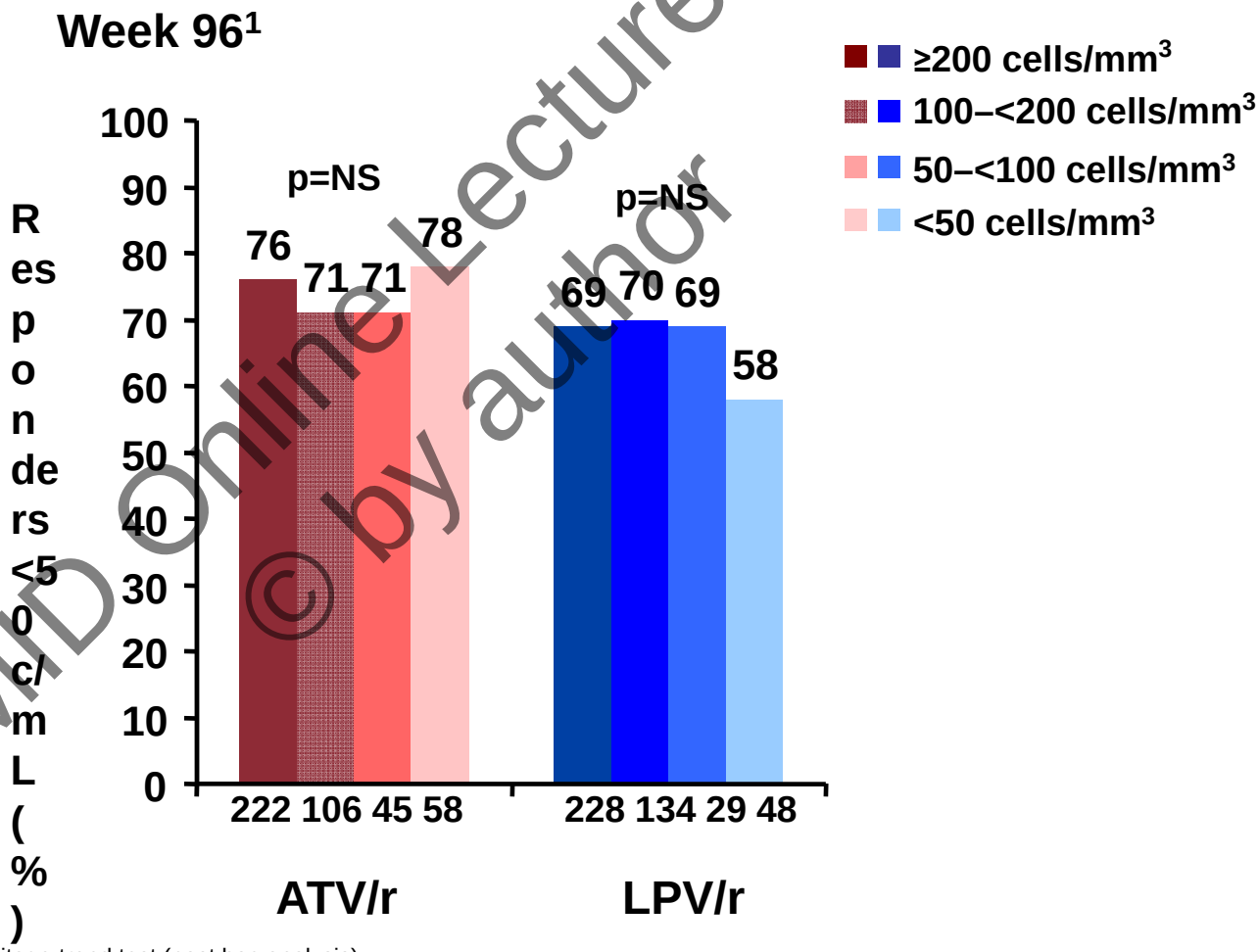
Which Boosted PI is best at Low CD4 Counts?

CASTLE: ITT-confirmed virological response (NC=F) by baseline CD4 cell count



p-values are from Cochran–Armitage trend test (post hoc analysis)

1 Molina J-M, et al. ICAAC/IDSA, Washington, USA, 2008, Poster H-1250d

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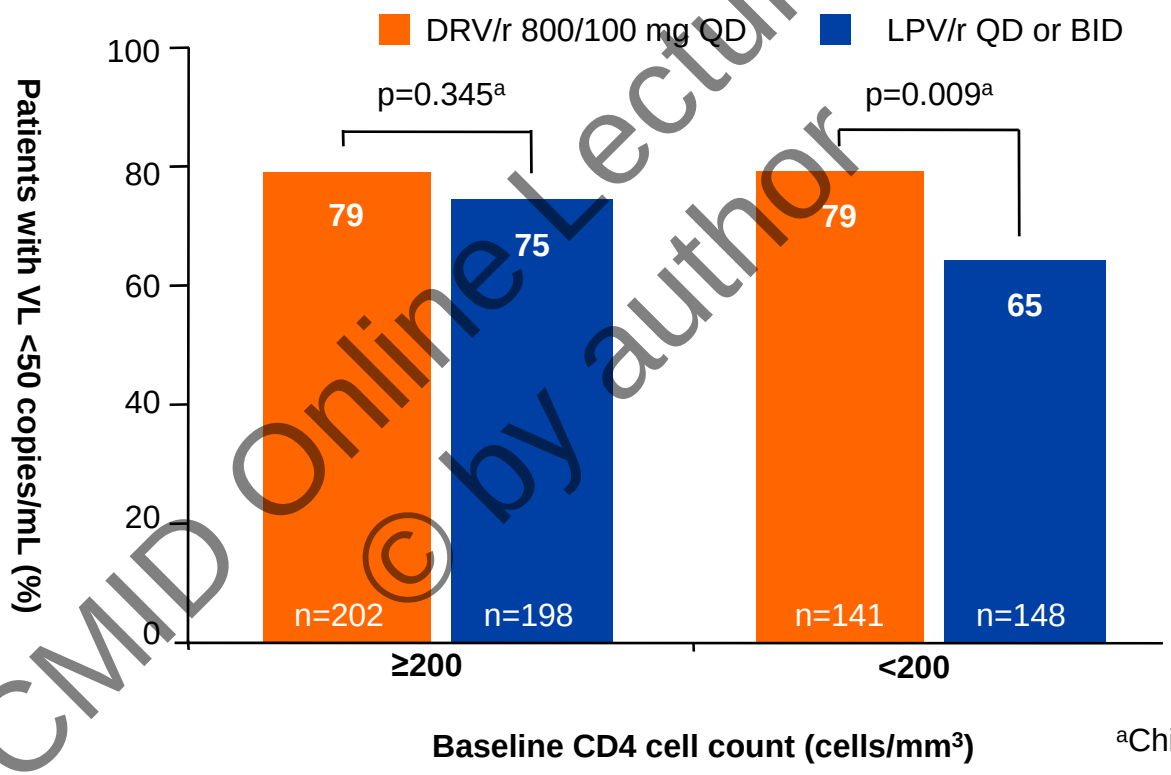
ARTEMIS: response by baseline CD4 at Week 96 (ITT-TLOVR)



aChi square analysis

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Mills A, et al. 48th ICAAC Conference. 2008, Washington DC; Abstract H-1250c.

Abacavir ,Rilpivirine, Lopinavir/r

Can you sequence to these drugs when the Viral load has become undetectable and the CD4 has increased?

Maybe…..

Some issues remain

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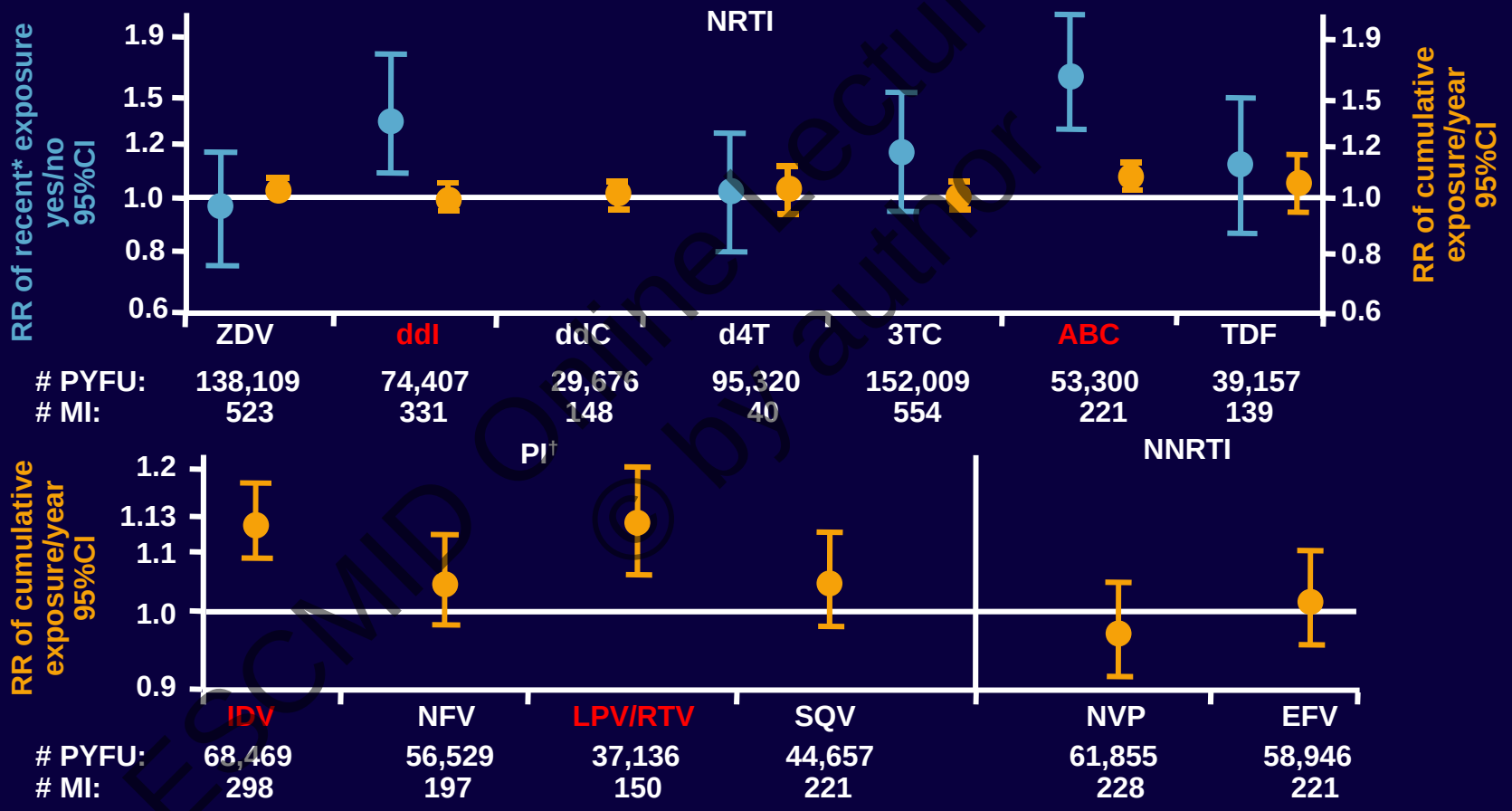
Abacavir and Lopinavir and cardiac disease D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI



*Current or within last 6 months. †Approximate test for heterogeneity: *P* = 0.02

•Lundgren JD, et al. CROI 2009. Abstract 44LB..

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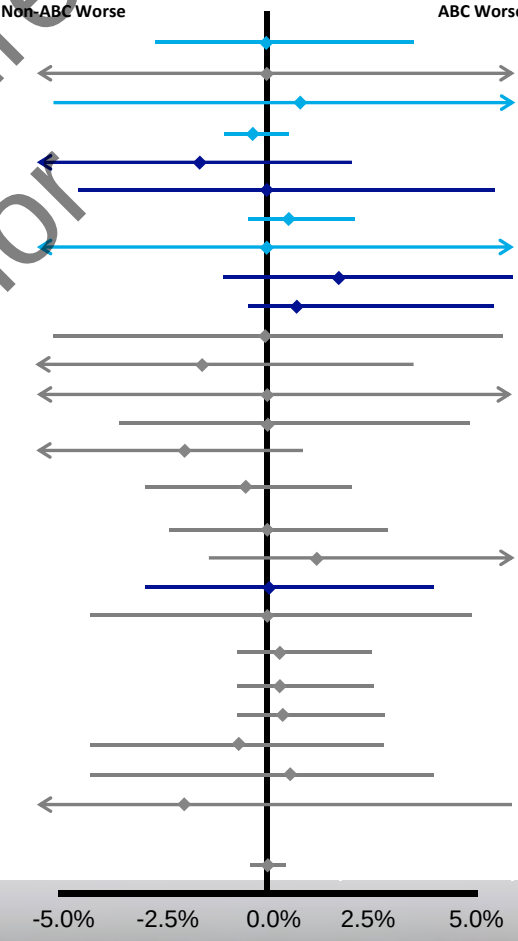
FDA Meta-Analysis
No Association Between ABC and MI

- 26 RCTs involving ABC
  - 5028 subjects on ABC, 4840 controls
  - Average 1.62 person/years of F/U
- Overall events/subjects: 28/5628 ABC vs. 22/4840 controls (OR 1.02 95%CI 0.56, 1.84)
- Authors conclude that the findings 'raise significant uncertainty about the likelihood of an ABC-MI risk association'

Forest Plot of Meta Analysis Results:
Trials Sorted Based on Duration of Person –Years of Follow-up

Study	ABC	Non-ABC	Risk Difference (95% CI)
		Non-ABC Worse / ABC Worse	
ACTG 368 [xii]	0/140 (0%)	0/143 (0%)	0 (-2.73, 2.87)
COL30305	0/58 (0%)	0/29 (0%)	0(-13.79, 6.38)
ACTG 372A [xiii]	4/116 (3.45%)	3/113 (2.65%)	0.79 (-4.77, 6.54)
ACTG A5202 [xiv]	2/923 (0.22%)	5/925 (0.54%)	-0.32 (-1.08, 0.33)
ABCDE [xv]	0/115 (0%)	2/122 (1.64%)	-1.64 (-6.17, 1.64)
FIRST [xvi]	0/93 (0%)	0/89 (0%)	0(-4.49, 4.13)
ACTG 5095 [xvii]	6/758 (0.79%)	1/376 (0.27%)	0.53 (-0.75, 1.5)
ACTG A5110 [xviii]	0/48 (0%)	0/53 (0%)	0 (-7.01, 8.34)
STEAL [xix]	4/178 (2.25%)	1/175 (0.57%)	1.68 (-1.27, 5.17)
NEFA [xx]	1/149 (0.67%)	0/311 (0%)	0.67 (-0.55, 4.04)
CNAF3007	1/96 (1.04%)	1/91 (1.1%)	-0.06 (-5.23, 4.9)
CNA30017	0/80 (0%)	2/127 (1.57%)	-1.57 (-5.61, 3.38)
ESS 40003	0/51 (0%)	0/44 (0%)	0 (-9.09, 7.08)
CNAA3006	0/102 (0%)	0/103 (0%)	0 (-3.79, 3.88)
NZTA4002	0/150 (0%)	3/152 (1.97%)	-1.97 (-5.94, 0.58)
CNA109586	0/192 (0%)	1/193 (0.52%)	-0.52 (-3.12, 1.55)
CNAB3014	0/165 (0%)	0/164 (0%)	0 (-2.42, 2.4)
ESS40002	1/85 (1.18%)	0/166 (0%)	1.18 (-1.14, 7.08)
BIOCOMBO [xxi]	1/167 (0.6%)	1/166 (0.6%)	0 (-3.15, 3.11)
CNAB3002	0/91 (0%)	0/93 (0%)	0 (-4.35, 4.19)
EPZ104057	1/343 (0.29%)	0/345 (0%)	0.29 (0.86, 1.75)
CNA30024	1/324 (0.31%)	0/325 (0%)	0.31 (0.91, 1.86)
CNAC3005	1/262 (0.38%)	0/264 (0%)	0.38 (-1.13, 2.29)
ESS100327	0/137 (0%)	1/141 (0.71%)	-0.71 (-4.27, 2.21)
CNAC3003	1/156 (0.54%)	0/80 (0%)	0.64 (-4.21, 3.6)
CNAB3001	0/49 (0%)	1/50 (2%)	-2(-11.05, 5.37)
Mantel-Haenszel			0.01 (-0.26, 0.27)



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Ding X, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 808.

Should we sequence based on ease of administration?

Regimen	Dosing	Food requirements
EFV/TDF/FTC	▪ 1 pill once daily	▪ Empty stomach (recommended dosing at bedtime)
ATV/RTV + TDF/FTC	▪ 3 pills once daily	▪ Must be taken with food ▪ Must be separated from proton-pump inhibitors
DRV/RTV + TDF/FTC	▪ 4 pills once daily	▪ Must be taken with food
RAL + TDF/FTC	▪ 3 pills divided across 2 daily doses	▪ With or without food
RPV/TDF/FTC	▪ 1 pill once daily	▪ Must be taken with at least 500 cal of food ▪ May not take with proton-pump inhibitors ▪ ? High viral load efficacy

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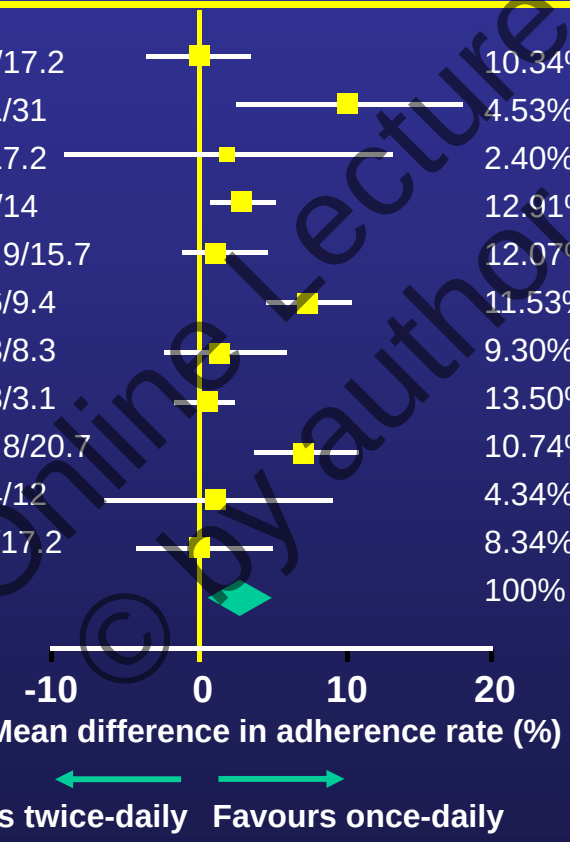
Better adherence with once-daily antiretroviral Regimens

Author [ref]	Year	One-daily N/Mean/SD	Twice-daily N/Mean/SD	Weight (%)	Association measure with 95% CI
Benson	2004	294/90/18.3	146/90/17.2	10.34%	
Boyle	2008	205/87.1/31	95/77.1/31	4.53%	
Eron	2004	19/94/18.3	19/92/17.2	2.40%	
Gallant	2006	244/90/11.7	243/87/14	12.91%	
Kubota	2006	411/94.3/15.8	195/92.9/15.7	12.07%	
Molina	2007	115/99.8/11	75/92.6/9.4	11.53%	
Parienti	2007	27/95/6.2	25/93.3/8.3	9.30%	
Porthsmouth	2005	22/96.1/3.6	21/95.8/3.1	13.50%	
Rode	2008	310/90.8/20.7	296/83.8/20.7	10.74%	
Ruane	2006	18/85.4/9.1	13/84.4/12	4.34%	
Sosa	2005	119/93/18.3	117/93/17.2	8.34%	
META-ANALYSIS:				100%	2.88 (0.98 to 4.78)



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Adapted from Parienti J-J et al Clin Infect Dis 2009; 48:484–488

Should we sequence based on pill burden?

Single Pill Regimens (STRs)

2 already Licensed in EU and USA- Atripla and eviplera
Quad Pill almost here
Dolutegravir and 3TC / abacavir in development
Darunavir and cobicistat and FTC in development

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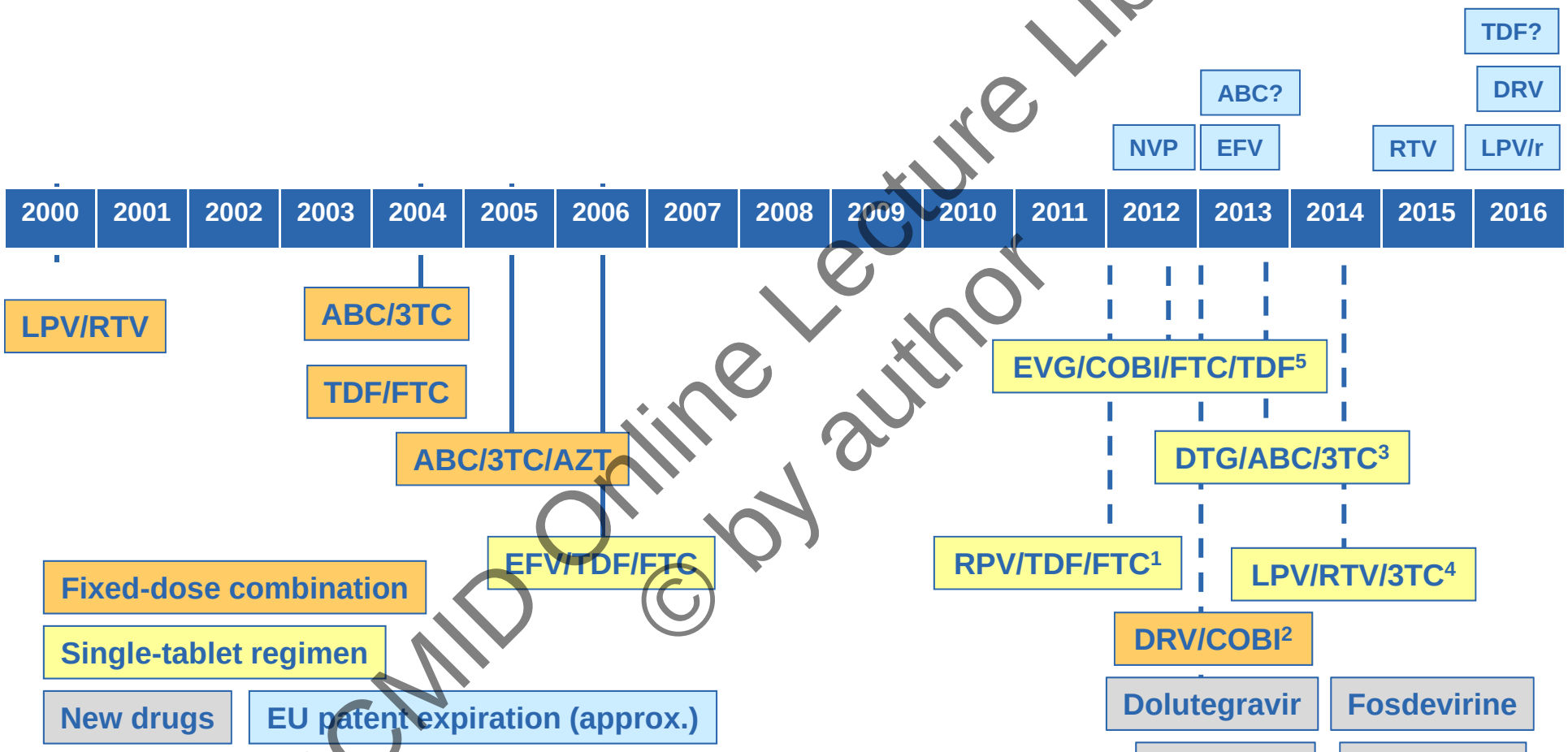
An evolving competitive landscape
Single Tablet regimens



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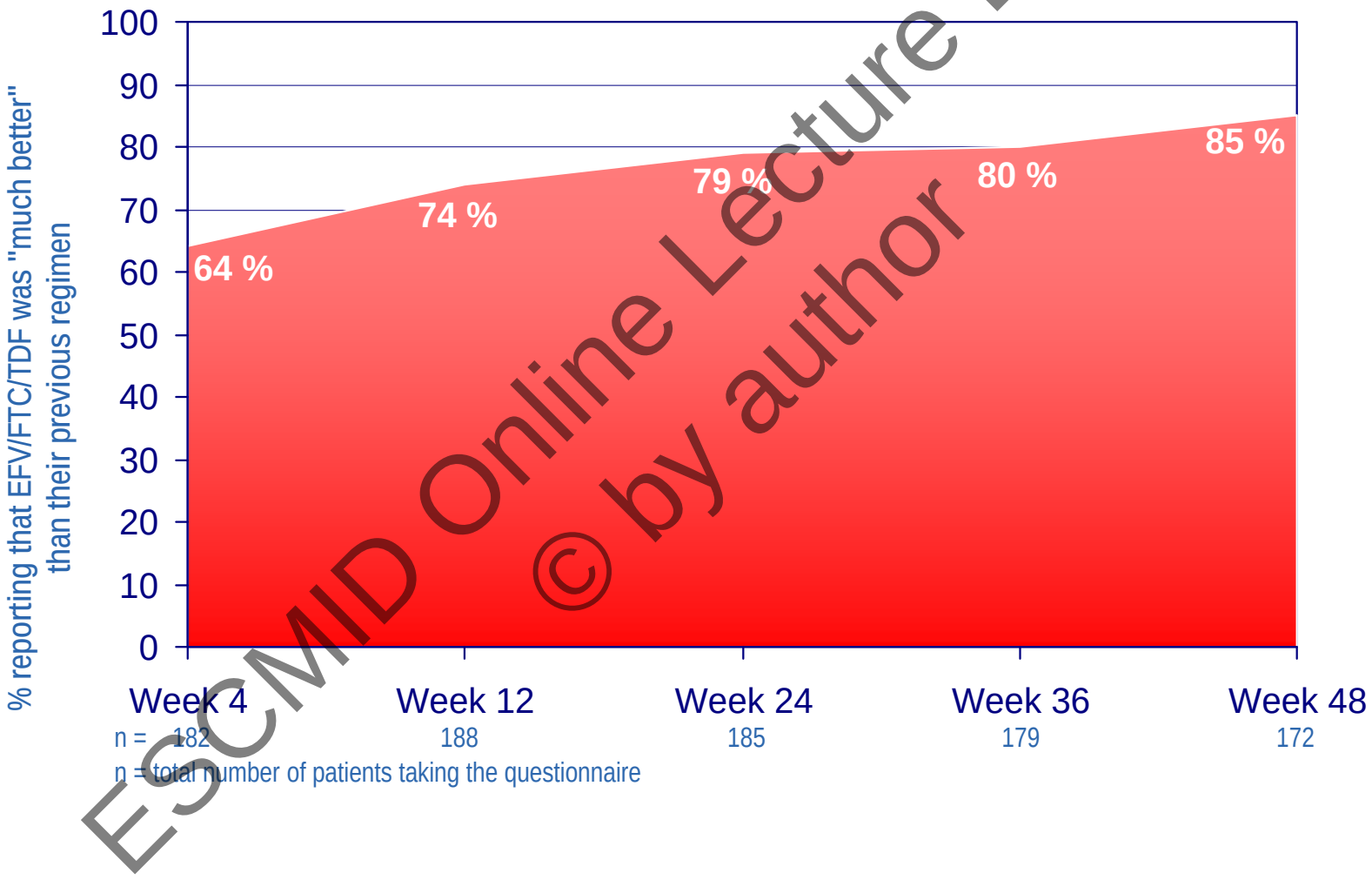
1. http://www.aidsmeds.com/articles/hiv_complera_gilead_1667_20970.shtml
2. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle_pf&id=1580287
3. http://www.viivhealthcare.com/media-room/press-releases/2011-02-03.aspx
4. http://www.abbott.com/press-release/2011-july15.htm
5. http://www.gilead.com/pr_1596378

Preference of medication questionnaire in patients randomized to EFV/FTC/TDF Single tablet



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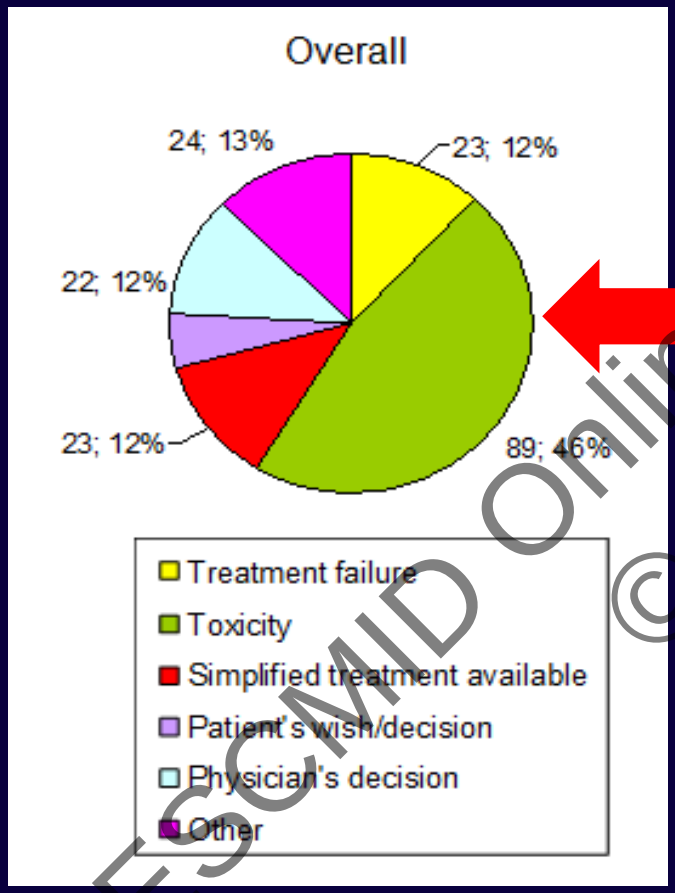
Hodder et al. 9th International Congress on Drug Therapy in HIV Infection, November 9–13 2008, Glasgow, UK

Should we sequence based on potential Toxicity ?



TOXICITY.

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Moreno et al. Congreso GESIDA 2010. PO 27.

Should we sequence based on potential Toxicity ?

- FTC/3TC very low incidence of toxicity
- Efavirenz well recognised neuropsychiatric effects but managed well in practice
- Few side effects to Raltegravir
- Few side effects of atazanavir (Hyperbilirubinaemia and triglycerides) and darunavir (rash and triglycerides)
- Tenofovir potential renal and bone toxicity

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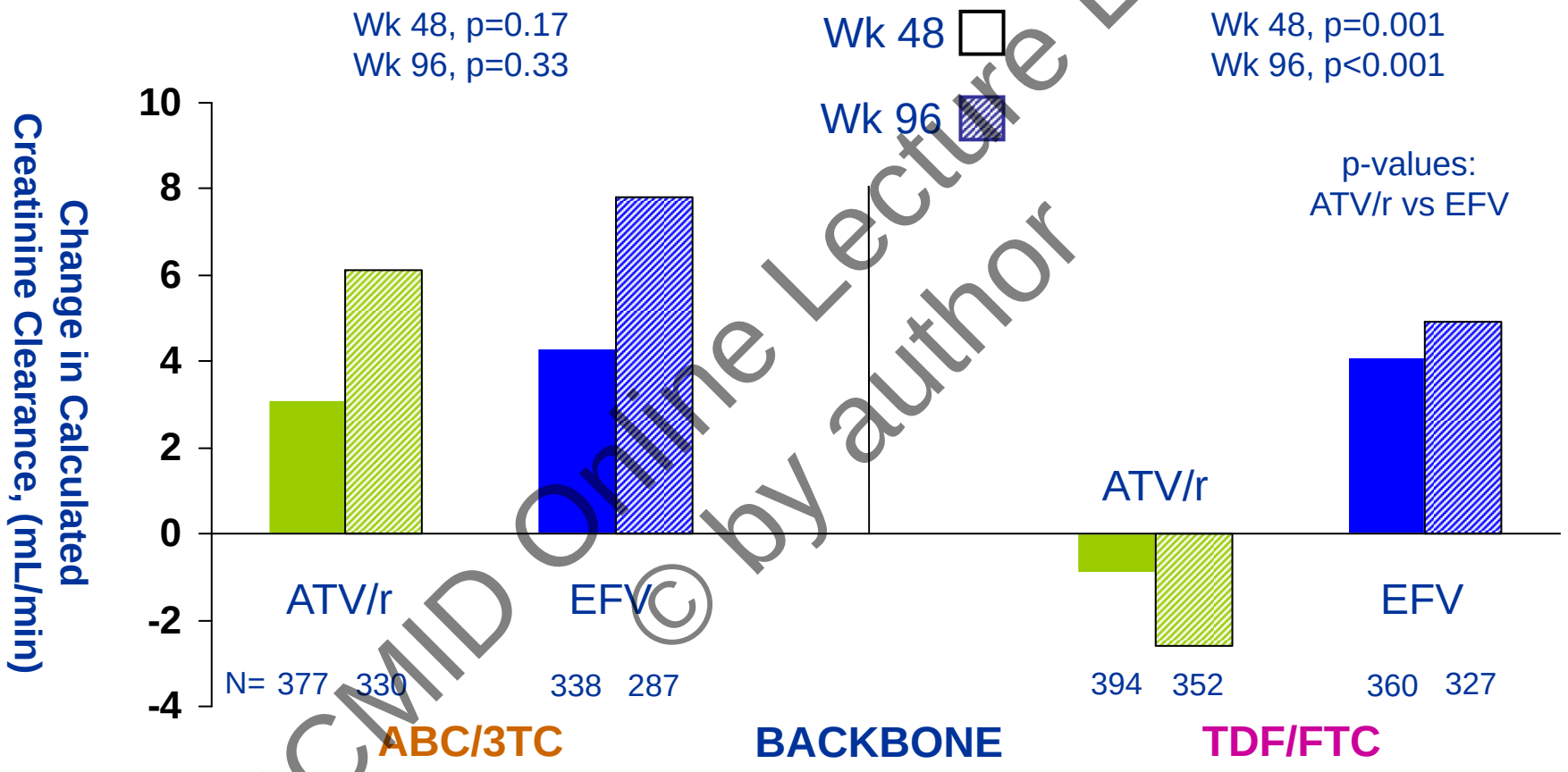
Median Change in Creatinine Clearance Atazanavir/r vs Efavirenz (Overall As-Treated)



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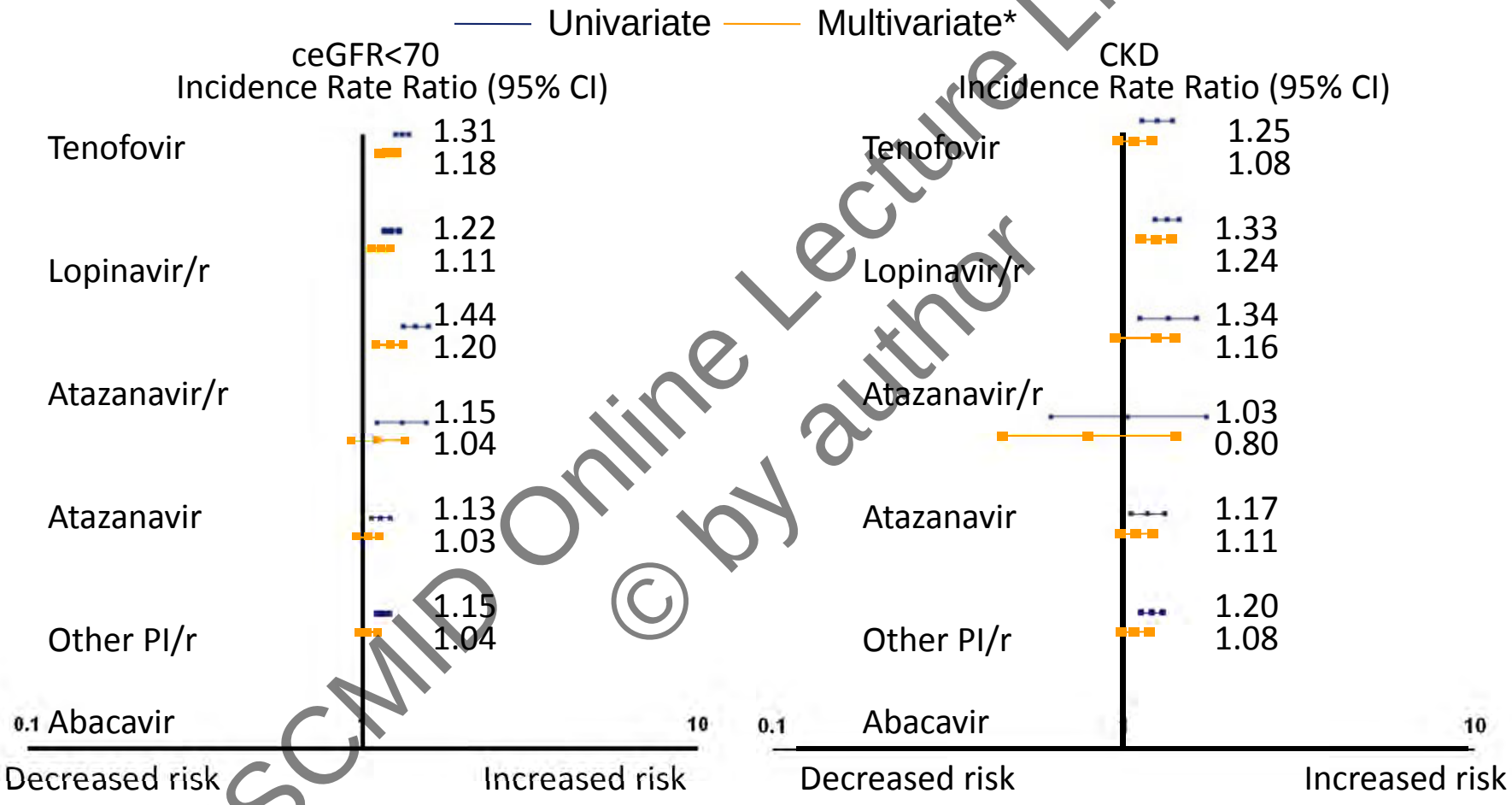
D:A:D: ARV use (per year) and Risk of ceGFR<70 and CKD from eGFR>90



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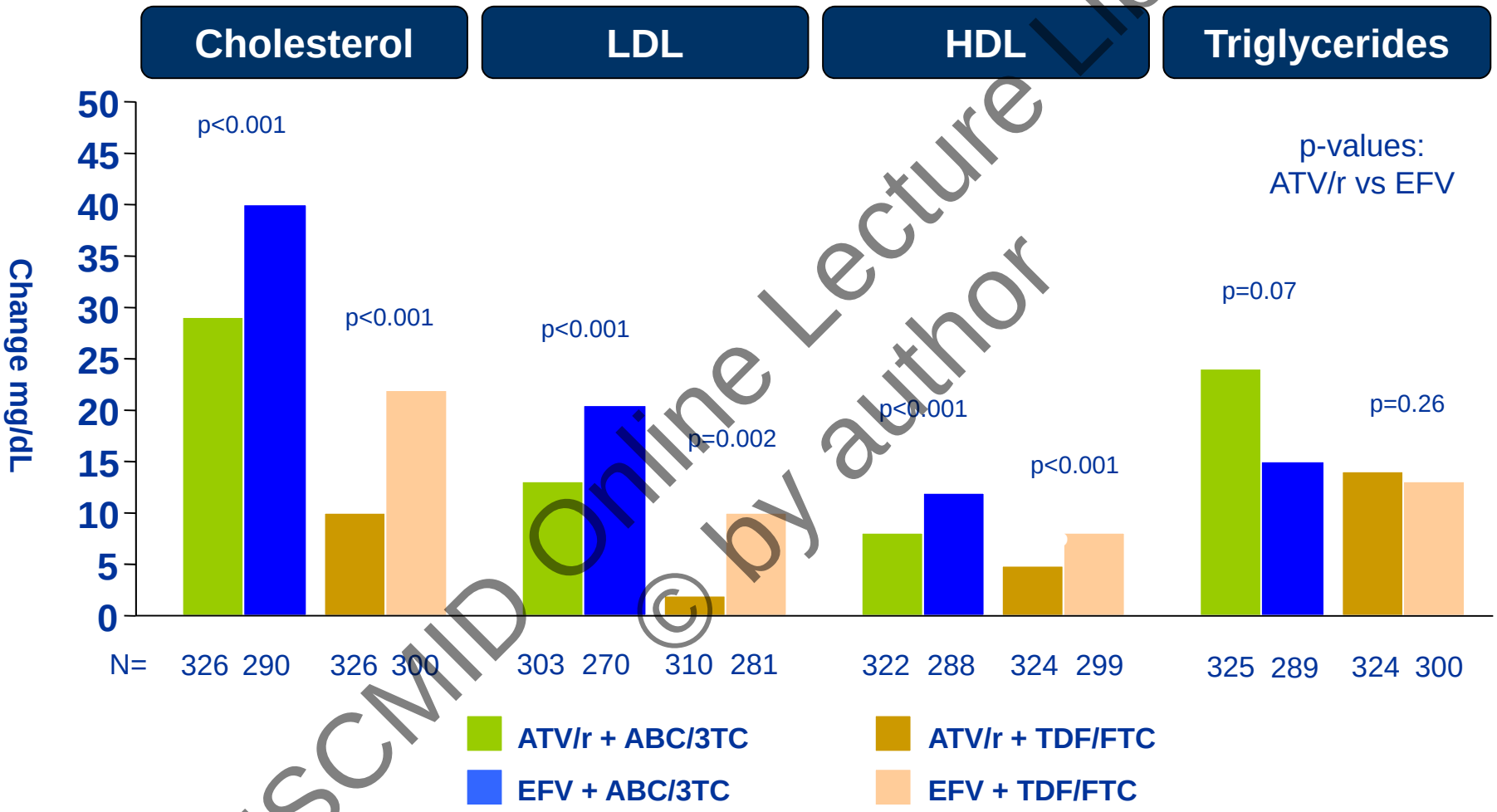
* Adjusted for gender, race, HIV risk group, enrolment cohort, Prior AIDS, HBV/HCV status, smoking status, hypertension, diabetes, prior CV event, baseline eGFR, age (per 10 yrs), CD4 per doubling/nadir, VL and cumulative exposure (per year) tdf, ind, lpv/r, atv, atv/r, abc and other PI/r

Ryom L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 865.

Median Change in Fasting Lipids (mg/dL) Atazanavir/r vs Efavirenz, Week 48 (Overall As-Treated)



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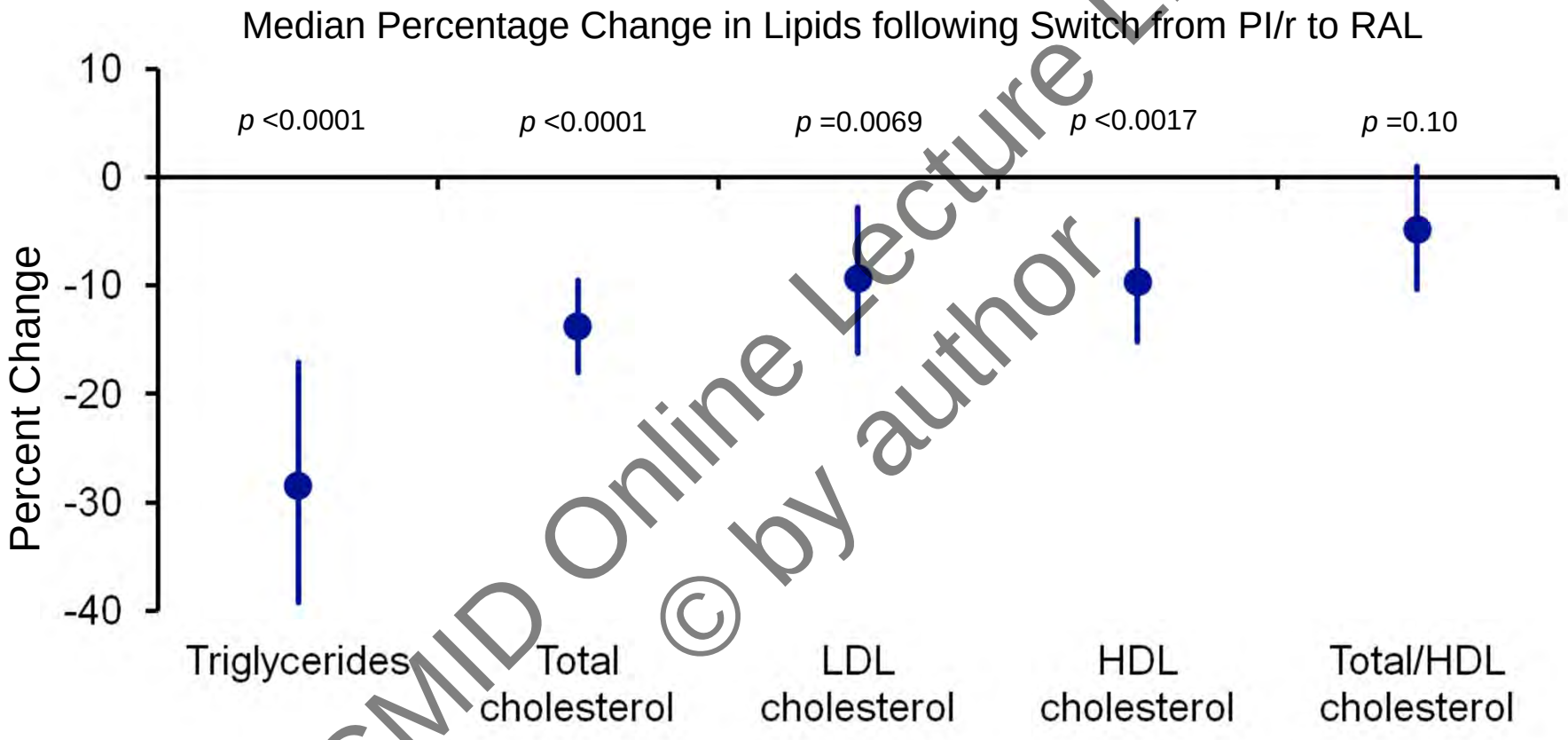
SPIRAL: PI/r to Raltegravir Switch Improves Lipids



Conclusion: PI/r to RAL switch results in significantly improved lipids, but no change in Total/HDL cholesterol ratio.

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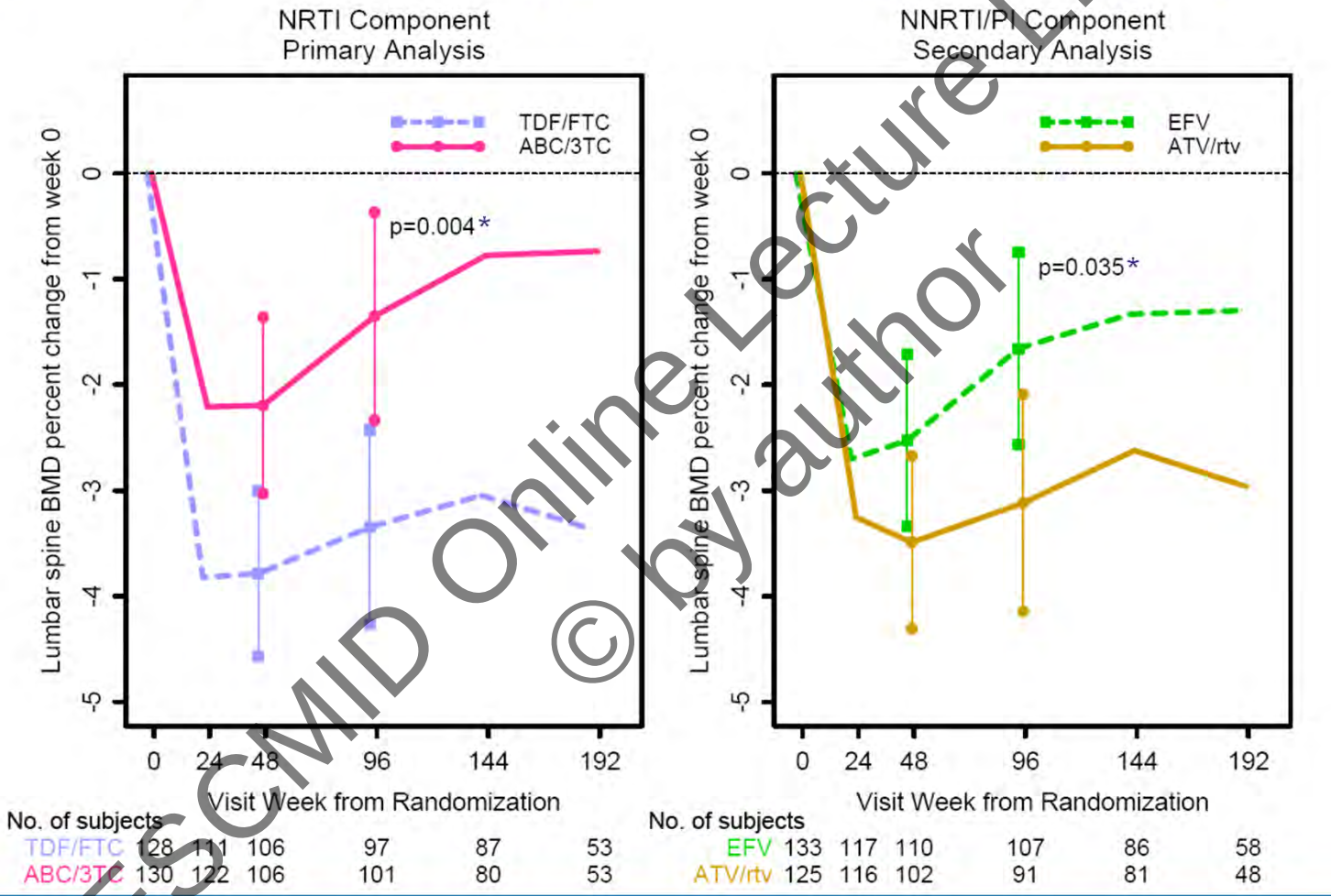
Martinez E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 834.

Bone mineral density and ARVs
Mean (95% CI) Percent Change in Lumbar Spine BMD (ITT)



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* -linear regression
No significant interaction of NRTI and NNRTI/PI components (p=0.63)

Should we sequence based on Cost? The rise of Generics

Advantages	Disadvantages
▪ Clear cost benefit	▪ May involve change of regimen for patients who are currently on coformulated drugs or single-tablet regimens • Either switch to different coformulated drug or to the same drugs administered separately with generic substitutions ▪ Possible problems with adherence

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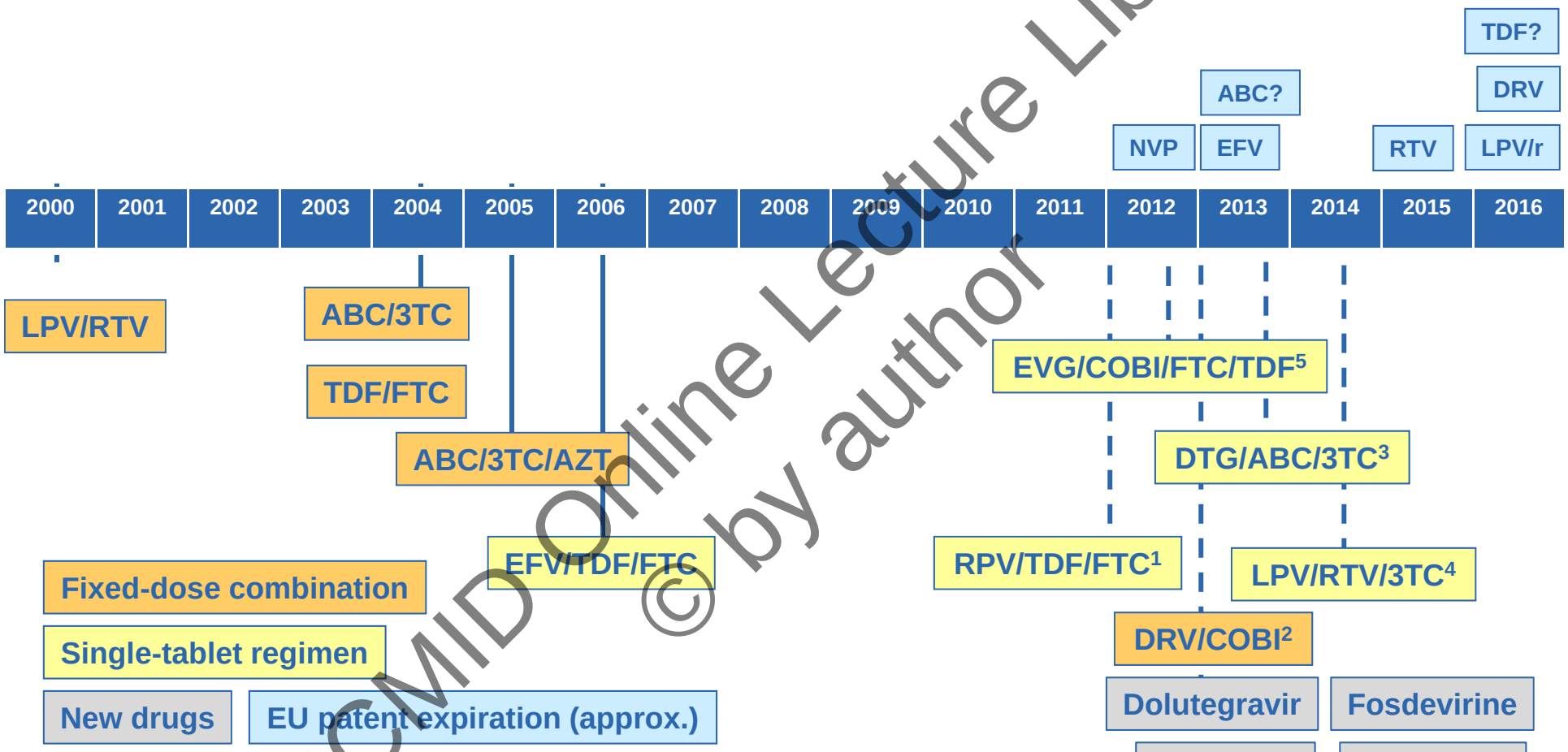
An evolving competitive landscape
Generics



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1. http://www.aidsmeds.com/articles/hiv_complera_gilead_1667_20970.shtml
2. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle_pf&id=1580287
3. http://www.viivhealthcare.com/media-room/press-releases/2011-02-03.aspx
4. http://www.abbott.com/press-release/2011-july15.htm
5. http://www.gilead.com/pr_1596378

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Developing countries

- Limited access

Could sequence without resistance tests if develops virological failure or clinical progression on initial regimen

- from NNRTI plus 2 nucleos(t)ides to Boosted PI plus integrase or CCR5 or tenofovir
- **But this strategy is not proven and drugs not all available**

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Sequencing-conclusions

- Individual regimen choices will still be important and switchingto different regimens will be based on regimen acceptability, tolerability and resistance
- Few data sets to validate a sequencing approach
- Little desire at present for formal sequencing in guidelines
- Sequencing may be useful where there are limited drugs with non overlapping resistance and toxicity profiles and limited access to resistance testing- but need access to drugs!

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