

Off label/Generic treatment

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Off-label and generic treatment

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off-label treatment

“Unapproved use of an approved drug”¹

..use in an unapproved age group, dosage, disease or route of administration.²

Common in pediatrics / rare disease

Might vary between countries

1. FDA definition - <http://www.fda.gov>

2. Stafford RS. *N Engl J Med.* 2008 Apr 3;358(14):1427-9

off-label treatment

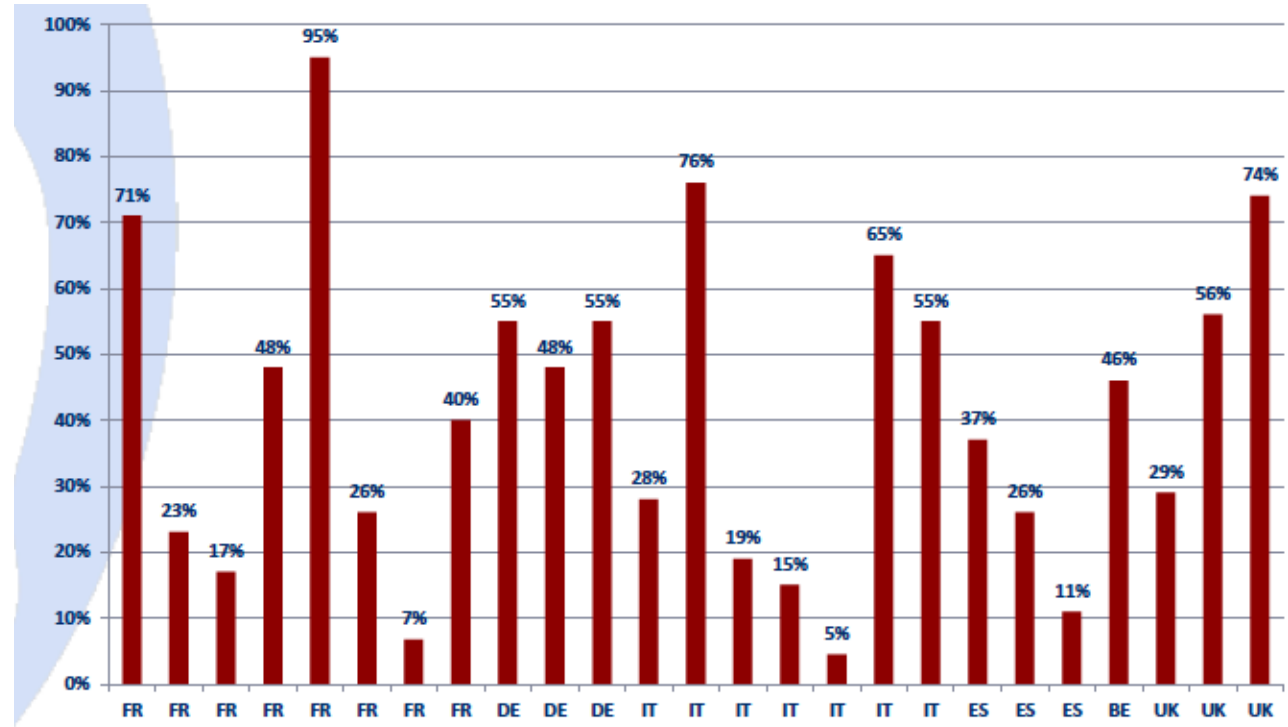
- Common examples
 - Unboosted AZV (U.S. vs EU)
 - Crushing pills or opening capsules
 - Special circumstances (renal impairment, TB..)
 - Most salvage therapies
 - De-escalation strategies

off-label treatment

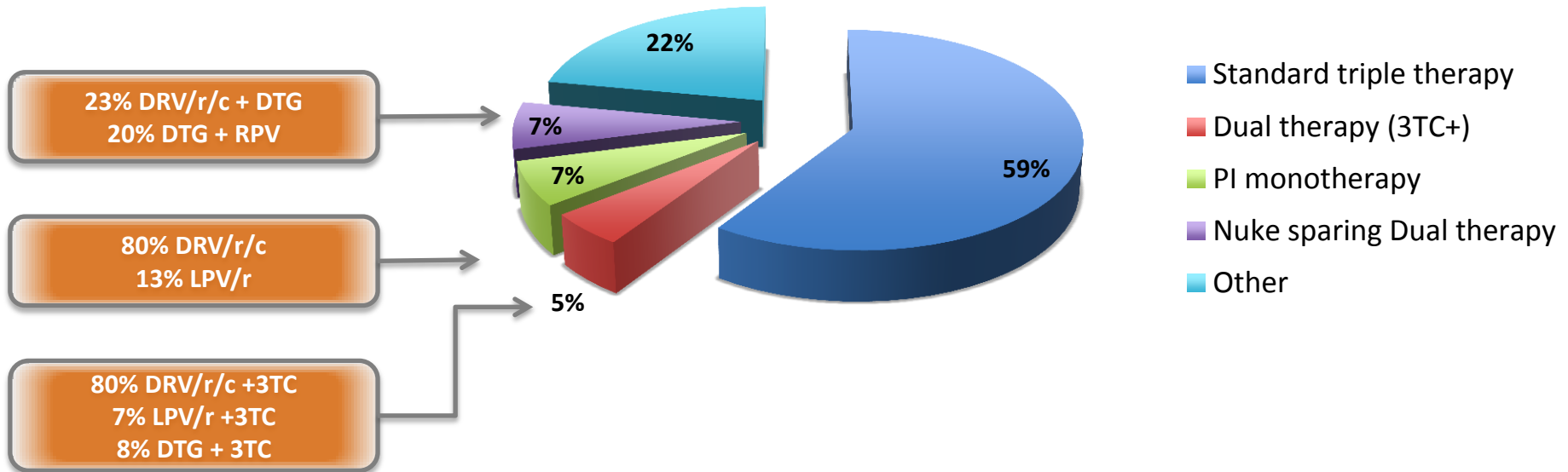
...when there are even recommendations (EACS)
what's the problem than?

- Often anecdotal reports → little or selective follow-up
- Lack of interest of sponsors → no high qual. studies
- Legal issues → pt. needs to be informed

European commission has initiated a study to describe the existing and foreseen practises of OLU across Member States. Prevalence Adults. Hospitals



Off label use-regimens in Hospital La Paz. Madrid

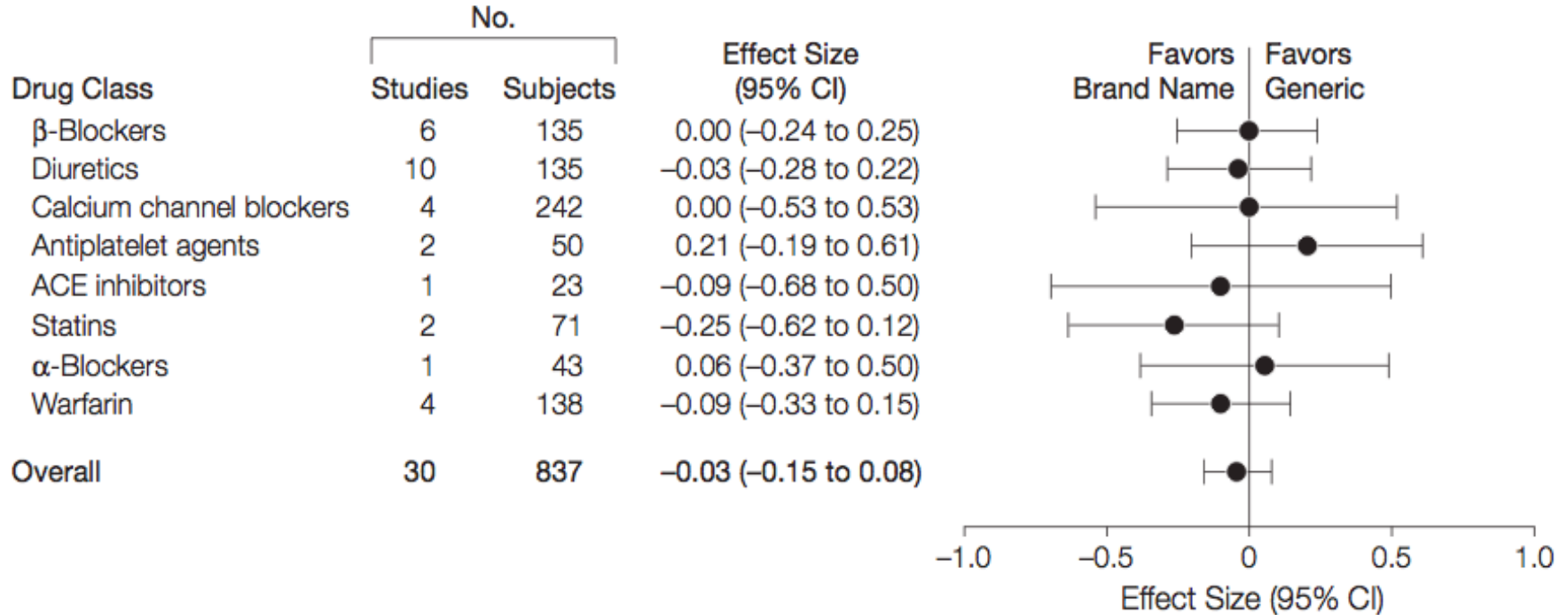


GENERICS

- **Any medicine that has the same qualitative and quantitative composition and active substance, the same pharmaceutical form and its bioequivalence with the originator product has been demonstrated with the appropriate bioequivalence studies**
 - A gen medicine must only show bioequivalence (except IV) and is used at the same doses to treat the same diseases
 - Can have different inactive ingredients, appearance and packaging
 - A different form of the active substance can be chosen (i.e. “hydrochloride salt”) if it is more stable and does not affect medicine’s activity
 - Gen medicines are manufactured according to the same quality standards as all other medicines (and periodically inspected by reg. authorities)

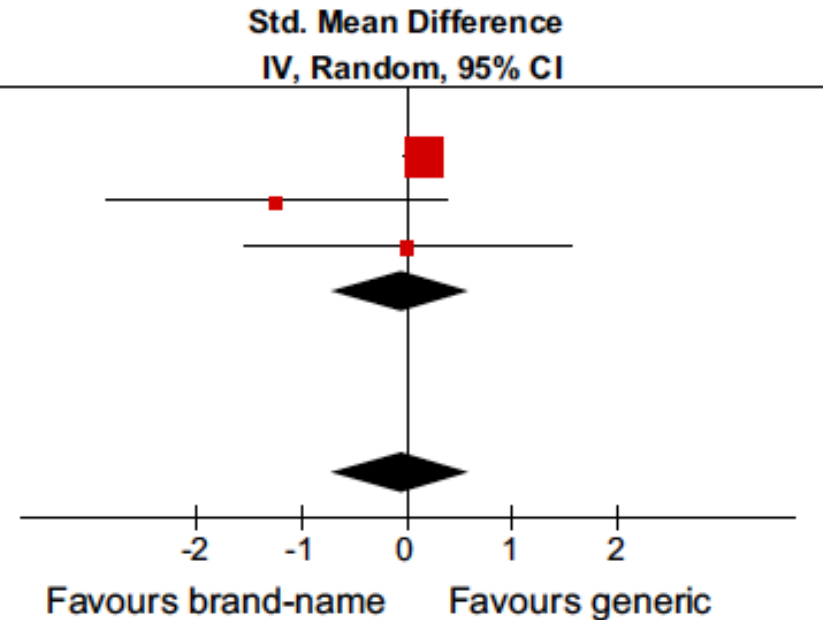
Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis



Generic versus brand-name drugs used in cardiovascular diseases. MACE or death

Study or Subgroup	Weight	Std. Mean Difference IV, Random, 95% CI	Year
1.2.3 Antiplatelet agents			
Khosravi 2011	72.3%	0.15 [-0.04, 0.34]	2011
Park 2013	13.4%	-1.25 [-2.87, 0.37]	2013
Seo 2014	14.3%	0.00 [-1.56, 1.56]	2014
Subtotal (95% CI)	100.0%	-0.06 [-0.71, 0.59]	
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 2.86$, $df = 2$ ($P = 0.24$); $I^2 = 30\%$			
Test for overall effect: $Z = 0.18$ ($P = 0.86$)			
Total (95% CI)	100.0%	-0.06 [-0.71, 0.59]	
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 2.86$, $df = 2$ ($P = 0.24$); $I^2 = 30\%$			
Test for overall effect: $Z = 0.18$ ($P = 0.86$)			
Test for subgroup differences: Not applicable			





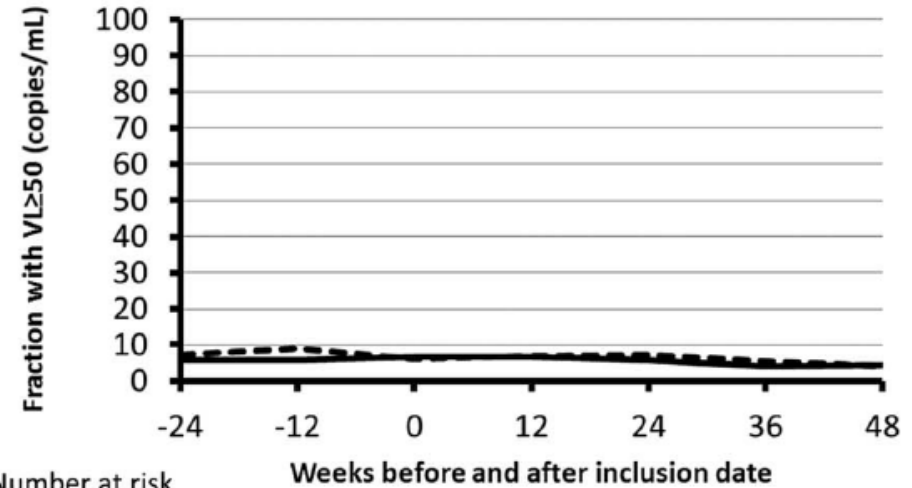
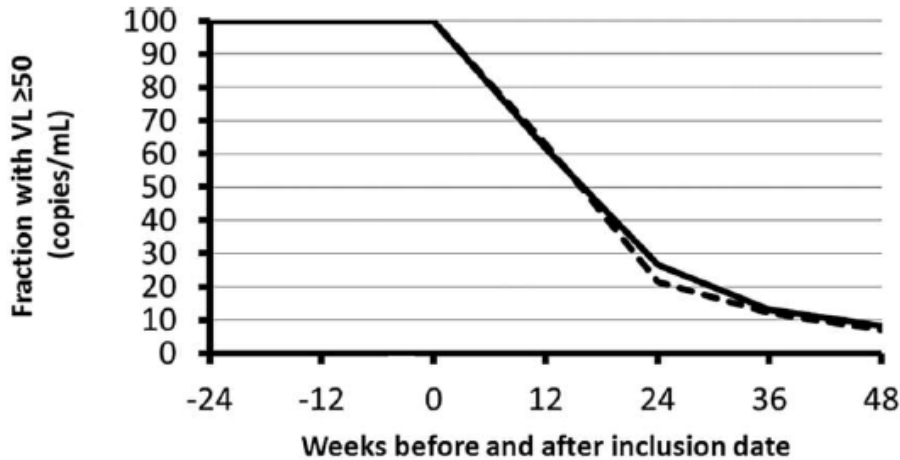
Effectiveness of generic and proprietary first-line anti-retroviral regimens in a primary health care setting in Lusaka, Zambia: a cohort study

- 14736 patients eligible
 - 7277, 49% generic and 7459, 51% branded
- No difference in post 90-dy mortality AHR 0.93 (95% CI 0.77-1.12)
- No longitudinal differences in
 - CD4 response
 - Weight change
 - Haemoglobin concentration

Switch From a Once-Daily Single-Tablet Regimen to a Triple-Tablet Regimen for Economic Reasons

Naïve patients

Suppressed patients



Number at risk	-24	-12	0	12	24	36	48
STR-TEE ----	47	49	111	105	79	58	43
TTR-TEL ___	22	29	56	47	34	23	12

Number at risk	-24	-12	0	12	24	36	48
STR-TEE ----	351	353	356	349	343	329	274
TTR-TEL ___	510	511	512	504	478	422	322

Case 1

- 40 y MSW, carpenter, CNS Toxo
 - CD4 10/ μ l, VL 1.320.000 c/ml
 - ABC/3TC + SAQ/r 1000/100 mg 1-0-1
 - Week 8: 23.000 c/ml =>M184I
 - Toxo lesions not fully regressed, KM enhancing
 - AZT / 3TC / ABC +SAQ/r
- ➔ 01/2006 – 04/2007 VL<40 c/ml + CD4 420/ μ l

40y, m, C3, M184I,
AZT 3TC ABC SAQ/r, <40 c/mL

- Leave it like that?

40y, m, C3, M184I,
AZT 3TC ABC SAQ/r, <40 c/mL

- Leave it like that?
- ABC 3TC SAQ/r 1-0-1
- ➔ 04/2007 – 09/2009 VL 150-280 c/ml, CD4 668/μl
- ➔ GT: only M184I

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- pt wishes QD treatment

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AZT 3TC ABC SAQ/r, <40 c/mL

- Leave it like that?
- ABC 3TC SAQ/r 1-0-1
- ➔ 04/2007 – 09/2009 VL 150-280 c/ml, CD4 668/μl
- ➔ GT: only M184I
- Leave it like that?
- pt wishes QD treatment
- TVD DRV/r 800/100 mg 1-0-0
- ➔ 09/2009 – 04/2012 VL <20 – 60 c/ml, CD4 574/μl

40y, m, C3, M184I,
AZT 3TC ABC SAQ/r, <40 c/mL

- Leave it like that?
- ABC 3TC SAQ/r 1-0-1
- ➔ 04/2007 – 09/2009 VL 150-280 c/ml, CD4 668/ μ l
- ➔ GT: only M184I
- Leave it like that?
- pt wishes QD treatment
- TVD DRV/r 800/100 mg 1-0-0
- ➔ 09/2009 – 04/2012 VL <20 – 60 c/ml, CD4 574/ μ l
- ➔ pt. claims DRV/r responsible for erectile dysfunction

40y, m, C3, M184I, TDF FTC DRV/r, <60 c/mL

- TVD / AZT 250 mg 1-0-0
- ➔ 04/2012 – 06/2014 VL <20 c/ml, CD4 630/μl
- Eversince TVD / AZT 100 mg 1-0-0
- ➔ VL < 20 c/ml CD4 608/μl (30%)

Case 2 – 38y female

Datum	Text	CD4Abs	HIVPCR
29.11.2010	Candidia esophageal		
29.11.2010	HIV Encephalopathy		
29.11.2010	Pneumocystis-carinii pneumonia		
01.12.2010		50	640000
14.12.2010	FTC,TDF,RGV		
03.02.2011		40	3400000
02.03.2011			530000
03.05.2011		50	1600000
20.06.2011		40	2700000

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02.03.2011			530000
03.05.2011		50	1600000
20.06.2011		40	2700000
02.08.2011	M184V, N155H		



date	text	CD4Abs	CD4Proz	CD4Ratio	HIVPCR
02.08.2011	FTC,TDF,LPV,RTV				
30.08.2011		140			16000
24.11.2011					17000
06.12.2011		127	12.70	0.21	11536
12.01.2012		135	12.28	0.21	30074



date	text	CD4Abs	CD4Proz	CD4Ratio	HIVPCR
02.08.2011	FTC,TDF,LPV,RTV				
30.08.2011		140			16000
24.11.2011					17000
06.12.2011		127	12.70	0.21	11536
12.01.2012		135	12.28	0.21	30074
12.01.2012	AZT,FTC,TDF,LPV,RTV,MRV				
09.02.2012		195	16.26	0.27	702
22.03.2012		195	10.84	0.15	114
31.05.2012		216	13.48	0.20	28
20.09.2012		194	13.87	0.20	<20
06.12.2012		236	14.78	0.23	<20
21.03.2013		228	13.39	0.20	<20
13.06.2013		323	19.00	0.33	<20
09.09.2013		210	15.00	0.26	<20
12.12.2013	wish to become pregnant	252	18.00	0.36	<20



date	text	CD4Abs	CD4Proz	CD4Ratio	CD8CD38Proz	HIVPCR
18.12.2013	AZT,FTC,TDF,LPV,RTV					
20.03.2014		270	18.00	0.34		<20
04.07.2014		210	21.00	0.45		<20
27.11.2014		275	25.00	0.59		<20
24.03.2015		286	22.00	0.48	56	<20
25.06.2015		299	23.00	0.52	56	<20
16.09.2015		378	27.00	0.62	55	<20
08.10.2015	QD treatment desired					
08.10.2015	DRV,RTV,MRV					
08.12.2015		336	24.00	0.53	62	99
23.03.2016		378	21.00	0.46	58	115
29.06.2016		264	22.00	0.46	53	711
04.07.2016	AZT,FTC,TDF,DRV,RTV					
09.09.2016		312	24.00	0.53	50	<20
05.12.2016						

Summary

- Old / generic drugs can have several benefits
 - Very well established clinical profile
 - (pregnancy, dose adjustments, AIDS, toxicity)
 - Less expensive and widely available
 - When you loose them, you loose them

