Generic antiretrovirals in Europe: a blessing or a curse?

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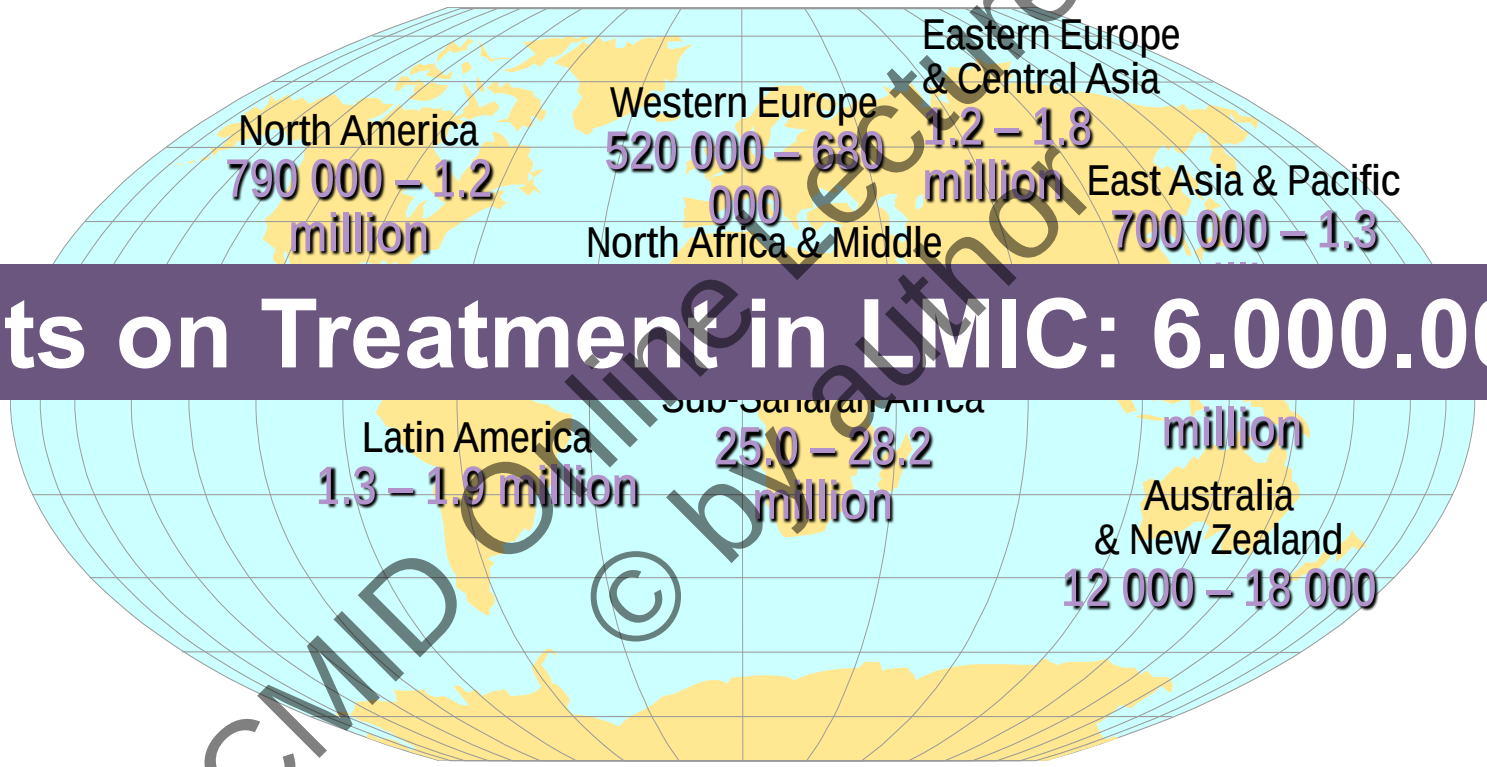
Adults and children estimated to be living with HIV/AIDS



Pts on Treatment in LMIC: 6.000.000

Total: 34 – 46 million

Generic Drugs and Quality Control

- 45 patients, intolerant to NNRTIs, receiving a Lopinavir/r generic drug as part of their first line regimen in South Africa
- 15 virologic failures (33,3%), with several PI drug resistance mutations

GLOBAL HEALTH

Bioavailability of Generic Ritonavir and Lopinavir/Ritonavir Tablet Products in a Dog Model

KEVIN W. GARREN, SIBTAIN RAHIM, KENNAN MARSH, JOHN B. MORRIS

Abbott Laboratories, 200 Abbott Park Road, Abbott Park, Illinois 60064

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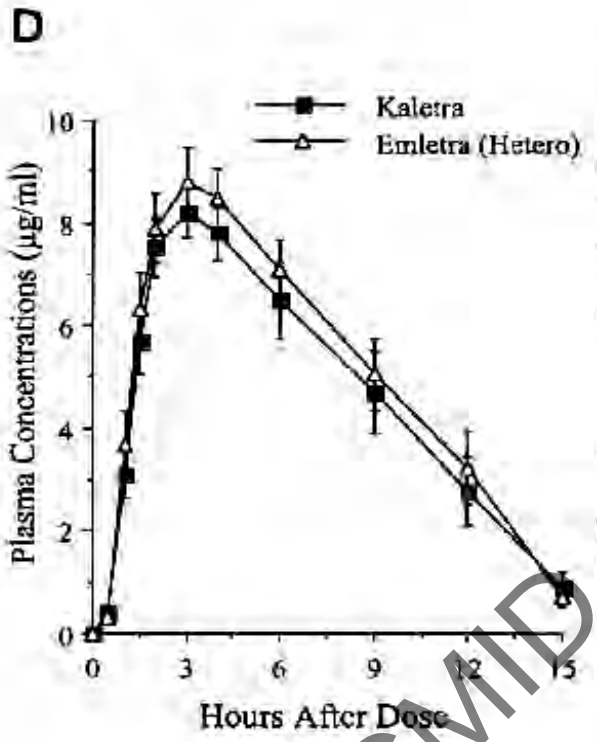
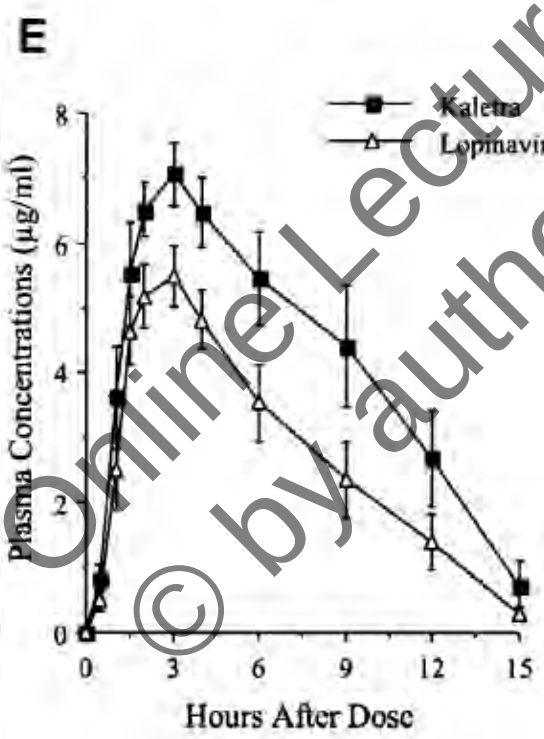
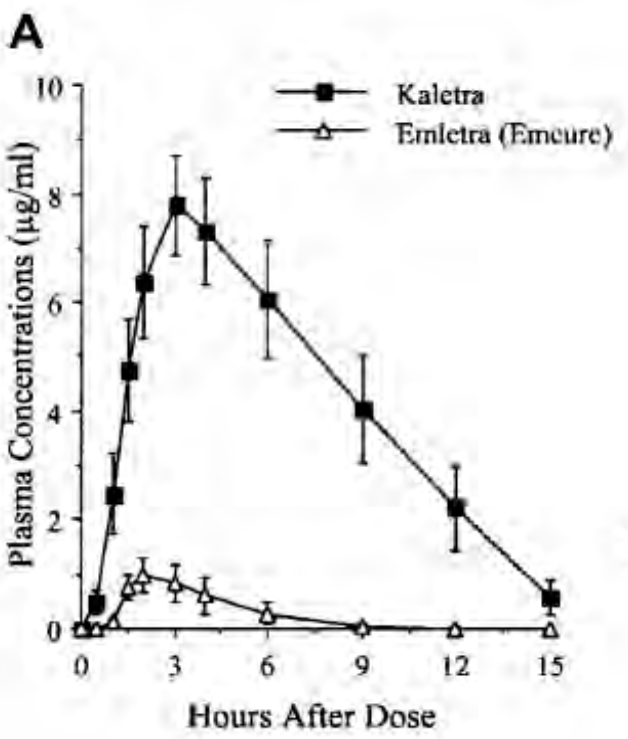
- 5 generic formulations of Lopinavir/r
  LPV: 79% - 104,6%
  RTV: 89% - 102%

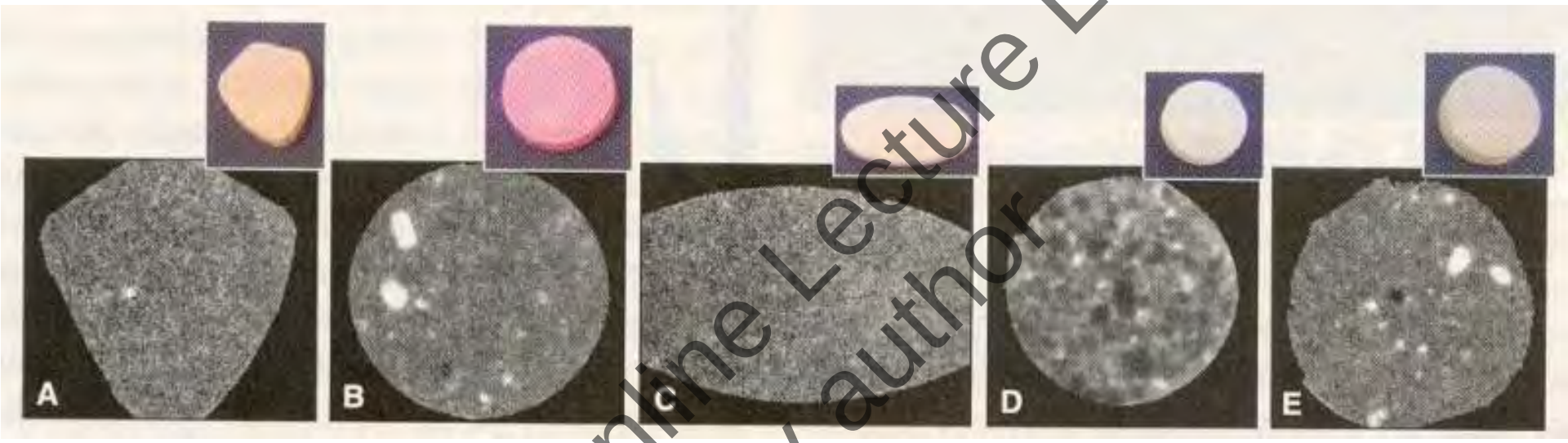
- 3 generic formulations of Ritonavir
  RTV: 96,6% - 101,2%







Simvastatin Pills: original MSD (A), generics from Mexico (B), Thailand (C), India (D) e Brazil (E)



Analysis using near-infrared spectroscopic imaging techniques, which are designed to detect formulation defects of drug products during the manufacturing process

Science 305(5683):481. .

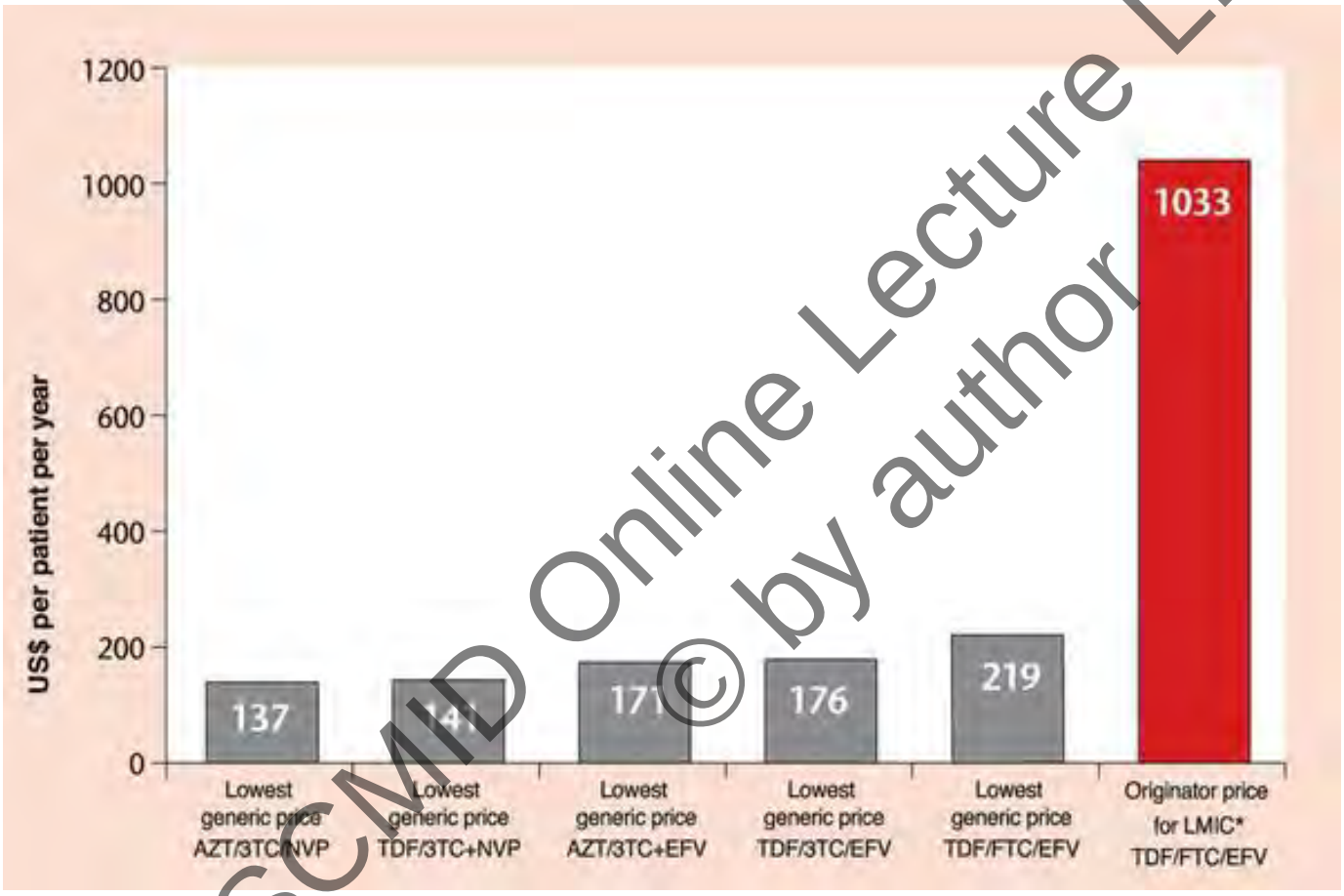
Patent expiration dates for antiretrovirals

Patent Expiration Dates

2005	2006	2011	2012	2013
Zidovudine	Stavudine	Lamivudine	Nevirapine	Combivir
	Didanosine		Indinavir	Efavirenz
			Saquinavir	Ritonavir

2014	2016	2018	2019	2022
Abacavir	Trizivir	Tenofovir	Kivexa (Epzicom)	Raltegravir
Tipranavir	Lopinavir/r	Atripla	Fosamprenavir	Maraviroc
	Emtricitabine	Truvada	Etravirine	
	Darunavir	Atazanavir		

The Blessing



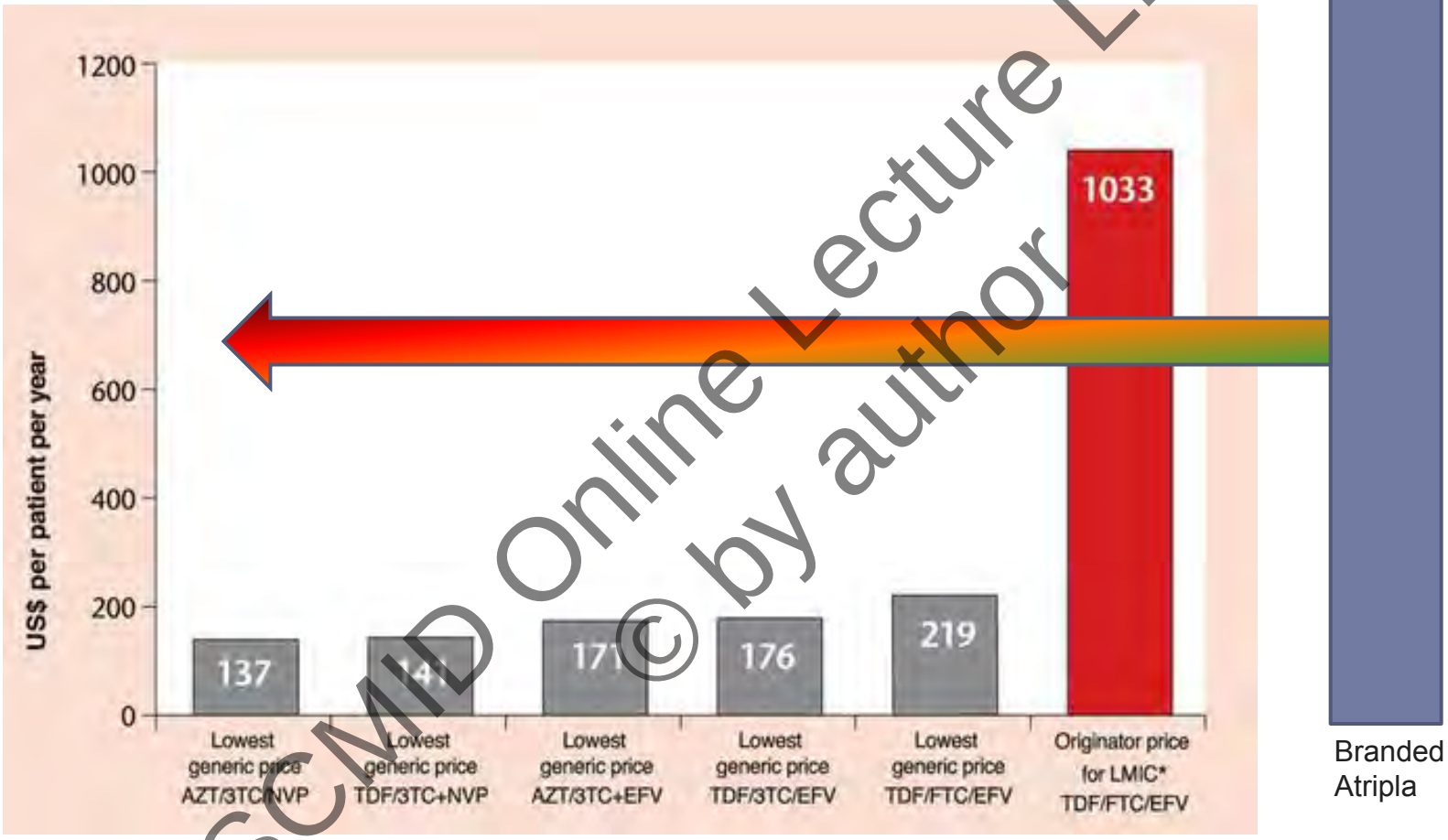
Branded Atripla

Atripla: price per patient per year = US$12.480 (1 € = 1.25 US$)

Hospital Egas Moniz, Lisbon

- 1.951 HIV-1 and HIV-2 patients on treatment (~8% of all HIV infected patients on treatment in Portugal)
- 2011: 13.000.000 € on antiretrovirals
- 150 patients starting ARV therapy each year
- Spending estimate for 2015: 21.000.000 €

A Blessing? A Curse?



Atripla: price per patient per year = US$12.480 (1 € = 1.3 US$)

A return to BID regimens? Higher pill burden?

- There's not a single randomized, prospective clinical trial proving superiority of OD vs BID regimens.

Clin Infect Dis. 2009 Feb 15;48(4):484-8.

Better adherence with once-daily antiretroviral regimens: a meta-analysis.

Parienti JJ, Bangsberg DR, Verdon R, Gardner EM.
Department of Biostatistics and Clinical Research, Côte de Nacre University Hospital, Caen, France. parienti-jj@chu-caen.fr

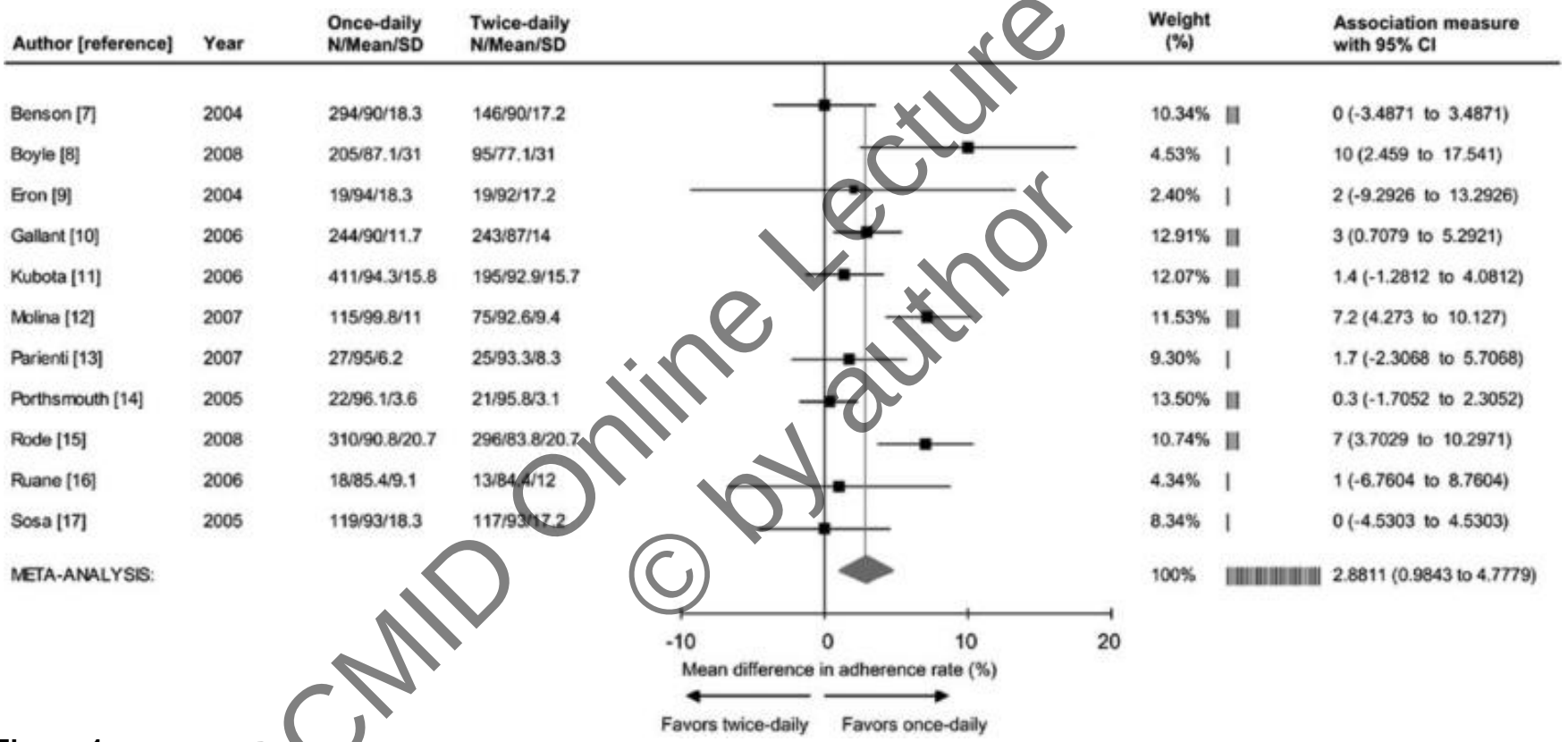


Figure 1
Forrest plot of the effect of once-daily versus twice-daily antiretroviral regimens on the rate of adherence. Adherence rate was defined as follows: (no. of taken doses/no. prescribed doses)×100. Cochrane Q test for heterogeneity: χ^2=29.7; degrees of freedom, 10; ***P*=<.001**; I^2=66.4%. Test for overall random effect: Z=2.98; ***P*=<.003**.

Clin Infect Dis. 2009 Feb 15;48(4):484-8.

Better adherence with once-daily antiretroviral regimens: a meta-analysis.

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Department of Biostatistics and Clinical Research, Côte de Nacre University Hospital, Caen, France. parienti-jj@chu-caen.fr

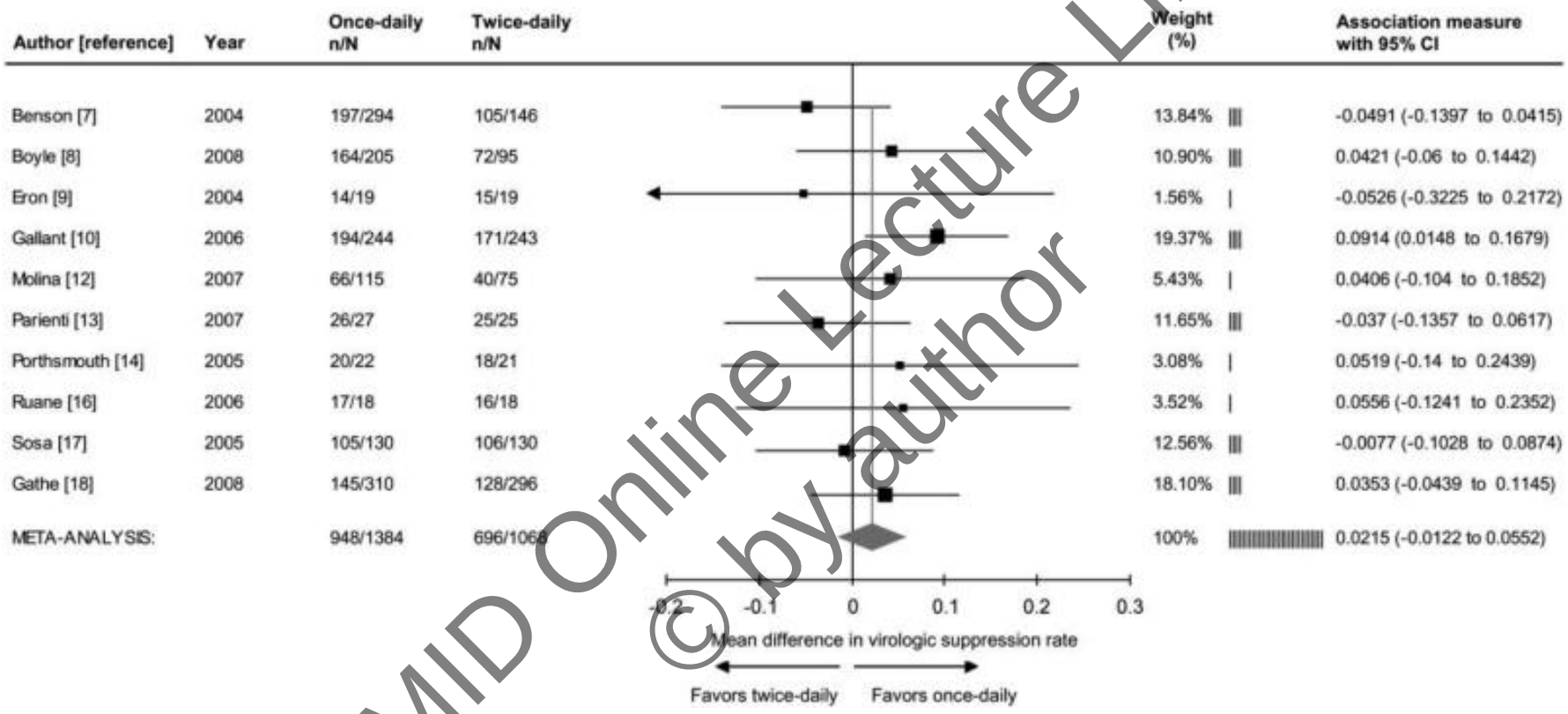


Figure 2
Forrest plot of the effect of once-daily versus twice-daily antiretroviral regimens on viral suppression. Viral suppression was defined as a plasma RNA HIV level <50 copies/mL in the intent-to-treat analysis, with missing equals failure. In the study by Gathe et al. [18], data represent week 12 results among subjects with Medication Event Monitoring System evaluation (Dr. Rode, personal communication, December 2008). **Week 48 results are 77% and 76% for once-daily and twice-daily regimens**, respectively. Cochrane Q test for heterogeneity: χ^2=8.2; degrees of freedom, 9; ***P*=.43**; I^2=0.0%. Test for overall random effect: Z=1.25; ***P*=.21**. n, No. of subjects with viral suppression; N, total sample size.

ACTG 5175/PEARLS

BID, twice daily; QD, once daily.
*Dose adjusted by weight.
†Arm discontinued after May 2008 data and safety monitoring board review based on inferior efficacy; current analysis limited to efavirenz-based arms.

Campbell T et al, ACTG A5175/PEARLS: CROI 2011, Late Breaker 149

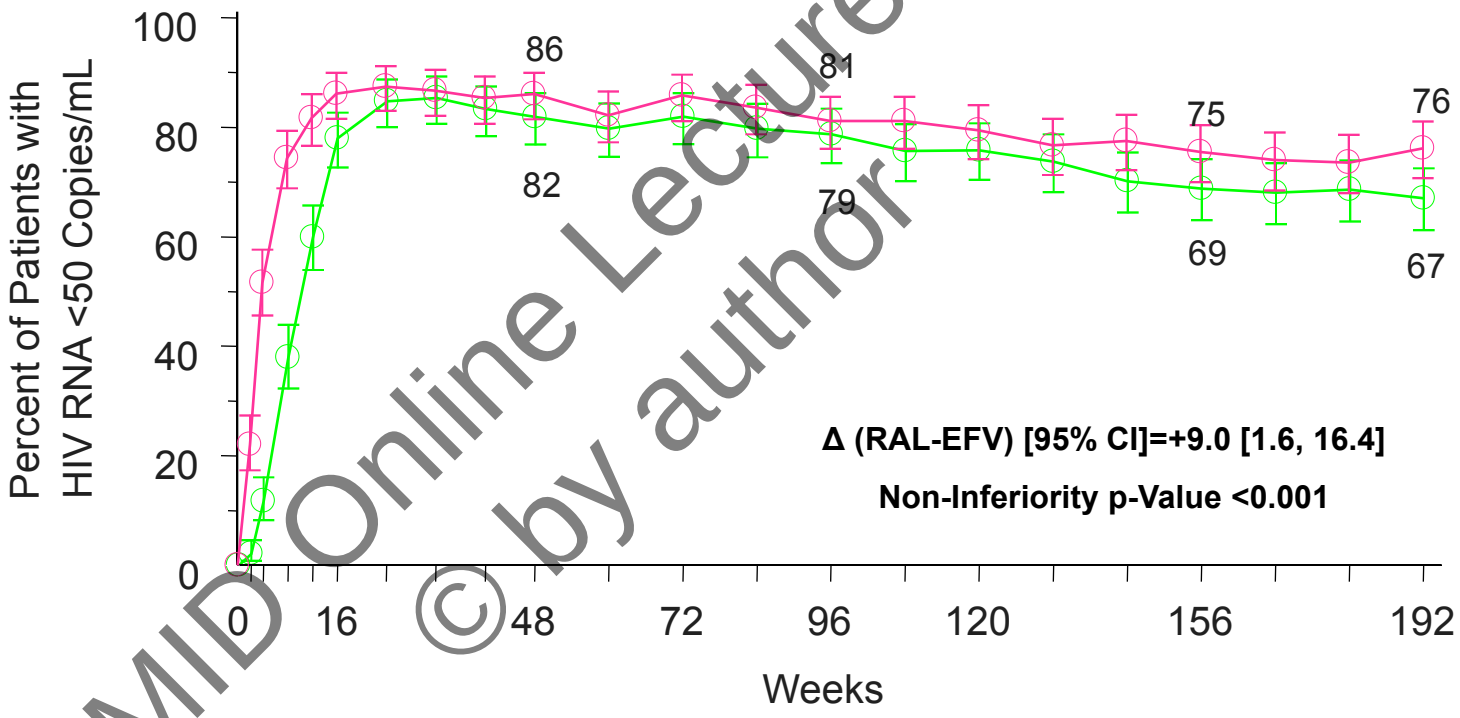
A curse: return to higher toxicities?

Events, n	TDF+FTC+ EFV (n = 526)	AZT+3TC+EFV (n = 519)	HR (95% CI)	P Value
Total efficacy endpoints	95	98	0.95	.74
Confirmed virologic failure	78	78	0.99	.95
New AIDS event	11	12	0.89	.77
Death	18	20	0.99	.74

Events, n	TDF+FTC+EFV	AZT-3TC-EFV	HR	P Value
Total safety endpoints	243	313	0.64	<0.0001
Initial dose modification	140	222	0.54	<0.0001
Grade 3-4 clinical events	115	116	0.96	.73
Grade 3-4 laboratory events	98	154	0.55	<0.0001

Campbell T et al, ACTG A5175/PEARLS: CROI 2011, Late Breaker

Proportion (%) of Patients (95% CI) with HIV RNA < 50 copies/mL (Non-Completer = Failure)



Number of Contributing Patients

○ Raltegravir group	281	281	280	281	281	277	281	281
○ Efavirenz group	282	281	281	282	282	281	282	282

Pill Burden

Pill burden and adherence?

AIDS Patient Care STDS. 2009 Nov;23(11):903-14.
An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications.
Atkinson MJ, Petrozzino JJ.
PRO-Spectus LLC, San Diego, California, USA. mjatkinson@ucsd.edu

Less adherence when pill burden > 10 pills/day

HIV Study: AZT/3TC vs AZT and 3TC with a PI

- Pts recently started on separate tablet regimen for >10 weeks, VL<4 log

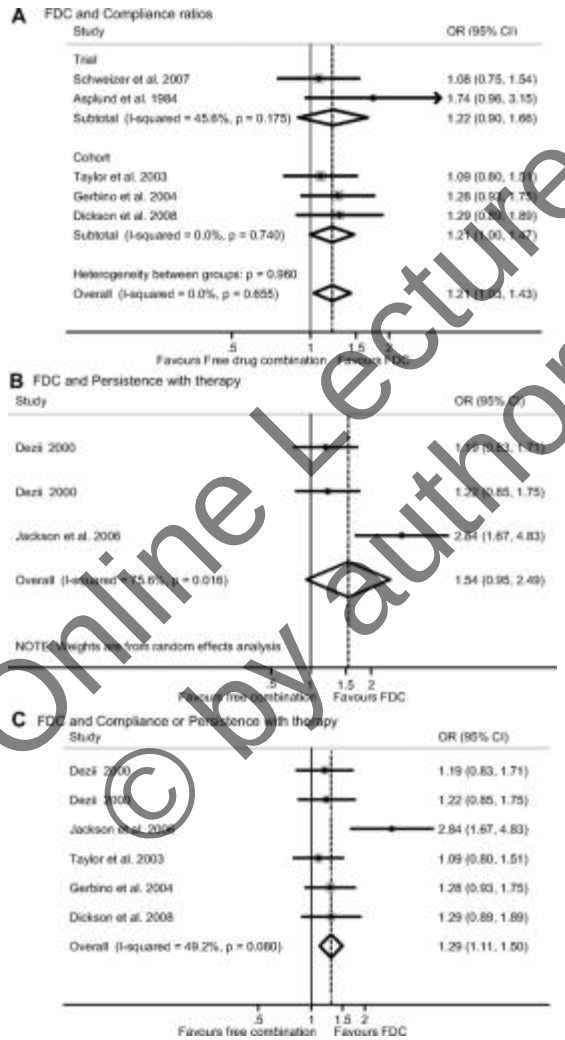
- Randomized, open label of:
  - Combination AZT/3TC tablet (n=110), *versus*
  - Continue AZT and 3TC separate tablets (n=113)

Results:

- Virologic response:
  - 94% (com) vs 91% (sep) achieved undetectable VL (*P*=0.06)
  - n=4 vs n=8 with viremia respectively

- Adherence Qaire: significantly fewer missed doses at weeks 8 (*P*=0.007) and 16 (*P*<0.046)

Figure 2. Compliance and persistence with therapy associated with the use of an FDC of 2 antihypertensive agents as compared with its corresponding free-drug combination.

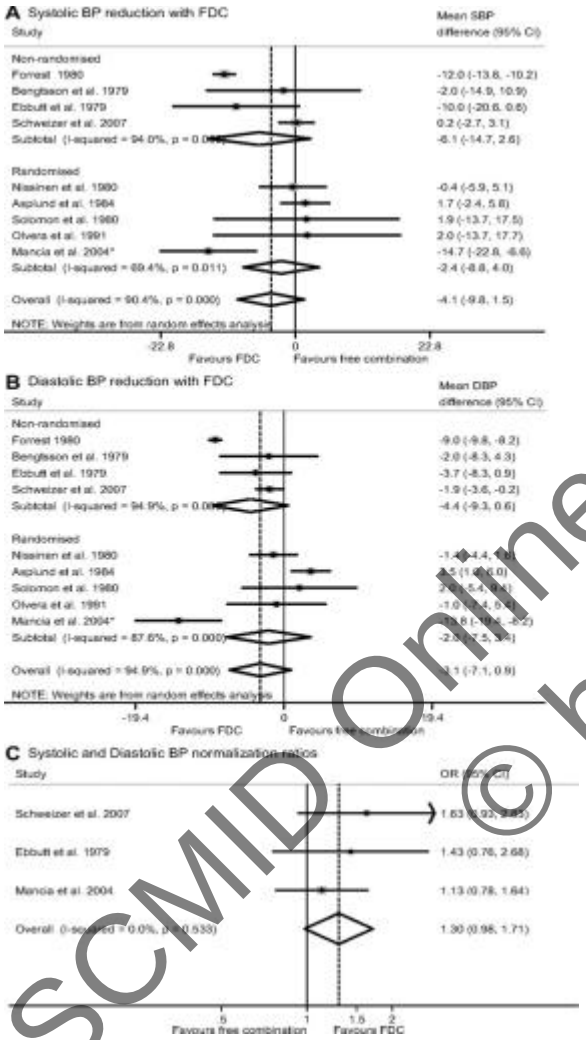


In the cohort studies, the use of an FDC was associated with a **21% increase in compliance** with medications as compared with the use of the free-drug combination (OR: 1.21 [95% CI: 1.00 to 1.47]).

The use of FDCs as compared with the use of the free-drug combination was associated with more than a **50% increase in persistence with therapy, but this difference was not statistically significant** (OR: 1.54 [95% CI: 0.95 to 2.49]).

Gupta A K et al. Hypertension 2010;55:399-407

Figure 3. Systolic (A) and diastolic BP (B) reduction and BP normalization ratios (C) with use of an FDC as compared with its free-drug combination.



Assessment of the mean change in BP among 1671 hypertensive patients in 9 trials revealed a **nonsignificant reduction** of 4.1 mm Hg (95% CI: −9.8 to 1.5 mm Hg; ***P*=0.15**) in systolic and 3.1 mm Hg (95% CI: −7.1 to 0.9 mm Hg; ***P*=0.13)** in diastolic BP, associated with the use of an FDC as compared with its free-drug combination

Gupta A K et al. Hypertension 2010;55:399-407

Patient Prefer Adherence. 2010 May 13;4:115-25.

One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects.

Airoldi M, Zaccarelli M, Bisi L, Bini T, Antinori A, Mussini C, Bai F, Orofino G, Sighinolfi L, Gori A, Suter F, Maggiolo F.

Source

Division of Infectious Diseases, Ospedali Riuniti, Bergamo;

OBJECTIVE:

The aim of the ADONE (ADherence to ONE pill) study was to verify the effect of a reduced number of pills on adherence and quality of life (QoL) in HIV-infected patients on highly active antiretroviral therapy (HAART).

DESIGN:

Prospective, multicenter, study.

METHODS:

Patients chronically treated with emtricitabine (FTC) + tenofovir (TDF) + efavirenz (EFV) or lamivudine (3TC) +TDF +EFV and with a HIV-RNA < 50 copies/mL were switched to the single-pill fixed-dose regimen (FDR) of FTC +TDF +EFV. Data were collected with SF-36 using visual analog scales. Results of the final (6 months) primary as-treated analysis are reported.

212 pts 202 pts

Adherence	93,8%	96,2%	P<0.01
QoL	68,7%	72,7%	P=0.042
CD4 (mean)	556	605	P<0.001
VL< 50 cps/ml (AT)		98%	
VL<50 cps/ml (ITT)		93,4%	
LTFU		4	
AE		6	

CONCLUSION:

By substituting a one-pill once-a-day HAART, we observed an improvement of both adherence and QoL while maintaining high virologic and immunologic efficacy. HAART simplicity is an added value that favors adherence and may improve long-term success.

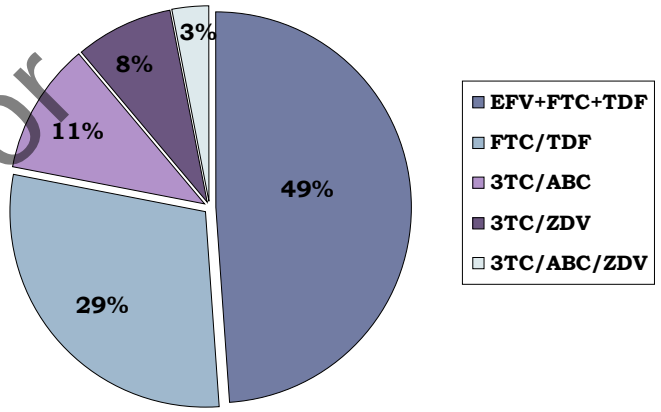
Balearic Islands (Spain) Single Centre Dataset Impact of Breaking Up the FDC/STR

Rectrospective, comparative cohort analysis of the incidence of drug-related AEs in 75 patients exposed to FDC/STR disruption compared to 150 matched non-exposed patients

Patients with EAs probably related to HAART by study visit

	Exposed N = 75	Non-Exposed N = 150	Odds Ratio (95% CI)
Visit -1	4 (5,3%)	1 (0,7%)	n.s.
Baseline	2 (2,7%)	1 (0,7%)	n.s
Visit + 1	14 (18,7%)*	2 (1,3%)	16,8 (3.7-76.9)
Visit + 2	2 (2,7%)	2 (1,3%)	n.s

* Neuropsychiatric disorders related to efavirenz was the main AE reported (9 patients out of 14).



Breaking up the FDC/STR leads to,

- An approx. 17 fold increase in the risk of AEs probably related to HAART
- An increase in healthcare utilization and costs

Daily ARV Pill Burden and Hospitalization Risk in Medicaid HIV-Infected Population

- Chart review of Medicaid Multistate Database
- 7783 patients with ICD-9 code for HIV, diagnosed in 2005-2009, who started a HAART regimen for ≥ 60 days
  - n = 1838 received fixed-dose TDF/FTC/EFV at any time
  - n = 5945 received ≥ 2 pills/day and never received fixed-dose TDF/FTC/EFV
- Adherence (based on pharmacy records) consistently higher among TDF/FTC/EFV recipients

Number of Hospitalization per 100 Patients

Subgroup	TDF/FTC/EFV	≥ 2 Pills/Day
Treatment naive	39.2	53.3
Treatment experienced	39.7	53.9
Women of childbearing age	28.4	47.3
Men with previous mental health diagnosis	30.8	51.3

- Significantly fewer hospitalizations per 100 patients in patients receiving TDF/FTC/EFV
  - In multivariate analysis, receipt of TDF/FTC/EFV associated with 25% ↓ risk of hospitalization
- **Caveats: Not a randomized study, no HIV-1 RNA or CD4+ data**

Cohen C, et al. ICAAC 2011. Abstract H2-791.

Daily ARV Pill Burden and Hospitalization Risk in Medicaid HIV-Infected Population

Joel E. Gallant, MD, MPH:
The results of this study are very interesting and will be the subject of much discussion. However, I remain unconvinced that this association is the result of a causal relationship. Rather, I suspect the findings may reflect a **prescribing bias** that I see in my own practice. **I typically prescribe fixed-dose tenofovir/emtricitabine/efavirenz to patients who have very few comorbidities, who are likely to be highly adherent, and who do not have mental illness or substance abuse issues.** When I have **concerns** about a patient's **comorbidities, adherence potential, or mental health factors, I often prescribe a boosted PI-based regimen**, and it would therefore not surprise me at all to find out that patients in my clinic receiving PIs are hospitalized more frequently than those receiving fixed-dose tenofovir/emtricitabine/efavirenz

Daily ARV Pill Burden and Hospitalization Risk in Medicaid HIV-Infected Population

Unfortunately, there is simply no way to compare the single tablet with the equivalent components separately, because no one administers these agents in that way. However, that comparison would provide the answer.

Joseph J. Eron, Jr., MD:
When the study author was questioned about that comparison, he stated that they considered it but **the number of patients who received tenofovir/emtricitabine and efavirenz as separate components was approximately 100 or fewer.**

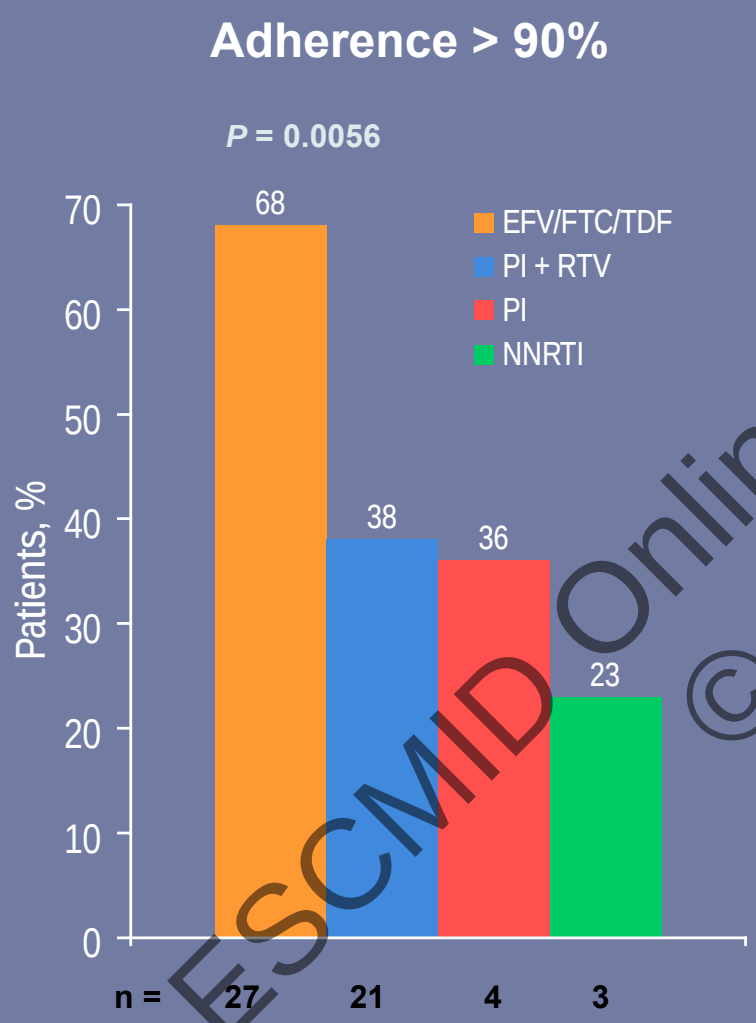
REACH Cohort Adherence Study
Methods

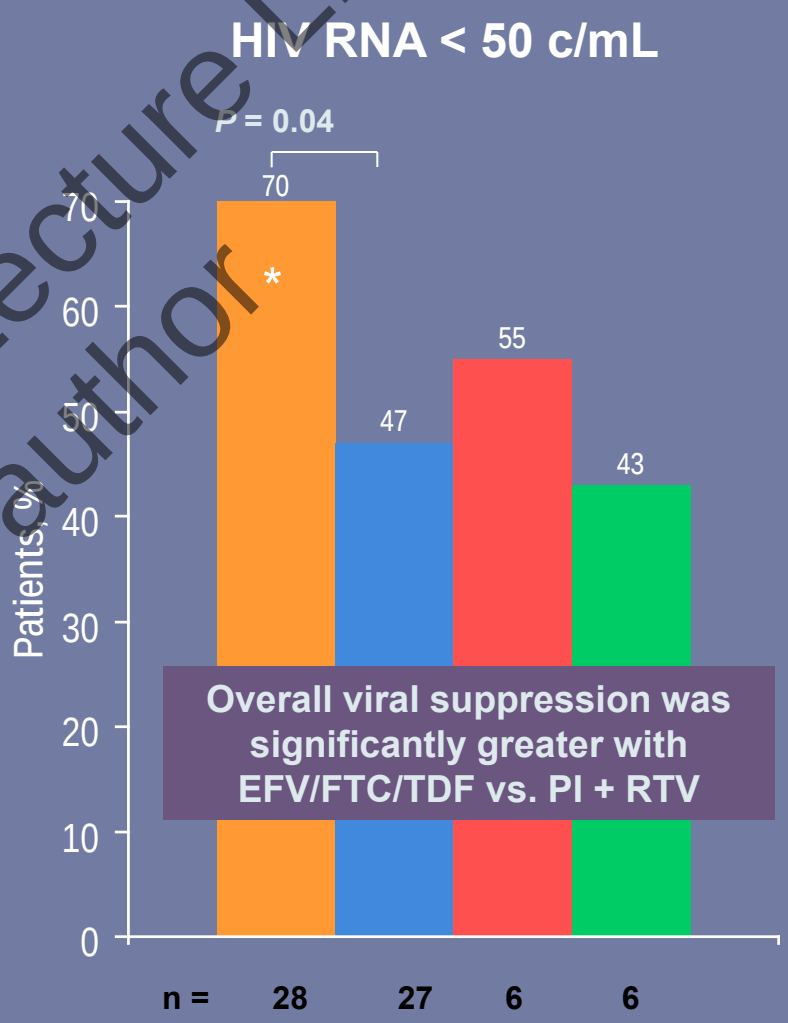
- Patients recruited from a cohort of HIV+ homeless and marginally housed individuals (REACH cohort) and from public health clinics in San Francisco serving the same population.
- Eligibility required initiation of ART within the prior 6 months with:
  - EFV/FTC/TDF (STR)
  - PI or PI + RTV + 2 NRTIs*
  - NNRTI + 2 NRTIs*
- 6-month adherence measured by monthly unannounced pill counts; a validated, "gold standard" method (comparable to MEMS)
- Regimens compared after controlling for confounders, including age, gender, race, education, injection drug use, homelessness, Beck Depression Inventory, and CD4 nadir

***Historical data from the same cohort used for these comparisons to EFV/FTC/TDF (STR)**

Bangsberg D, et al. AIDS 2010; 24:2835-40

REACH Cohort Adherence Study
Results



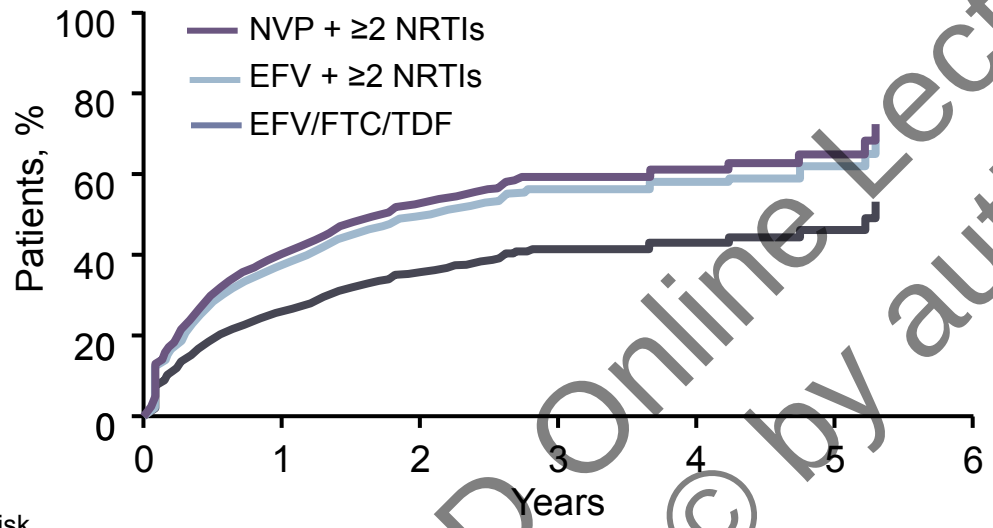


*data missing for 7 subjects

Bangsberg D, et al. CROI 2010. San Francisco. Poster #510

US PharMetrics Claims Database
Adherence and Persistency of Initial NNRTI-based ART Regimens

Adjusted Kaplan-Meier plots of time to non-persistency with NNRTI-based regimens



No. at Risk							
EFV/FTC/TDF	1874	743	288	55	0	0	0
EFV+ ≥2NRTIs	893	304	127	49	20	10	0
NVP+ ≥2NRTIs	207	85	34	18	10	0	0
Total	2974	1132	449	122	30	10	0

Multivariate analyses of non-adherence with NNRTI-based regimens

Regimen	Rate ratio	95% CI	*P* value
EFV/FTC/TDF	1.00	–	–
EFV + ≥2NRTIs[a]	1.57	1.32–1.86	<0.01
NVP + ≥2NRTIs	2.01	1.51–2.67	<0.01

[a] Excluding EFV/TDF/FTC

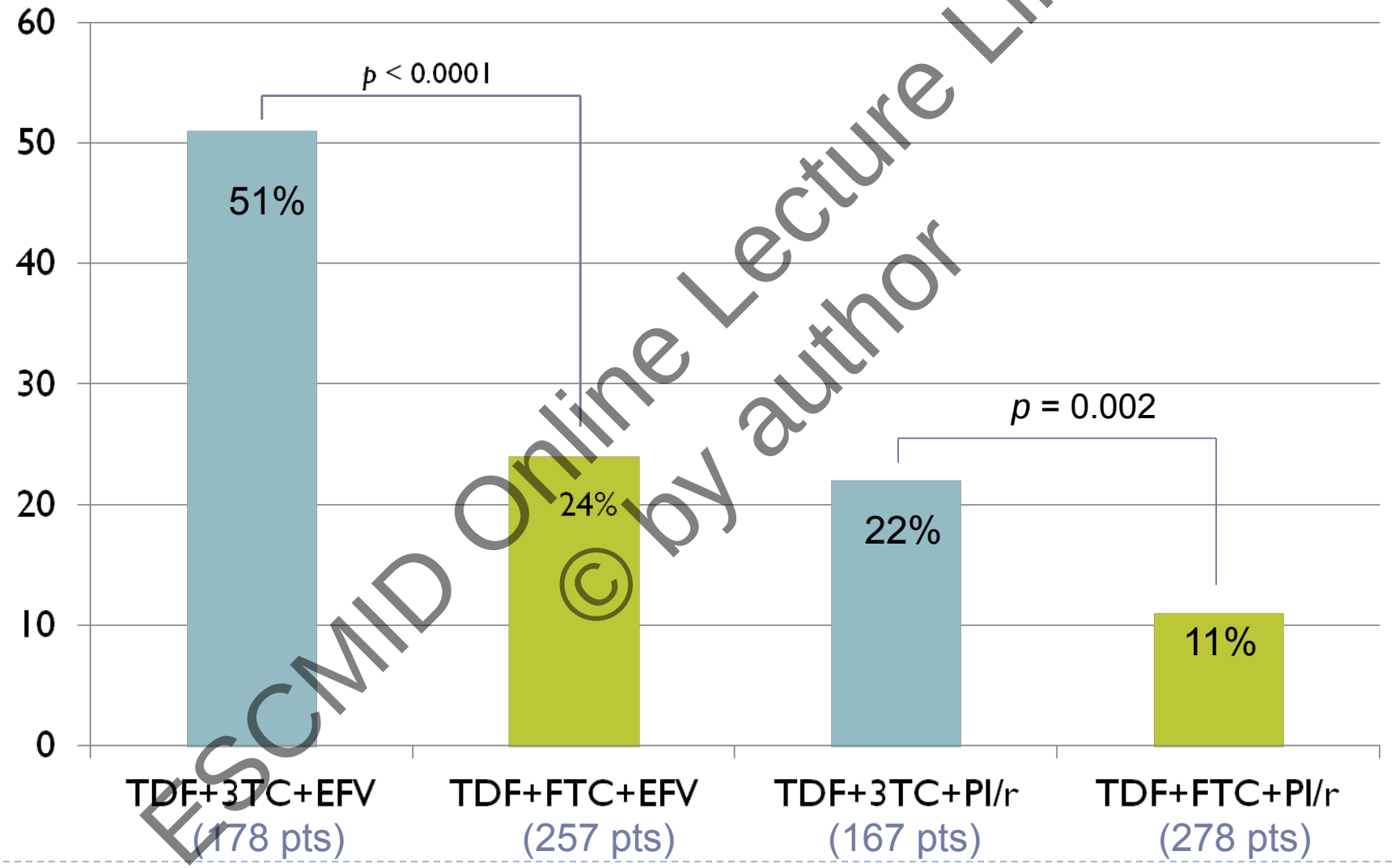
- Beginning treatment with the STR of EFV/FTC/TDF was associated with significantly better adherence and persistency compared to beginning treatment with an EFV-based regimen other than EFV/TDF/FTC or an NVP-based regimen

Taneja C, et al. EACS 2011. Belgrade, Serbia. #PE10.1/2

Single Tablet Regimens & Components

Pharmacoeconomics

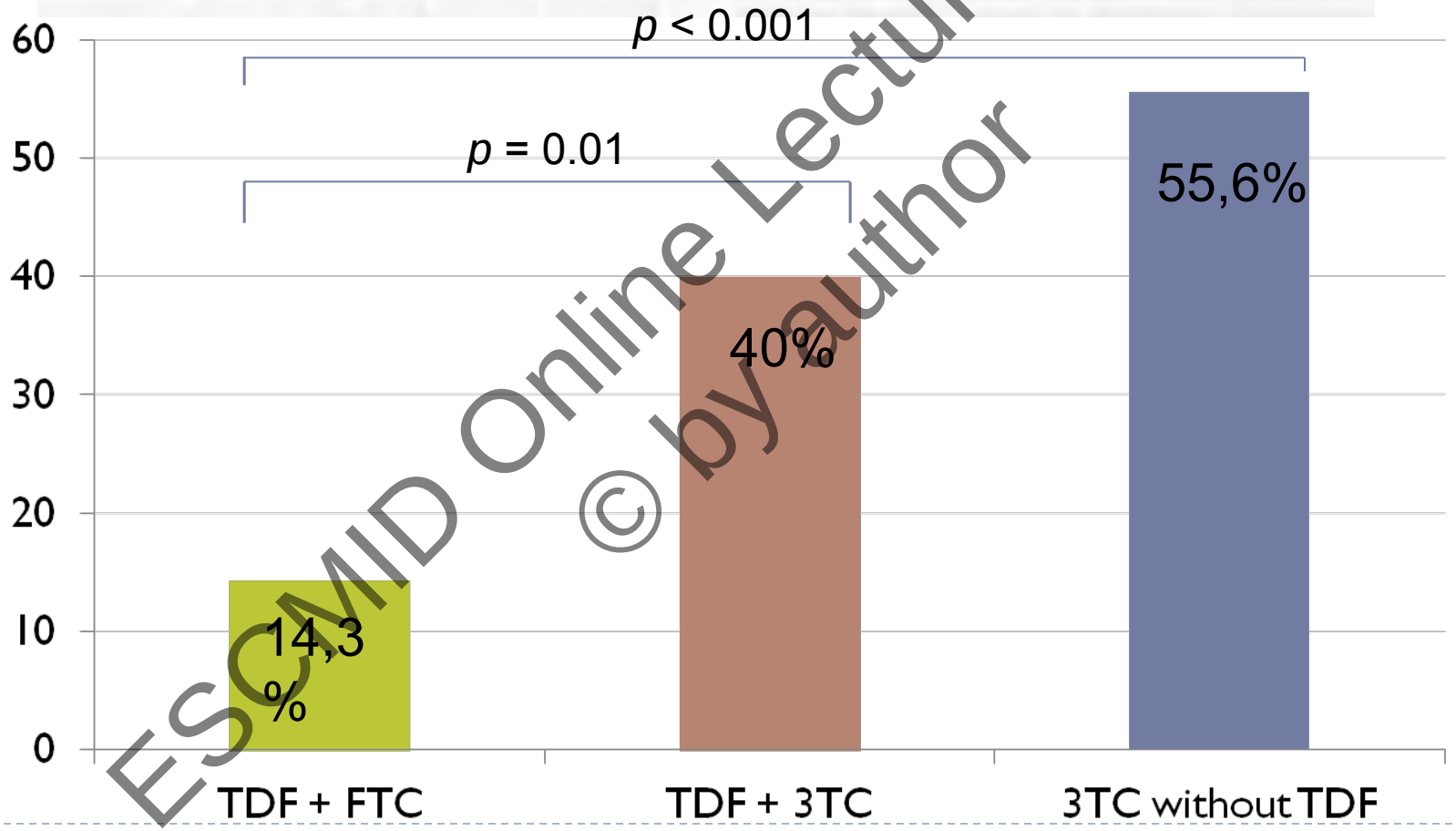
3TC vs FTC: selection of M184I/V



A-G Marcelin et al, CROI 2011, abstract 617

Different Evolution of Genotypic Resistance Profiles to Emtricitabine Versus Lamivudine in Tenofovir-Containing Regimens

Valentina Svicher, PhD, Claudia Alteri, PhD,* Anna Artese, PhD,† Federica Forbici, PhD,‡ Maria Mercedes Santoro, PhD,* Dominique Schols, PhD,§ Kristel Van Laethem, PhD,§ Stefano Alcaro, PhD,† Giosuè Costa,† Chiara Tommasi, MD,‡ Mauro Zaccarelli, MD,‡ Pasquale Narciso, MD,‡ Andrea Antinori, MD,‡ Francesca Ceccherini-Silberstein, PhD,* Jan Balzarini, MD, PhD,§ and Carlo Federico Perno, MD, PhD*‡*



We can expect an increase of resistance

- Is there an ‘acceptable’ level of resistance?
- Where will we draw the line between ‘acceptable’ and ‘unacceptable’ resistance?
- How will it affect resistance transmission?

Trade-Offs With Generics

Advantages	Disadvantageous
▸ 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

- EACS Guideline, October 2011: Generic HIV drugs are becoming more available and can be used as long as **they replace the same drug and do not break recommended fixed-dose combinations**

Impact of generics for research and development of new HIV Drugs

Impact of generics for research and development of new HIV Drugs

- R&D costs are extremely high.
- Resistance is declining in Europe and USA. A reasonable return for development of new drugs can only be achieved if the drug makes its way to first-line or, at most, second-line therapy.
- With cheap generics like efavirenz or darunavir in the market, and residual multiresistance, is it worth to invest on new, expensive drugs?
- If the decision is not to invest, what will be the long term consequences for HIV infected patients?

Conclusions

- Adequate quality control of generic drugs is vital.
- OD regimens improve adherence compared to BID; impact on virological outcome unclear.
- STR is associated with improved adherence and longer time on the initial regimen; impact on virologic outcome unclear, cost-effectiveness against a regimen incorporating a generic drug not known.
- Therapy switches for economical reasons in suppressed patients, taking a well tolerated regimen may increase the risk of failure.
- An increase in resistance is to be expected if FTC is replaced by 3TC and with the use of regimens without tenofovir. Impact on TDR unknown.
- Impact of the availability of generic drugs on the pipeline of new agents unknown, but perceived as negative.

Thank you for your attention…