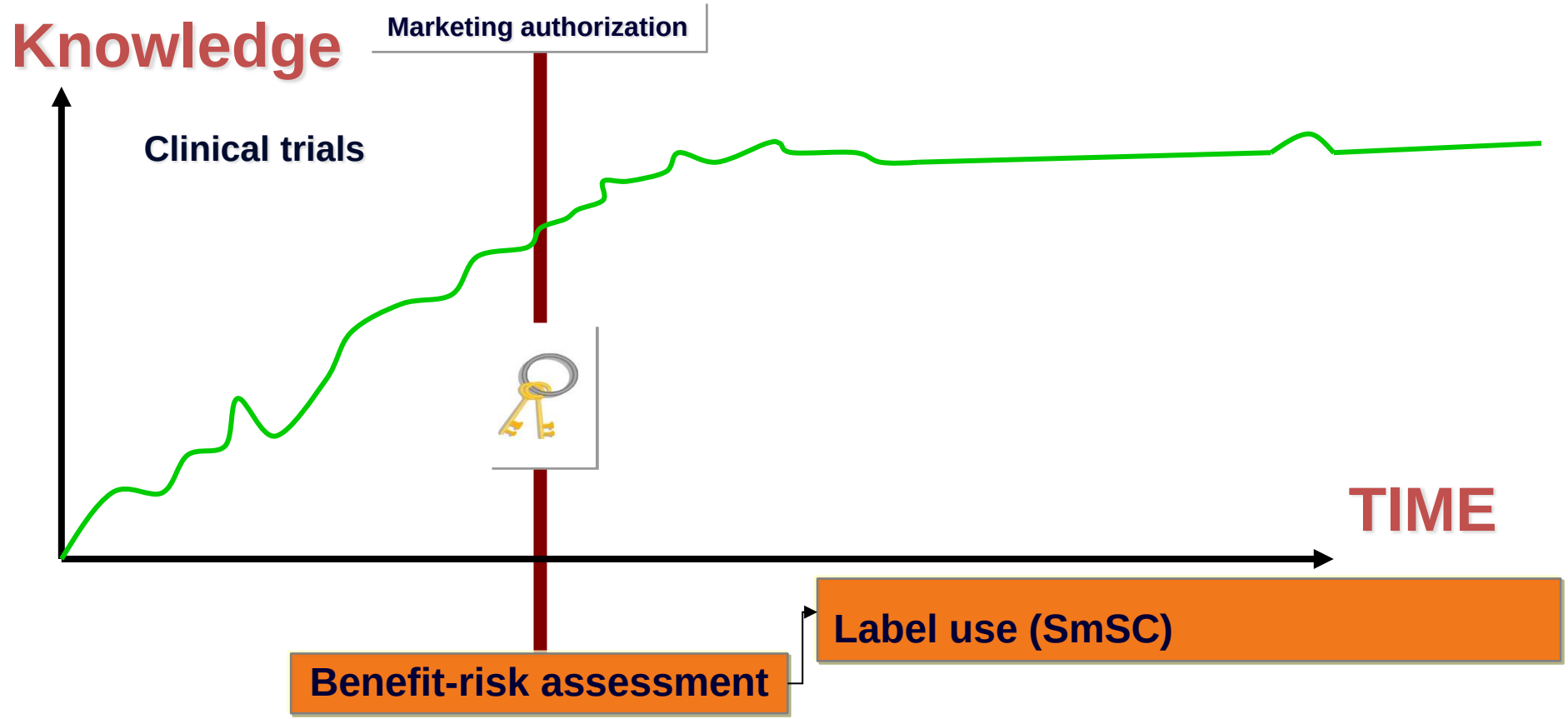
Off label/Generic treatment

Moderator: Nathan Clumeck, Belgium

Markus Bickel, Germany
Ignacio Bernardino, Spain

Off label/Generic treatment

Ignacio Bernardino, Spain


Knowledge
Marketing authorization
Clinical trials
TIME
Label use (SmSC)
Benefit-risk assessment

Knowledge

Marketing authorization

New therapeutic indications

Phamarcovigilance

Continuous benefit-risk balance assessment

TIME

New SmSC modifications

Benefit-risk assessment

Use of medicinal products in special situations…

The product information (SmPC) describes how can be used safely and effectively based on submitted data from clinical trials, post-marketing information and information from other products within the same class.

Therefore, the SmPC might not contain exhaustive recommendations for use in all possible situations.

OFF-LABEL USE DEFINITION: any use of an authorised medicinal product not covered by the terms of the marketing authorisation, including the use of the product for a **different indication**, **different dose or dosage** or for a **patient group not specified on the SmPC.**

4.1 Therapeutic indications

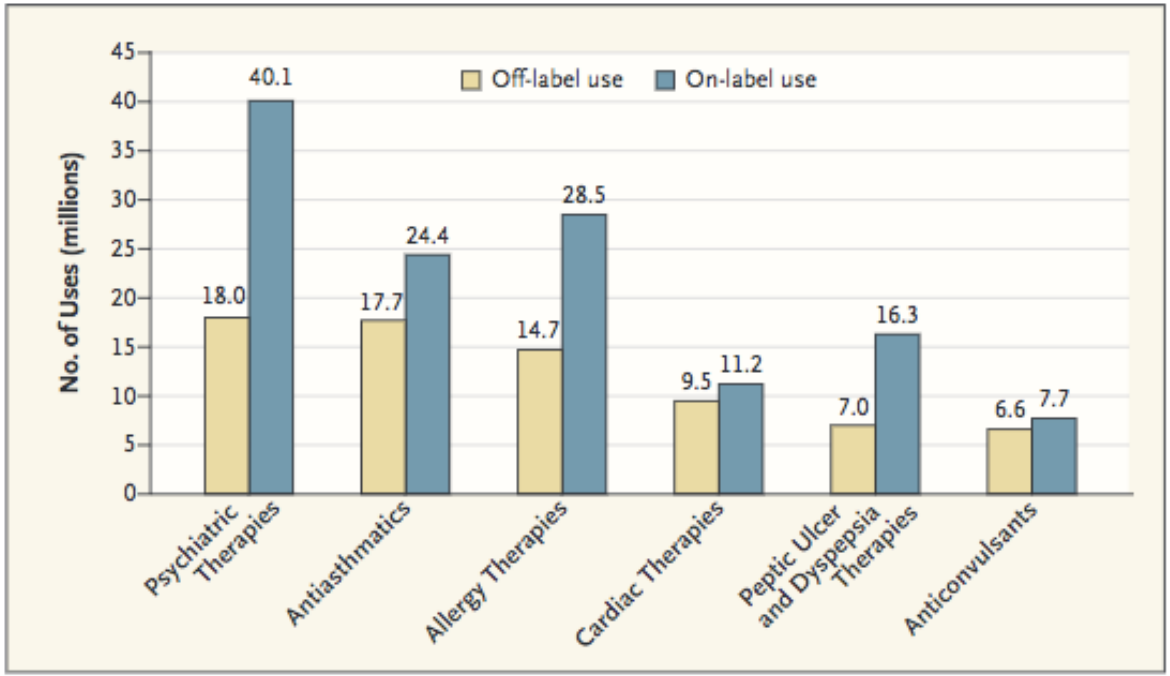
Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in

Genvoya is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir (see sections 4.2 and 5.1).

Regulating Off-Label Drug Use — Rethinking the Role of the FDA

Randall S. Stafford, M.D., Ph.D.

For the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approx. **21% of prescriptions**



Estimated Numbers of Prescriptions for On-Label and Off-Label Uses of Medications in Various Functional Classes, 2001.

Randall S *et al. N Engl J Med* 2008;358:1427-29

Q&A on Off-Label Use

Proposal in response to EFPIA paper of 3rd October 2014

EMA Industry Stakeholder Platform - Operation of EU Pharmacovigilance Legislation
12 January 2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Art 23 (2) of DIR 2001/83/EC requires the MAH to report to the competent authorities "*any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned*", including "*data on the use of the medicinal product where such use is outside the terms of the marketing authorisation*".

The expectations for the collection of off label use reports without adverse reaction are as follows:

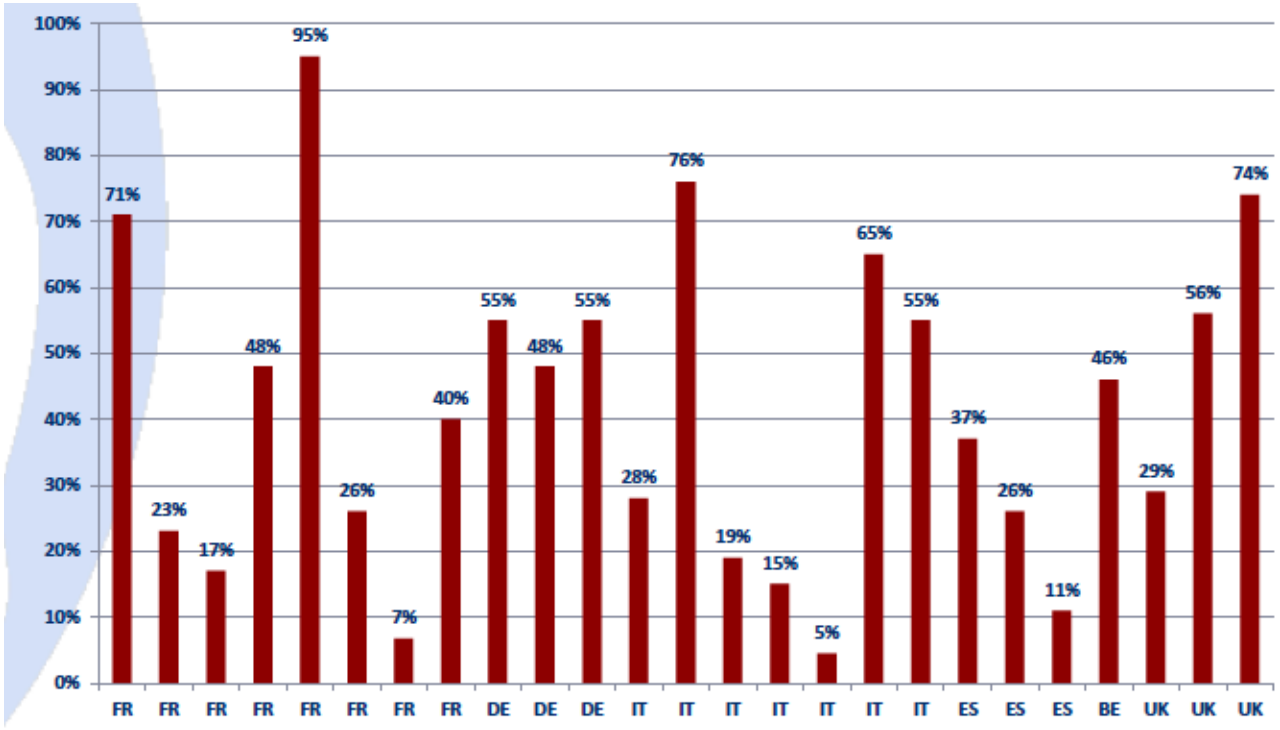
- Confirmed reports of off-label use e.g. "Use in an unauthorised indication":
  - These reports should be collected as part of the pharmacovigilance system in order that they may be easily collated for analysis and presentations during the production of a PSUR or RMP. In general, there is no expectation to follow-up on these reports except where they may be associated with an adverse reaction or on prospective reports of pregnancy.

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

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

epha
european public health alliance

nivel



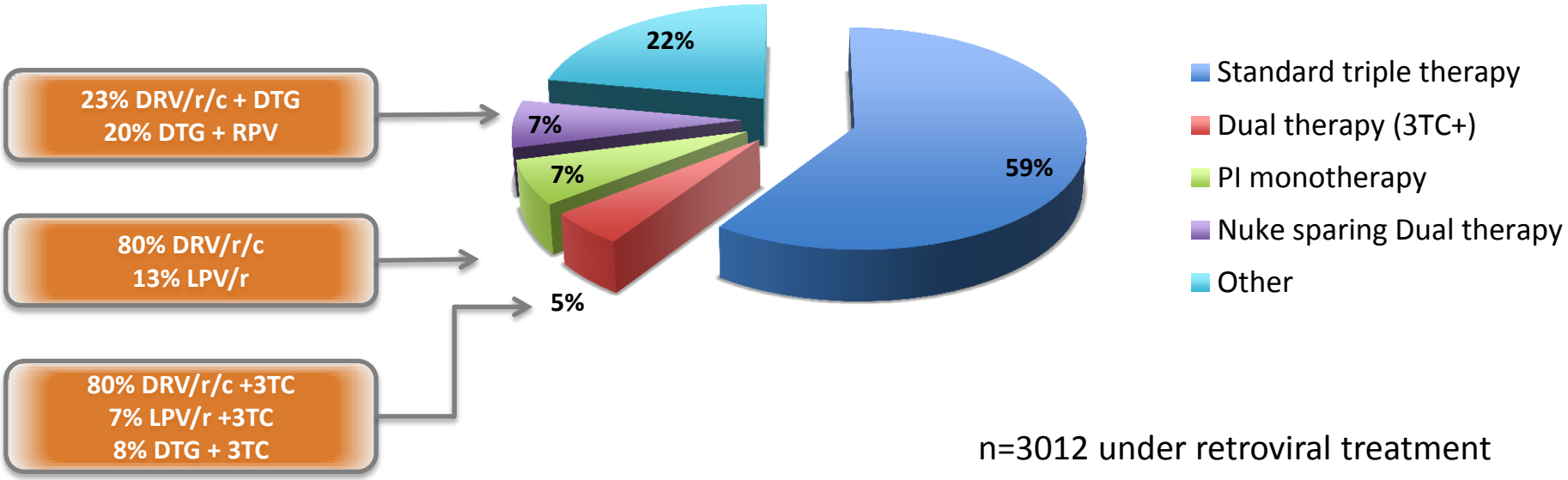
Off-label use (olu). Hot debate in EU

Indication: several cancers

Age-related macular degeneration

Off-label prescribing of Avastin® (bevacizumab) for the debilitating wet AMD eye condition has been relatively common even though the drug – unlike the more expensive Lucentis® (ranibuzimab), which is co-marketed by Novartis and Roche – is not approved for this licence.

Off label use-regimens in Hospital La Paz. Madrid



n=3012 under retroviral treatment

GENERICS

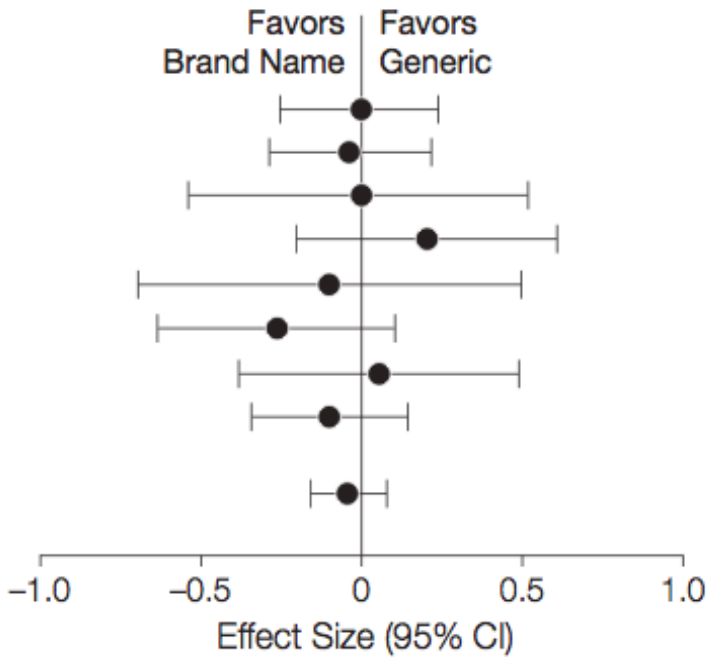
- **Any medicine that has the same qualitative and quantitative composition and active substance, the same pharmaceutical form and its bioequivalence with the originator product has been demonstrated with the appropriate bioequivalence studies**
  - A gen medicine must only show bioequivalence (except 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)

EMA. Q&A on Generic Medicines. Available at: http://www.ema.europa.eu/docs

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

A Systematic Review and Meta-analysis

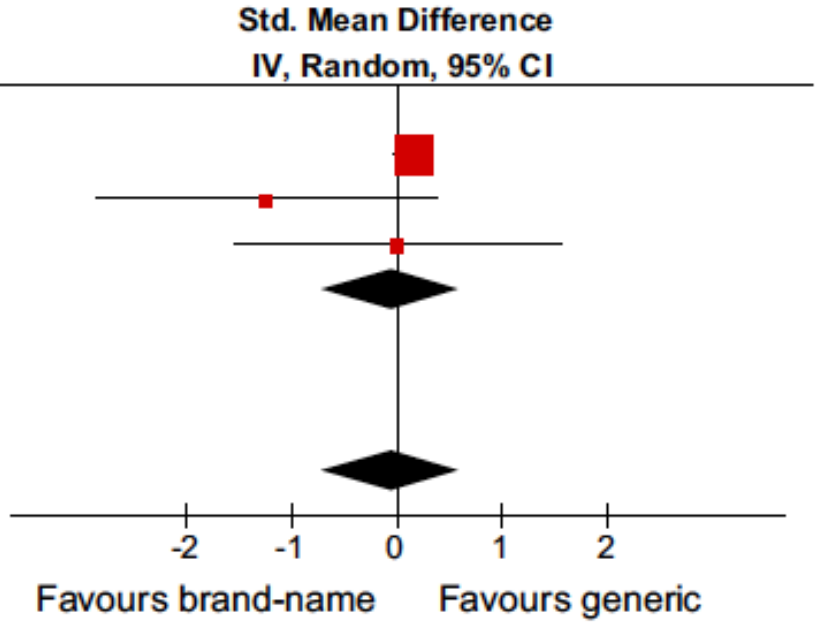
Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	**30**	**837**	**–0.03 (–0.15 to 0.08)**



Kesselheim AS *et al. JAMA* 2008;300:2514-2526

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: Tau² = 0.14; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%			
Test for overall effect: Z = 0.18 (P = 0.86)			
Total (95% CI)	**100.0%**	**-0.06 [-0.71, 0.59]**	
Heterogeneity: Tau² = 0.14; Chi² = 2.86, df = 2 (P = 0.24); I² = 30%			
Test for overall effect: Z = 0.18 (P = 0.86)			
Test for subgroup differences: Not applicable			



Manzoli L *et al. Eur J Epidemiol* 2016;31:351-368

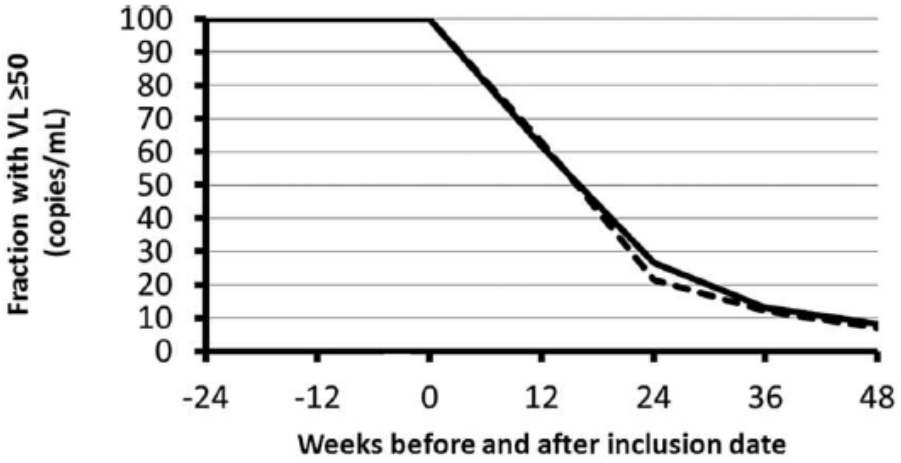
Effectiveness of generic and proprietary first-line anti-retroviral regimens in a primary health care setting in Lusaka, Zambia: a cohort study

- 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

Stringer JSA. *Int J Epidemiol* 2012;41:448-459

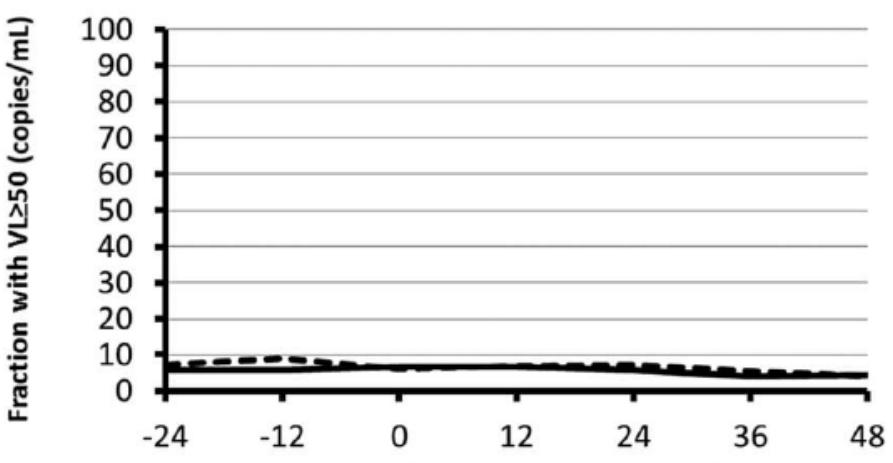
Switch From a Once-Daily Single-Tablet Regimen to a Triple-Tablet Regimen for Economic Reasons

Naïve patients



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

Suppressed patients



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

Engsig *F et al. JAIDS* 2014; 66: 407-413

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

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
02.08.2011	M184V, N155H		

38y, AIDS, 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

38y, AIDS, M184V, N155H,R5

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

38y, AIDS, M184V, N155H,R5

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

38y, AIDS, M184V, N155H

date	text	CD4Abs	CD4Proz	CD4Ratio	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	<20
25.06.2015		299	23.00	0.52	<20
16.09.2015		378	27.00	0.62	<20

38y, AIDS, M184V, N155H

date	text	CD4Abs	CD4Proz	CD4Ratio	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	<20
25.06.2015		299	23.00	0.52	<20
16.09.2015		378	27.00	0.62	<20
08.10.2015	QD treatment desired				
08.10.2015	DRV,RTV,MRV				
08.12.2015		336	24.00	0.53	99
23.03.2016		378	21.00	0.46	115
29.06.2016		264	22.00	0.46	711

38y, AIDS, M184V, N155H

date	text	CD4Abs	CD4Proz	CD4Ratio	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	<20
25.06.2015		299	23.00	0.52	<20
16.09.2015		378	27.00	0.62	<20
08.10.2015	QD treatment desired				
08.10.2015	DRV,RTV,MRV				
08.12.2015		336	24.00	0.53	99
23.03.2016		378	21.00	0.46	115
29.06.2016		264	22.00	0.46	711
04.07.2016	AZT,FTC,TDF,DRV,RTV				
09.09.2016		312	24.00	0.53	<20
05.12.2016					

Clinical case

- 36 y Peruvian male HSH HIV+ since 2006
- Nadir CD4+ 80 cells/mm^3
- Chronic Hepatitis B (HbsAb – HbsAg + HbcAc + HbeAg+ HbeAb -)
- Resistance test: wild type
- HPV anal infection (HPV 16 & 18). AIN grade II

ART initiation **(Jun 2006) TDF/FTC + LPV/r**

Rhabdomyolisis secondary to TDF (CK > 20,000)

Switch to **3TC/ABC + LPV/r**

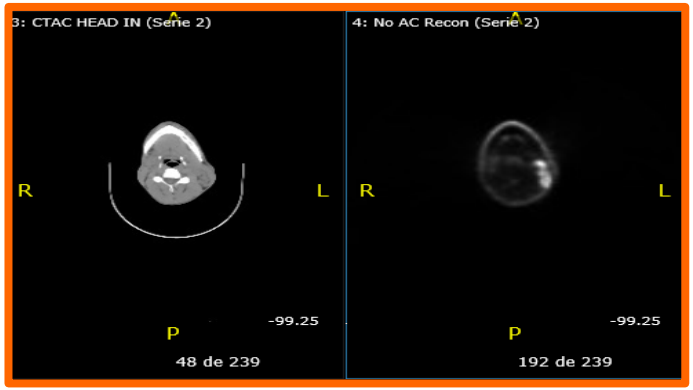
Due to GI toxicity related to abacavir

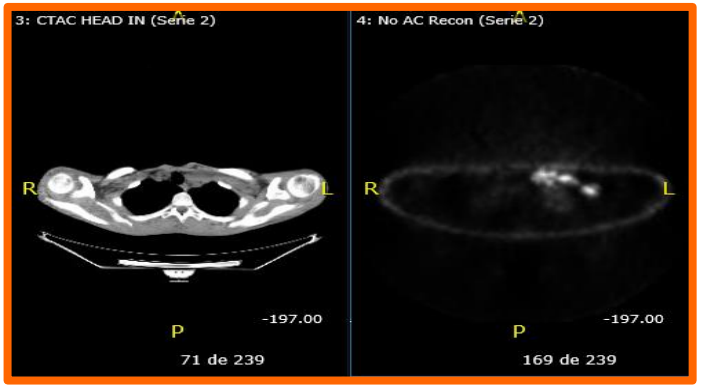
Changed to **3TC + Nevirapine + LPV/r**

Feb 2009: Simplification to **3TC+LPV/r**

CD4+ 170 cells/mm^3 PCR HIV < 50 copies/ml

July 2009: fever, anorexia and weight loss





Hodgkin disease

What would you suggest regarding the ARV treatment?

Hodgkin Complete Remission

	Feb 09	Jun 09	Dec 10	May 10	Jun 11	Oct 11
CD4+ T cells/mm^3	170	80	140	290	350	
Viral load Copies/ml	< 50	< 50	< 50	< 50	< 20	

After standard chemotherapy & radiotherapy, complete remission was obtained in Feb 2010 without changing ART treatment and without adding TDF to prevent HBV reactivation

Dual treatment with lopinavir–ritonavir plus lamivudine versus triple treatment with lopinavir–ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial

José R Arribas, Pierre-Marie Girard, Roland Landman, Judit Pich, Josep Mallolas, María Martínez-Rebollar, Francisco X Zamora, Vicente Estrada, Manuel Crespo, Daniel Podzamczer, Joaquín Portilla, Fernando Dronda, José A Iribarren, Pere Domingo, Federico Pulido, Marta Montero, Hernando Knobel, André Cabié, Laurence Weiss, José M Gatell, on behalf of the OLE/RIS-EST13 Study Group

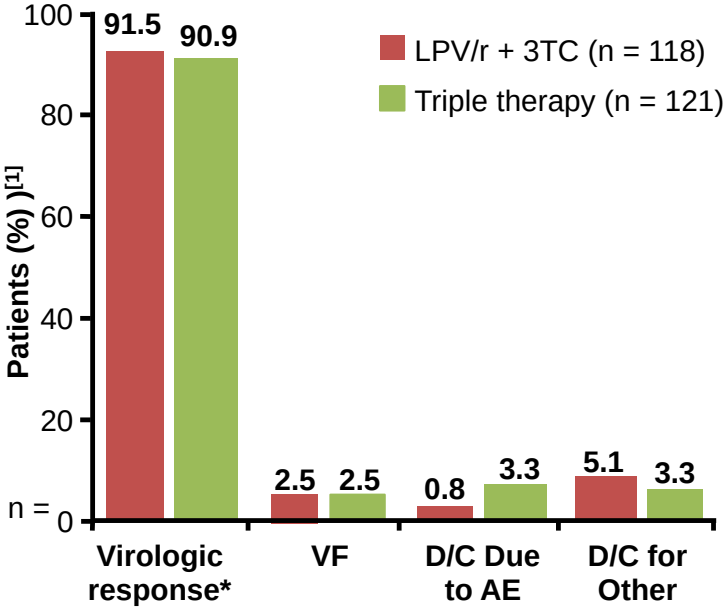
Dual treatment with atazanavir–ritonavir plus lamivudine versus triple treatment with atazanavir–ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial

José A Perez-Molina, Rafael Rubio, Antonio Rivero, Juan Pasquau, Ignacio Suárez-Lozano, Melcior Riera, Miriam Estébanez, Jesús Santos, José Sanz-Moreno, Jesús Troya, Ana Mariño, Antonio Antela, José Navarro, Herminia Esteban, Santiago Moreno, on behalf of the GESIDA 7011 Study Group

Lancet Infect Dis 2015 Jul;15(7):775-84
Lancet infect Dis 2015 Jul; 15(7): 785-92

OLE-trial: lopinavir/r plus 3TC *vs*. lopinavir/r plus TDF or FTC and a second NRTI

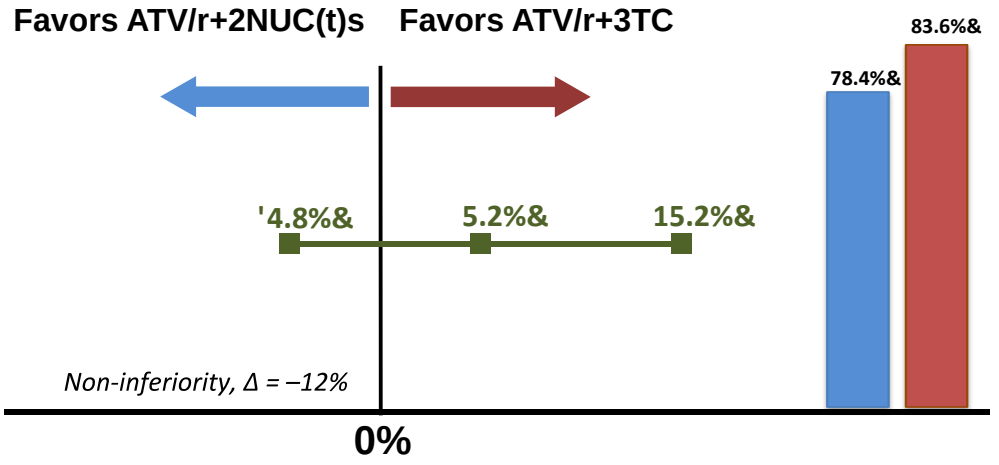
Δ -0.6%
(95% CI: -6.9% to 8.1%)



*PCR-HIV < 50 c/mL 48 week (mITT).

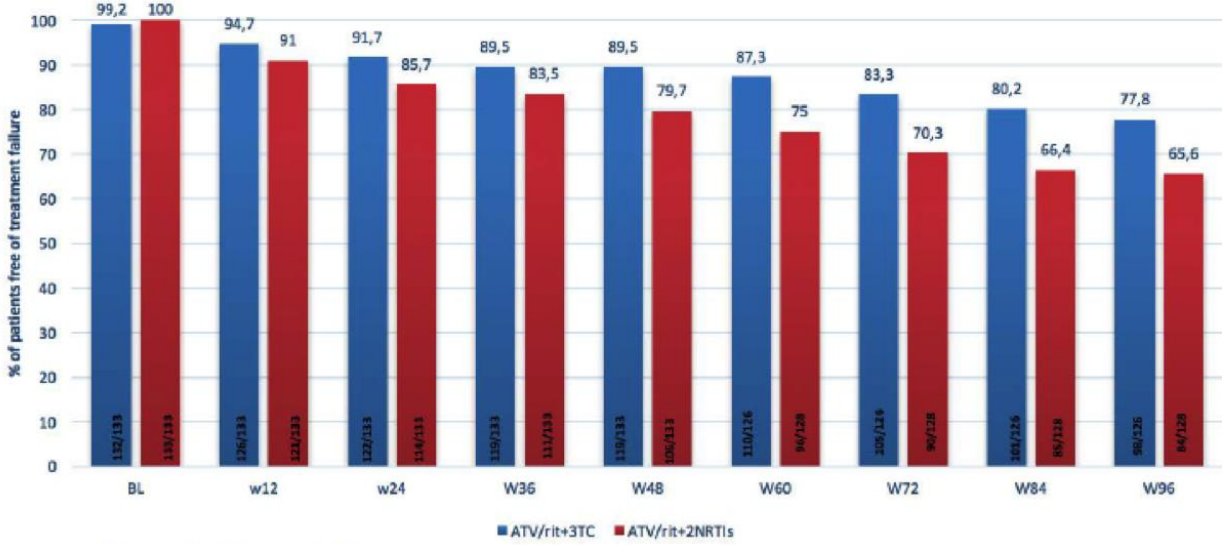
SALT-trial: atazanavir/r plus 3TC *vs*. atazanavir/r plus 2 NRTI

95% CI for the difference



Gatell J *et al. AIDS* 2014. Abstract LBPE17
Perez-Molina *et al. AIDS* 2014

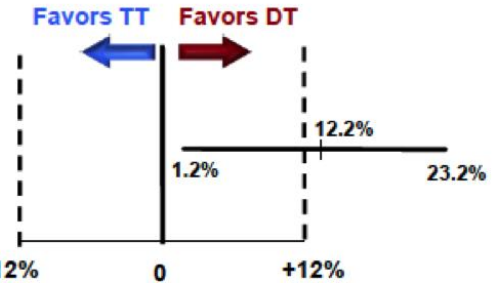
Patients free of treatment failure (ITT S=F)



96 weeks free of TF:

DT 77.8% (95% CI 70.5-85.1)

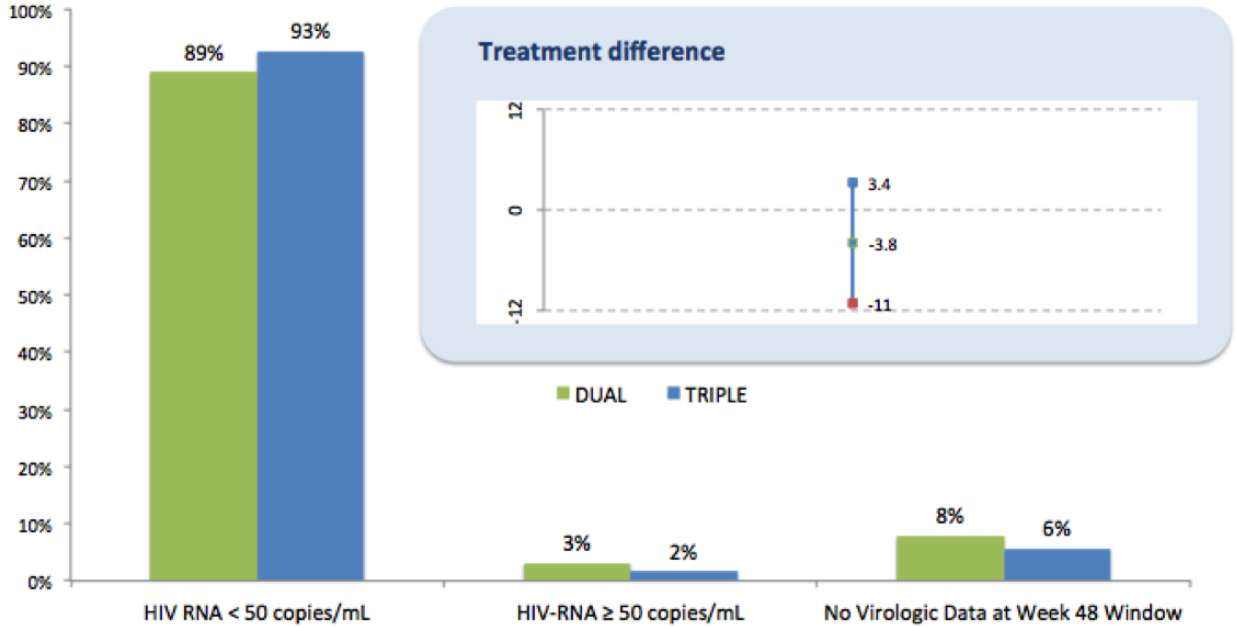
TT 65.6% (95% CI 57.4-73.8)



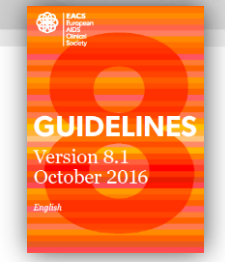
Di Giambenedetto S; ICAR 2016, 6-8 giugno, Milano (Italia)

DUAL: darunavir/r plus 3TC *vs.* darunavir/r plus TDF/FTC or ABC/3TC

Primary Endpoint: Snapshot, ITT-e population



Pulido F et al. Glasgow 2016; Abstract O331



Switch Strategies for Virologically Suppressed Persons

- Clinicians should review the complete ARV history and available resistance test and HIV-VL results before switching
- If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV status

- Dual therapy with 3TC + PI/r may only be given to persons without a) resistance to the PI, b) suppression of HIV-VL for at least the past 6 months and c) absence of chronic HBV co-infection
- Dual therapy: 3TC + DRV/r or + DRV/c or LPV/r or ATV/r or ATV/c. **This strategy has not been associated with more virological rebounds than triple therapy.** It might therefore be a better option than PI/r or PI/c monotherapy

	Oct 11	Dec 11	Feb 12	Jun 12	Oct 12	Jan 13	May 13	Sep 13
CD4+ T cells/mm^3	250	291	281	256	389	349	315	455
Viral load Copies/ml	**950**	< 20	< 20	**350**	22	< 20	< 20	**110**

M184V

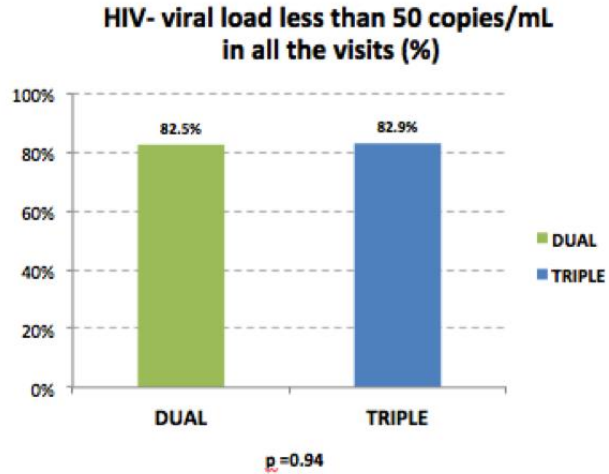
Oct 2012: Hbe Ac+

Would you change the current regimen (3TC + LPV/r) due to viral blips persistence?

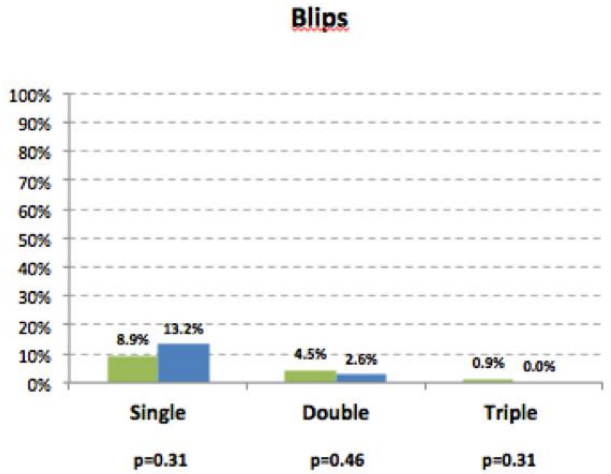
What would you do regarding the 184V mutation?

DUAL-trial

Continuous viral load suppression



Including all patients who completed 48 weeks of treatment and had viral loads measurements in all visits.



Only patients who had HIV-RNA < 50 copies at week 48.
Blip defined as a transitory viral load ≥ 50 copies/mL

***OLE-trial**: Blips*: DT n=12 (10%) *vs* TT n=12 (10%)

***SALT-trial**: Blips*: DT n=19 (14%) *vs* TT n=23 (16%) (Technical issue in a single centre)

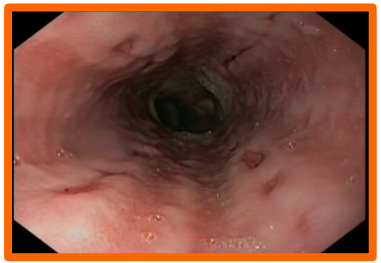
Pulido F et al. Glasgow 2016; Abstract O331

	Dec 11	Feb 12	Jun 12	Oct 12	Jan 13	May 13	Sep 13	Jan 14
CD4+ T cells/mm^3	291	281	256	389	349	315	455	351
Viral load Copies/ml	< 20	< 20	**350**	22	< 20	< 20	**110**	< 20

Jun 2014

GERD symptoms attributed to ritonavir

AST- 60 IU/ml ALT-84 IU/ml DNA-VHB 338 IU/mL



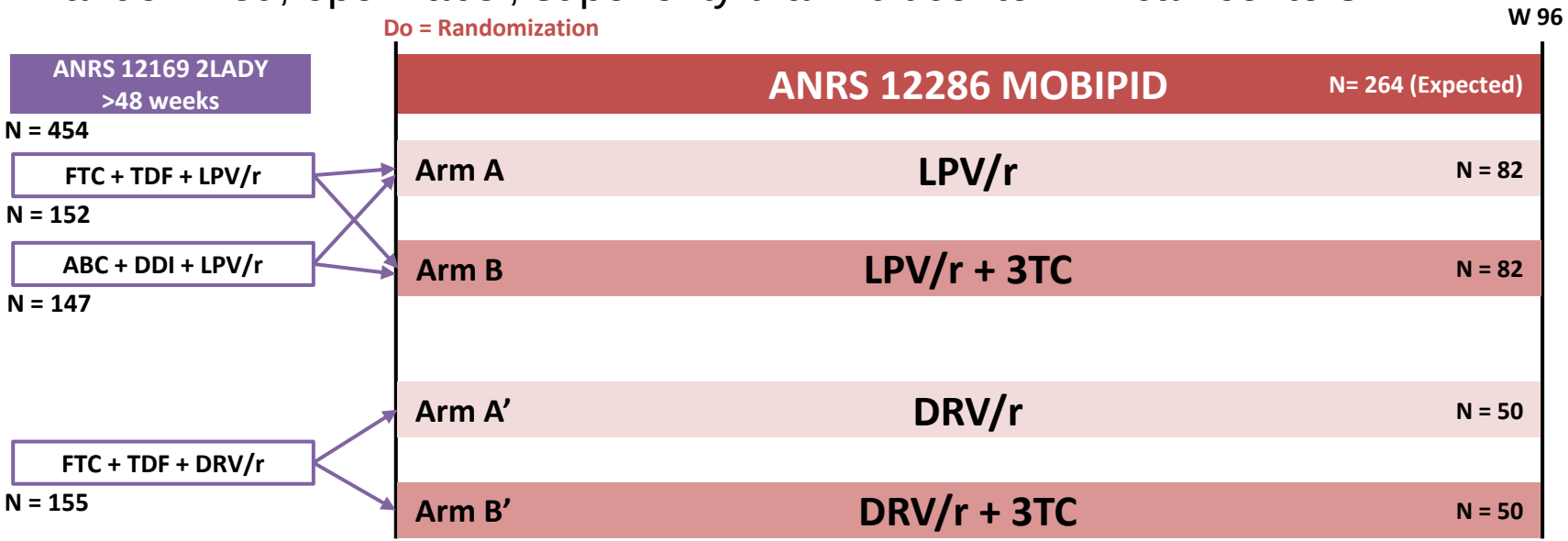
Fibroscan™: 4.2 Kpa IQR: 0.4

Abdominal US: normal

Entecavir was added to the regimen and ART switched to **3TC + DRV/r**

MOBIDIP Study: bPI + 3TC for Maintenance of Virological Suppression in Patients on Second Line Therapy in Africa

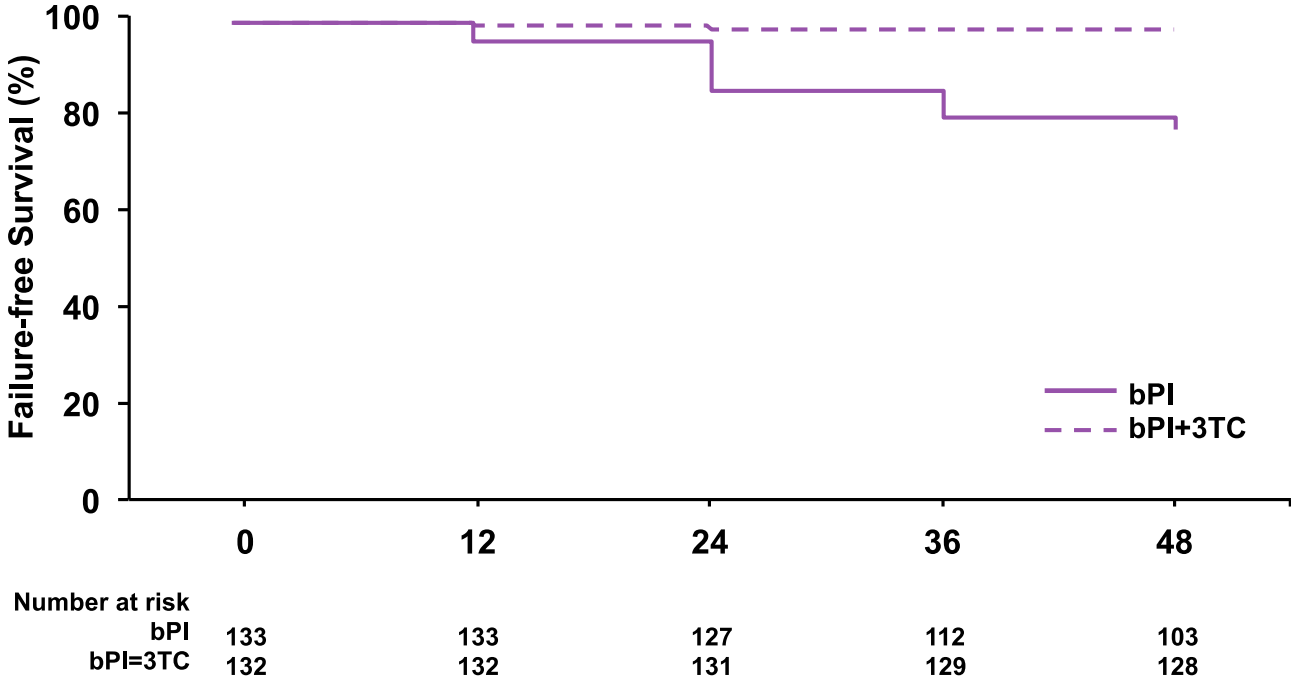
- Randomized, open-label, superiority trial Multicenter. African centers



Ciaffi L et al. HIV Glasgow; 23-26 October 2016; Glasgow, UK; Abst. O122

Baseline Characteristics	bPI n=133	bPI +3TC n=132	Total n=265
Site, n (%)			
Bobo Dioulasso	26 (20%)	27 (20%)	53 (20%)
Dakar	16 (12%)	16 (12%)	32 (12%)
Yaoundé	91 (68%)	89 (67%)	180 (16%)
Women, n (%)	101 (76%)	93 (70%)	194 (73%)
Age, median (IQR)	41 (36-49)	43 (37-50)	42 (36-50)
VL <50 copies/ml, n (%)	107 (80%)	110 (83%)	217 (82%)
CD4, median (IQR) n=259	498 (383-673)	472 (360-621)	475 (379-652)
CD4 <200/mm^3, n (%) n=259	3 (2%)	4 (3%)	7 (3%)
bPI = DRV/r,	56 (42%)	44 (33%)	100 (38%)
Nadir CD4 < 100, n (%) n=256	73 (56%)	65 (52%)	138 (54%)
Time on first line (months), median (IQR)	50 (33-69)	50 (34-68)	50 (33-68)
Time on second line (months), median (IQR)	37 (30-47)	38 (30-47)	37 (30-47)
M184V at inclusion, n (%) n=263	125 (95%)	127 (97%)	252 (96%)
Resistance to one 2nd line drug, n (%) n=263	81 (61%)	78 (60%)	159 (60%)
Resistance to two 2nd line drugs, n (%) n=263	20 (15%)	14 (11%)	34 (13%)

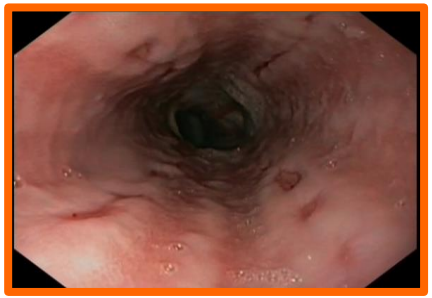
Ciaffi L et al. HIV Glasgow; 23-26 October 2016; Glasgow, UK; Abst. O122



- Neither adherence, nadir CD4 count, or PI drug were associated with failure

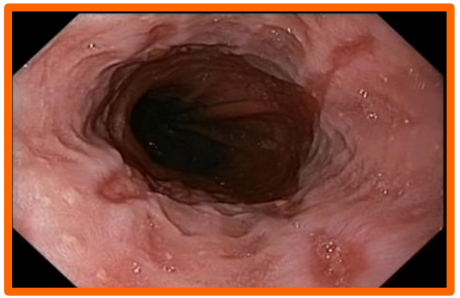
Ciaffi L et al. HIV Glasgow; 23-26 October 2016; Glasgow, UK; Abst. O122

June 2014



Progression to Barrett's Esophagus

December 2015



Switch to 3TC + Dolutegravir

	Jan 16	Feb 14	Apr 16	Jul 16	Dec 16
CD4+ T cells/mm^3	475	440		416	----
Viral load Copies/ml	< 20	< 20	< 20	< 20	----