

cART in 2014:
the Estonian experience

Matti Maimets
University of Tartu
Estonian Society of Infectious Diseases
June 6, 2014

MMaimets14

2013

30 years of HIV
25 years of HIV in Estonia

MMaimets14

2013

35 million HIV+

MMaimets14

Deaths 1970-2013

35 million

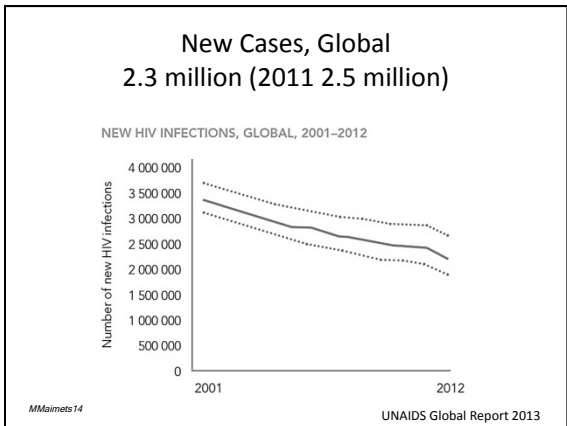
MMaimets14

Examples of Epidemic Emerging Infections

		Causal Agent	Deaths (est.)
430-426 BC	Plague of Athens	Unknown	40,000
1340s	Black death (plague)	<i>Yersinia pestis</i>	~50 million
1520-21	Smallpox in Aztec Empire	<i>Variola major</i>	3.5 million
1793-98	The American plague	Yellow fever virus	~25,000
1918-19	Spanish influenza	H1N1 influenza virus	>50 million
1981 →	AIDS pandemic	HIV	~30 million
1939-1945	WWII		50-80 million

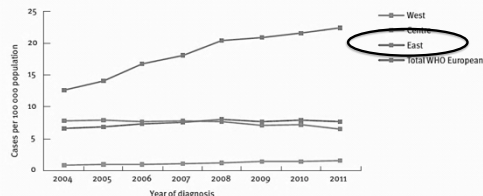
Source: Morens, Folkers, Fauci; Lancet Infect Dis, 2008; UNAIDS, 2011

MMaimets14



New Cases WHO European region

Figure 3.1: HIV infections, rates by geographical area, WHO European Region, 2004–2011



No data from Monaco; data not included from Russia, Uzbekistan.

MMaimets14

ECDC HIV/AIDS surveillance in Europe 2011

Major issues

- unsteady political commitment
- low testing rate
- late treatment, deaths, orphans
- loss to follow-up

MMaimets14

Effects of cART

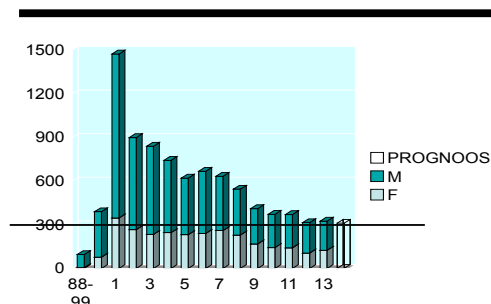
- normalises immune function (opportunistic infections, cancers)
- reduces inflammation and associated organ damage (inflammageing)
- **prevents HIV transmission**

MMaimets14

25 years of HIV in Estonia

MMaimets14

Notified HIV 30.5.2014: 8840



MMaimets05

www.terviseamet.ee

25 years of ART/cART

- 1988 1
- dec 2006 495
- dec 2008 1026
- dec 2011 2156
- apr 2014 2852
- dec 2014 prognosis 3200

MMaimets14

Mother-to-child transmission 1-2%

- 120 HIV+ pregnancies/year
- 1. HIV+ child in 2000
- 2014: **52**
- 1 lady has 3 HIV+ kids
- 4 deaths

MMaimets14

cART in Estonia

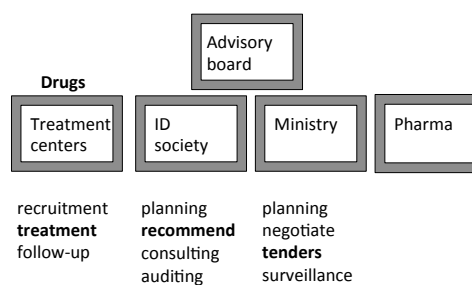
MMaimets14

Costs

- € 11 million/year
- € 3800 patient/year

MMaimets14

Organisation



MMaimets14

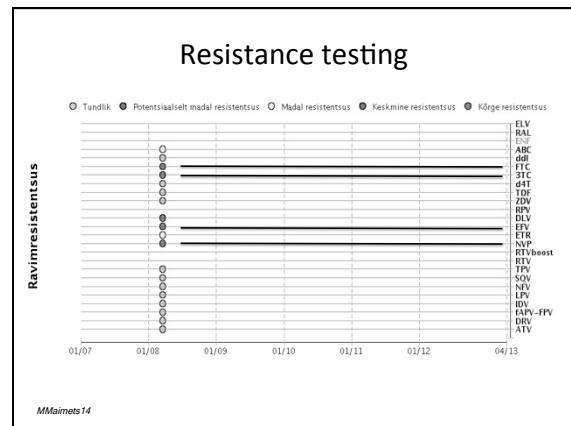
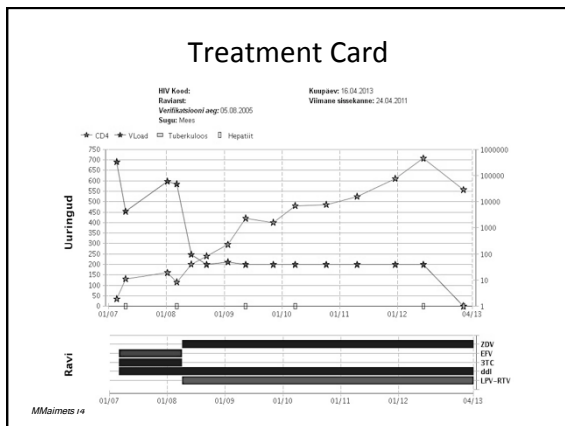
Estonian AD Board prognosis 2015: naïve pt

NRTI	ABC/3TC	40 %
	TDF/FTC	60 %
	ZDV/3TC	? %
NNRTI 55%	EFV	80 %
	RPV	20 %
PI 45%	LPV/r	40 %
	DRV + r	60 %

MMaimets14

Auditing

MMaimets14



2014: When to start HIV treatment

MMaimets 14

Major Guidelines for Initiation of Antiretroviral Therapy

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm ³	200-350	350-500	>500
DHHS-USA, 2014	Yes	Yes	Yes	Yes ¹	Yes ²
International AIDS Society-USA, 2012	Yes	Yes	Yes	Yes ¹	Yes ²
British HIV Association, 2013	Yes	Yes	Yes	Consider ³	Defer ³
European AIDS Clinical Society, 2013	Yes	Yes	Yes	Consider ³	Consider ³
World Health Organization, 2013	Yes	Yes	Yes	Yes ⁴	Defer ⁵

(1) Strong strength recommendation based on observational data. (2) Individuals with CD4 < 350. (3) But treat all HIV+ pregnant women, HBV co-infection, HCV co-infection, HIVAN, HIV related neurocognitive disorders, ITP, non-AIDS cancers and serodiscordant couples. (4) Individuals with CD4 < 350. (5) But treat all HIV+ pregnant women, TB co-infection with active disease and HBV co-infection with severe liver disease, and serodiscordant couples.

MMaimets 14

< 350 CD4 mm³ is considered to be too late

MMaimets 14

2014: What to start

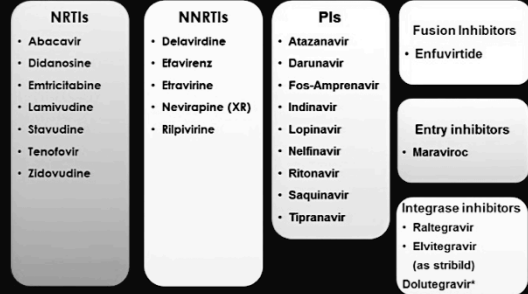
MMaimets 14

Desirable Characteristics of cART

- efficacy
- tolerability, toxicity
- convenience, simplicity
- compatibility with pregnancy and treatment of comorbidities
- no overlapping resistance in treatment sequencing
- few drug interactions
- cost
- etc.

MMaimets14

Approved in Europe and US 2014: 26



cART combinations in naïve patients

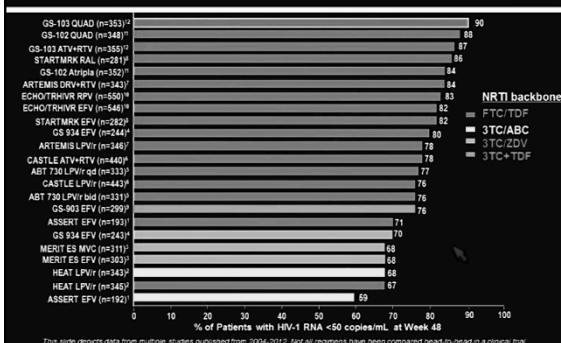
- 1NNRTI + 2 NRTIs
- 1PI + 2 NRTIs
- 1INSTI + 2 NRTIs

MMaimets14

ABC/3TC vs TDF/FTC

MMaimets14

Benchmark for efficacy? - Background: Cross-Study Comparison of Treatment-Naïve Clinical Trials HIV RNA <50 copies/mL at Week 48

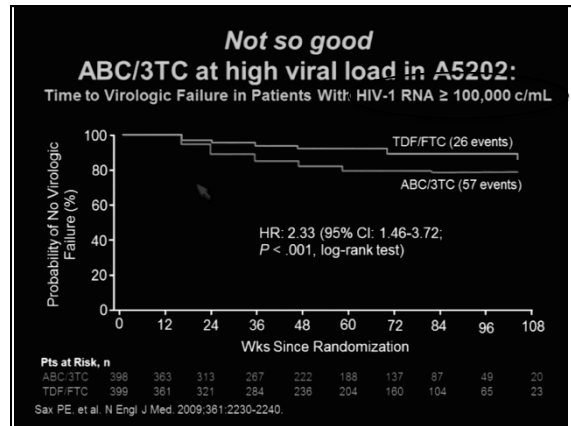
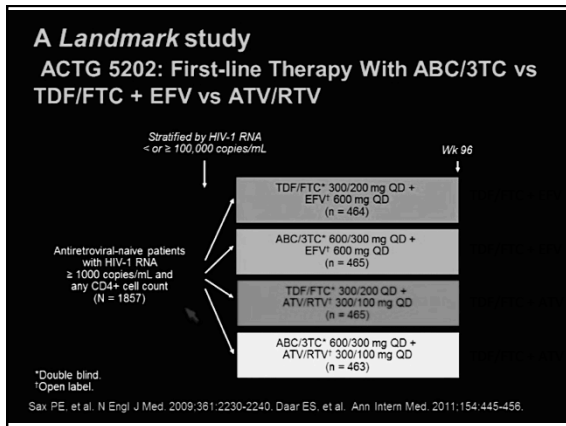


EACS ABC/3TC limitations

	DHHS	IAS	EACS
EFV + ABC/3TC	Alternative	Alternative	Recommended*
DRV/r + ABC/3TC	Alternative	Alternative	Recommended*
ATV/r + ABC/3TC	Alternative	Alternative	Recommended*
RAL + ABC/3TC	Alternative	Alternative	Recommended*

*contra-indicated if HLA B*5701 positive.
Even if HLA B*5701 negative, counselling on HSR risk still mandatory
ABC should be used **with caution** in persons with a high CVD risk and/or persons with a VL > than 100,000 copies/mL.

MMaimets14



EACS ABC/3TC limitations

	DHHS	IAS	EACS
EFV + ABC/3TC	Alternative	Alternative	Recommended*
DRV/r + ABC/3TC	Alternative	Alternative	Recommended*
ATV/r + ABC/3TC	Alternative	Alternative	Recommended*
RAL + ABC/3TC	Alternative	Alternative	Recommended*

*contra-indicated if HLA B*5701 positive.
Even if HLA B*5701 negative, counselling on HSR risk still mandatory
ABC should be used with caution in persons with a high CVD risk and/or persons with a VL > than 100,000 copies/mL.

MMaimets14

HLA B*5701 prevalence 4 %

Title: Prospective epidemiological study on the prevalence of HLA B* 5701 in HIV-1 infected patients in the Central Eastern European (CEE)

Author(s): A. Streinu-Cercel^{1,2}, A. Streinu-Cercel³, D. Banhegyi⁴, V. Uzdaviniene⁵, T. Petrova Tchervenakova⁶, M. Maimets⁷, J. Tomazic⁸, I. Januskevica⁹, Dr. Tania Chervenakova Bulgaria taniacher@abv.bg, Prof. Matti Maimets Estonia matti.maimets@klinikum.ee, Dr. Denes Banhegyi Hungary immunol@mail.datanet.hu, Dr. Inga Januskevica Latvia inga.januskevica@lic.gov.lv, Dr. Vilma Uzdaviniene Lithuania vilma@aids.lt, Dr. Janez Tomazic Slovenia janez.tomazic@kclj.si

Institute(s): ¹Carol Davila University- National Institute for Infectious Diseases Matei Bals, Infectious Disease, Bucharest, Romania, ²European HIV AIDS Academy, HIV AIDS, Bucharest, Romania, ³National Institute for Infectious Diseases Matei Bals, Infectious Disease, Bucharest, Romania, ⁴5th Dept. of Medicine, Saint Laszlo Hospital, Budapest, Hungary, ⁵Head of out-patient department Lithuanian AIDS center, Vilnius, Lithuania, ⁶Hospital of Infectious, Parasitic and Tropical Diseases., Sofia, Bulgaria, ⁷Tartu University Hospital, Tartu, Estonia, Tartu, Estonia, ⁸Medical Centre Ljubljana, Department of Infectious Disease. Japljeva 2, Ljubljana., Slovenia, ⁹Latvian Infectology Centre, Riga, Latvia

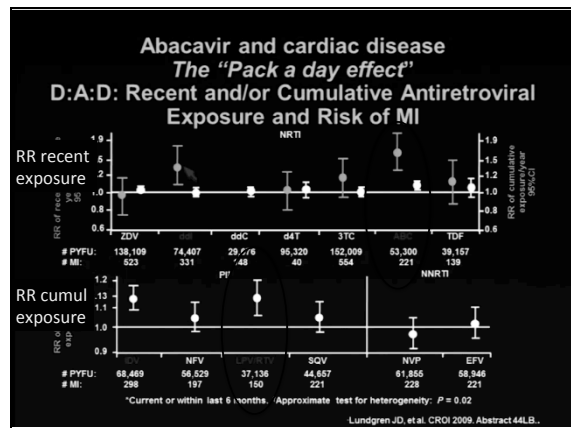
MMaimets14

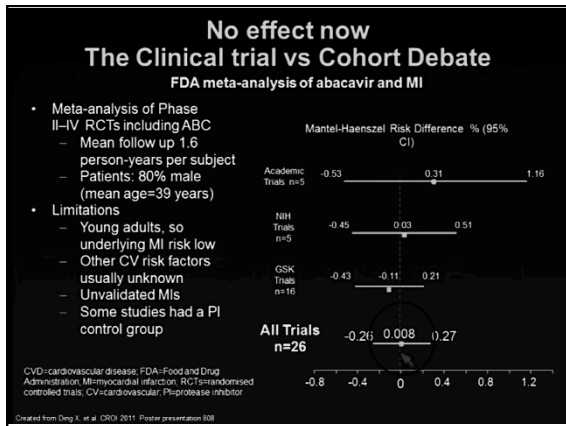
EACS ABC/3TC limitations

	DHHS	IAS	EACS
EFV + ABC/3TC	Alternative	Alternative	Recommended*
DRV/r + ABC/3TC	Alternative	Alternative	Recommended*
ATV/r + ABC/3TC	Alternative	Alternative	Recommended*
RAL + ABC/3TC	Alternative	Alternative	Recommended*

*contra-indicated if HLA B*5701 positive.
Even if HLA B*5701 negative, counselling on HSR risk still mandatory
ABC should be used with caution in persons with a high CVD risk and/or persons with a VL > than 100,000 copies/mL.

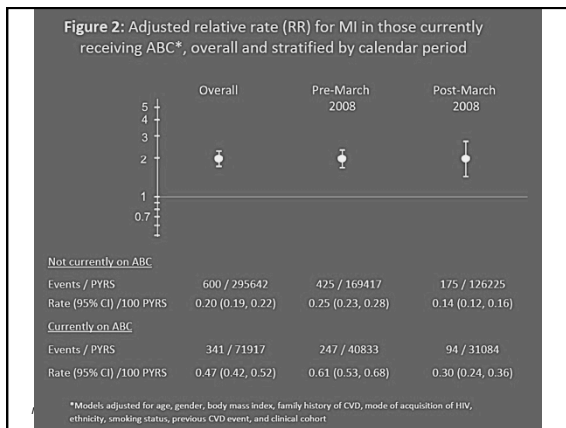
MMaimets14





D:A:D CROI 2014

MMaimets14



Tenofovir kidney problem

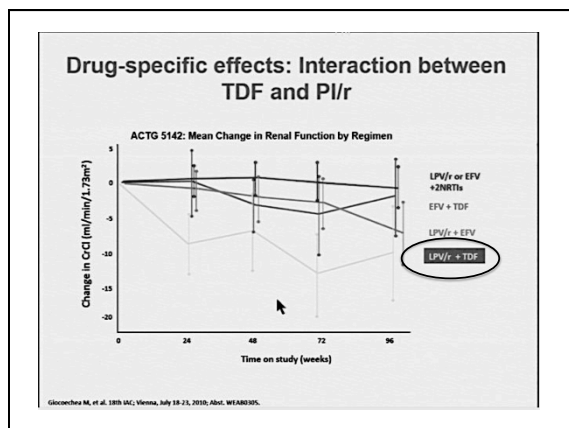
MMaimets14

Hazard of CKD incidence

• Tenofovir	1.16	1.06-1.25
• Indinavir	1.12	1.06-1.18
• Atazanavir	1.21	1.09-1.34
• Lopinavir/r	1.08	1.01-1.16

Mocroft et al. AIDS 2010, EuroSIDA Study Group

MMaimets14



Tenofovir Renal Adverse Events (AEs) in Treatment-Naive Prospective TDF Studies

Study (Third Agent)	TDF Subjects (n)	DISCONTINUED		Follow-up (weeks)
		n	%	
TDF alone	426	<1.5	240	
GS-102, 103 (TDF for HIV)	563	NR	48	
STARTMRK (RAL or EPV)	770	NR	48	
QEMRQ (RAL)	299	0	144	
Unboosted Regimens	257	0	144	
GS-236 (EPV)	1096	0	96	
ACTO THRIVE (RPV or EPV)	296	0	48	
GS-236, 102, 104 (EPV)	192	0	48	
A25257 (EPV)	664	0	96	
ABT-720 (LPVn)	689	0	96	
ARTEMIS (DRV + RTV or LPVn)	227	0	48	
GERMIN (DRV + RTV or LPVn)	265	0.2%	48	
GS-263, 102, 103, 104 (Qdaz)	749	0.8%	48	
GS-263, 102, 103, 104 (Qdaz)	878	<1%	96	
Boosted Regimens	240	<1%	96	
CAPELLA (ATV+RTV or LPVn)	969	<1%	48	
ARTEN (ATV+RTV or RPV)	190	<1%	96	
ABT-418 (LPVn)	898	1%	96	
ACTO 8020 (ATV+RTV or EPV)	190	1%	48	
SAISON (ATV+RTV)	771	1.6%	48, 96	
GS-216, 105, 114 (ATV+RTV or ATV+COBI)	190	2.6%	48	
ALERT (FPV+RTV or ATV+RTV)	10,657	0 - 2.8%	48-144	
Total				

MMaimets14

proteinuria

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR category (mL/min/1.73m ²) Description and range	GFR description and range	Persistent albuminuria categories Description and range		
		A1	A2	A3
		Normal to mildly increased	Moderately increased	Severely increased
		<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	>90		
G2	Mildly decreased	60-89		
G3a	Mildly to moderately decreased	45-59		
G3b	Moderately to severely decreased	30-44		
G4	Severely decreased	15-29		
G5	Kidney failure	<15		

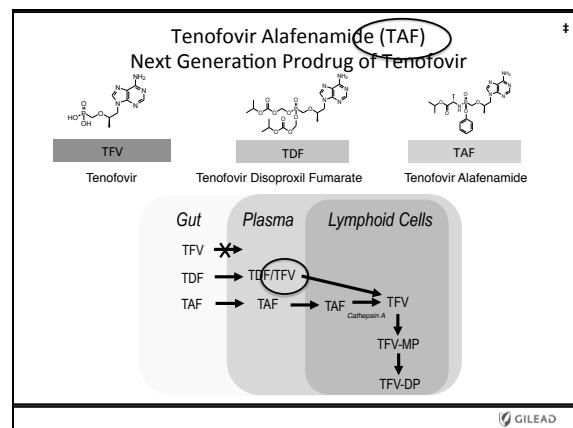
eGFR

MMaimets14

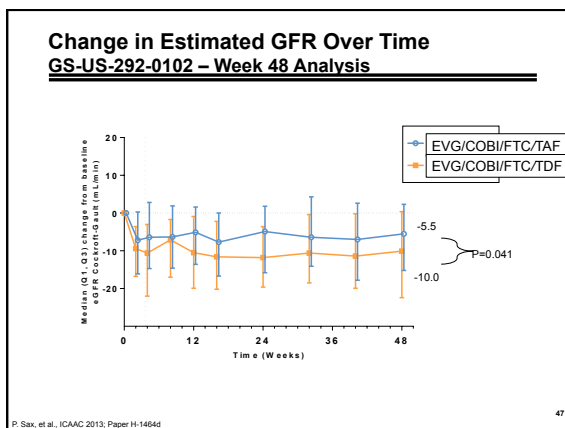
Kidney International Supplements 2013;3:19

Tenofovir Alafenamide (TAF)

MMaimets14



GILEAD

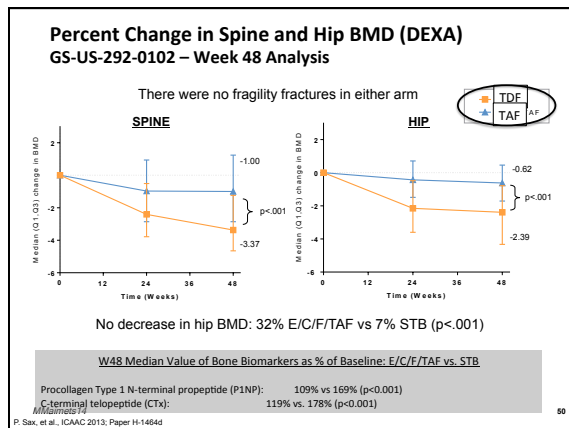
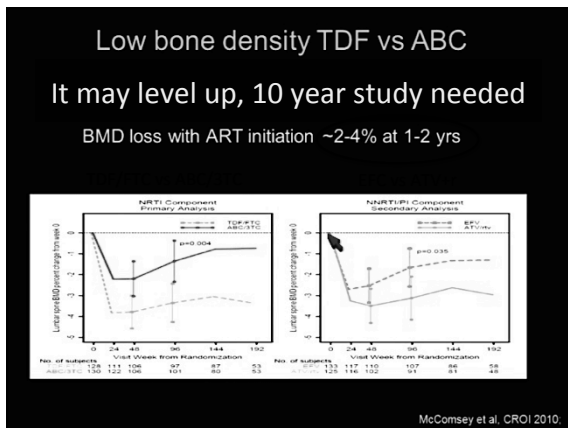


P. Sax, et al., ICAAC 2013, Paper H-14644

47

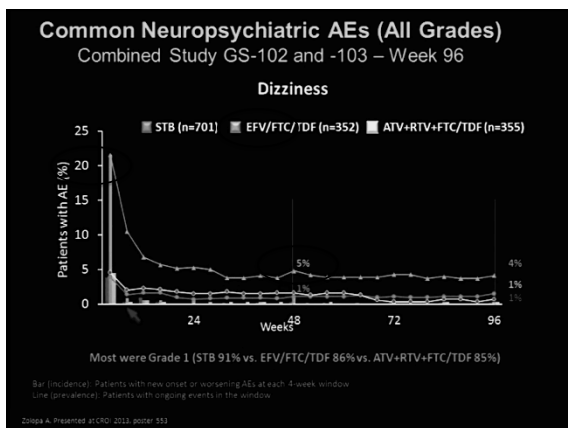
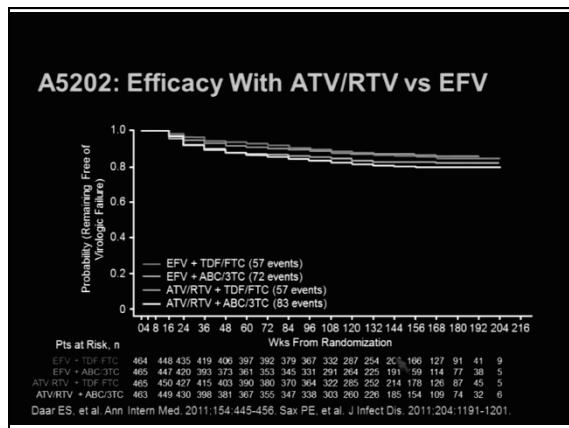
Bone mineral density

MMaimets14



NNRTI

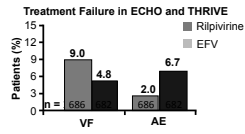
MMAims14



Second NNRTI: Rilpivirine

MMAims14

ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events



Wk 48 Outcome	Rilpivirine (n = 686)	Efavirenz (n = 682)
VF with resistance data, n	62	28
No NNRTI or NRTI RAMs, %	29	43
≥ 1 Emergent NNRTI RAM, %	63	54
• Most frequent NNRTI RAM	E138K	K103N
≥ 1 Emergent NRTI RAMs, %	68	32
• Most frequent NRTI RAM	M184I	M184V

MMaimets14

Cohen C, et al. AIDS 2010. Abstract TH1500206. Table used with permission.

Adverse Events and Discontinuation

Wk 48 Outcome, %	Rilpivirine (n = 686)	Efavirenz (n = 682)	P Value
DC for AE	3	8	.0005
Most Common AEs of Interest			
neurologic	17	38	.0004
psychiatric	15	23	.0002
rash	3	14	.0004

European license

- “EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤100,000 HIV-1 RNA copies/ml.”

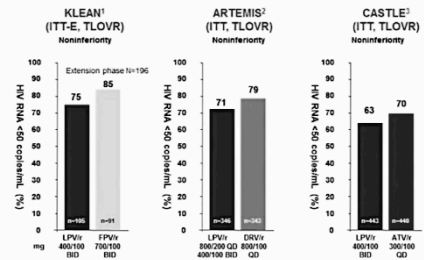
MMaimets14

Edurant Summary Product of Characteristics; Janssen-Cilag International NV, 28th November 2011; accessed 12th May 2012

PI vs PI

MMaimets14

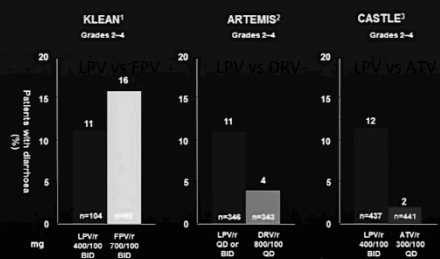
So if you choose a PI/r Which has best efficacy in ARV-naïve patients? Virological suppression at 96 weeks



Data in figures are from different studies and cannot be compared directly. ITT, intent-to-treat; ITT-E, intent-to-treat exposed; MMR, missing = non-response; NC/r, 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.

But...Drug-related diarrhoea in treatment-naïve patients at 96 weeks



LPV/r, QD is not approved in the EU.

Data in figures are from different studies and cannot be compared directly.

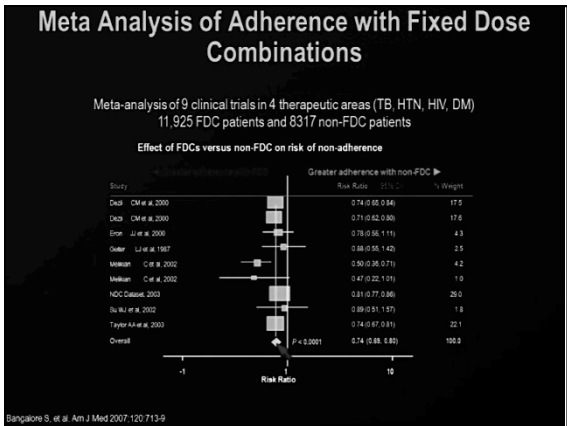
Adapted from: 1. Pulido F, et al. 47th ICAAC Chicago, 17-20 Sept. 2007. Abstract H-361. 2. Mills A, et al. 48th ICAAC, Washington DC, Oct 25-28, 2008. Abstract H-1250c. 3. Molina JM, et al. 48th ICAAC, Washington, DC, Oct 25-28, 2008. Abstract H-1250d.

Metabolic changes with RTV 200 mg/day

MMaimets14

Fixed Dose Combinations

MMaimets14



Commonly used fixed-dose combinations

2 NRTIs

- Truvada (TDF/FTC)
- Kivexa (ABC/3TC)

TDF FTC + NNRTI

- Atripla
- Eviplera

TDF FTC + EVG/c

- Stribild

TDF = Tenofovir; FTC = Emtricitabine; ABC = Abacavir; 3TC = Lamivudine
 NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor
 EVG/c = Efavirenz/zalcitabine

Geretti ECCMID14

- ### Conclusions
- start **BEFORE** ≤ 350 CD4 cells/mm³
 - consider **earlier**
 - patients health
 - transmission
 - the decision as to which regimen to select
 - efficacy
 - safety
 - adherence
 - baseline viral load
 - comorbid conditions
 - concomitant meds
- MMaimets14